5 Minute JournalClub

Key SABCS Presentations

Issue 5, 2011

Correlation between Tamoxifen-Metabolizing Enzymes Genotypes/Phenotypes and Clinical Outcomes in Patients with Breast Cancer Treated with Tamoxifen

For more visit ResearchToPractice.com/5MJCSABCS2011

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CME INFORMATION

OVERVIEW OF ACTIVITY

The annual San Antonio Breast Cancer Symposium (SABCS) is unmatched in its significance with regard to the advancement of breast cancer treatment. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results from a plethora of ongoing clinical trials lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across all breast cancer subtypes. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of the rapidly evolving data sets in breast cancer. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest SABCS meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for breast cancer.

LEARNING OBJECTIVE

- Employ an understanding of new data to address concerns expressed by patients and providers over CYP2D6 genotype and the efficacy and tolerability of tamoxifen.

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Clifford Hudis, MD
Chief, Breast Cancer Medicine Service
Solid Tumor Division
Department of Medicine
Memorial Sloan-Kettering Cancer Center
Professor of Medicine
Weill Cornell Medical College
New York, New York

Paid Research: Merck and Company Inc, Onyx Pharmaceuticals Inc.

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This program is supported by educational grants from AstraZeneca Pharmaceuticals LP, Genentech BioOncology, Genomic Health Inc, Novartis Pharmaceuticals Corporation and Sanofi-Aventis.

Last review date: February 2011
Expiration date: February 2012

5 MinuteJournalClub

Key SABCS Presentations
Issue 5, 2011

Click here for key papers on endocrine/metabolic issues from the 2010 SABCS

The first targeted therapy for cancer came in the form of an innocuous-appearing pill that for many patients with ER-positive breast tumors was more efficacious than chemotherapy (CT). Thanks to mavens like Craig Jordan, we have known for quite a while that the antitumor effect of tamoxifen (TAM) comes via a metabolite (endoxifen), and thus it made sense that patients with genetic deficiencies of the activating enzyme (CYP2D6) might experience less or no treatment benefit. That being said, prior studies attempting to validate this concept have yielded conflicting results.

Related to this issue, a number of prominent TAM/investigator advocates have hypothesized that the 20 percent reduction in recurrences in trials of adjuvant AIs versus TAM wasn't the result of inherently greater antitumor efficacy but rather because a fraction of women in these studies actually had CYP2D6 deficiency. **Two major presentations** at San Antonio pretty much debunked that theory and added several more nails to the CYP2D6 coffin.

For these studies, investigators accessed available tissue from patients enrolled in two of the largest AI trials — ATAC (anastrozole) and BIG 1-98 (letrozole) — assayed for CYP2D6 genotypes and found no correlation with recurrence rate in patients receiving AIs (as would be expected) or TAM. Although investigators seem ready to abandon CYP2D6 testing in clinical practice outside a protocol setting, it is important to consider that the majority of the available data — including these two new reports — are in postmenopausal subsets. However, TAM is now most commonly used in premenopausal patients, where the hormonal environment (high estrogen levels) is very different. Vered Stearns and ECOG just opened a new trial in metastatic disease to further study this continuing story. Our recent Patterns of Care survey demonstrated that 41 percent of community oncologists have ordered a CYP2D6 assay at least once, and although that practice now seems more questionable than ever, it still makes sense to avoid inhibitors of the enzyme like SSRIs in patients receiving TAM.

We've come a long way in understanding endocrine and metabolic issues in breast cancer in the four decades since TAM first entered oncology practice, and in this issue of *5-Minute Journal Club* we peruse several other interesting related San Antonio papers.

1. **More on 500-mg fulvestrant dosing**

John Robertson presented additional data from the FIRST trial evaluating front-line fulvestrant in metastatic disease, which continues to report benefit with the increased monthly dose after loading. The current data demonstrate a median time to progression of 23.4 months for fulvestrant 500 compared to 13.1 months with anastrozole.

2. **Treatment of breast cancer during pregnancy**

This landmark European registry reported on 313 women diagnosed with breast cancer during pregnancy, including 142 who received CT while still pregnant and 118 who received it immediately after childbirth (with medians of 20 and 28 weeks of gestation, respectively, at the time of diagnosis). Breast cancer and fetal outcomes were similar in the two groups but premature delivery was more common (33 percent) in the delayed group, probably to hasten the time to receive CT. The authors concluded that oncologists should generally use CT during pregnancy rather than expose women and fetuses to the potential complications of premature delivery.

3. **Three papers demonstrating the negative prognostic impact of obesity in the adjuvant setting**

The 2005 presentation by Rowan Chlebowski of the WINS trial demonstrated fewer breast cancer recurrences in women randomly assigned to counseling to reduce dietary fat, and this sparked a series of related analyses along with three new important data sets in San Antonio. Of particular note was an extraordinary presentation by Joe Sparano of data from several recent ECOG randomized trials demonstrating that obese (BMI > 30 kg/m^2) patients had an increased risk of recurrence independent of other factors. This general body of work continues to have important practice and translational research implications.

Next up on this San Antonio highlights series: More on the increasingly complex world of HER2-positive breast cancer.

Neil Love, MD
Research To Practice
Miami, FL

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Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

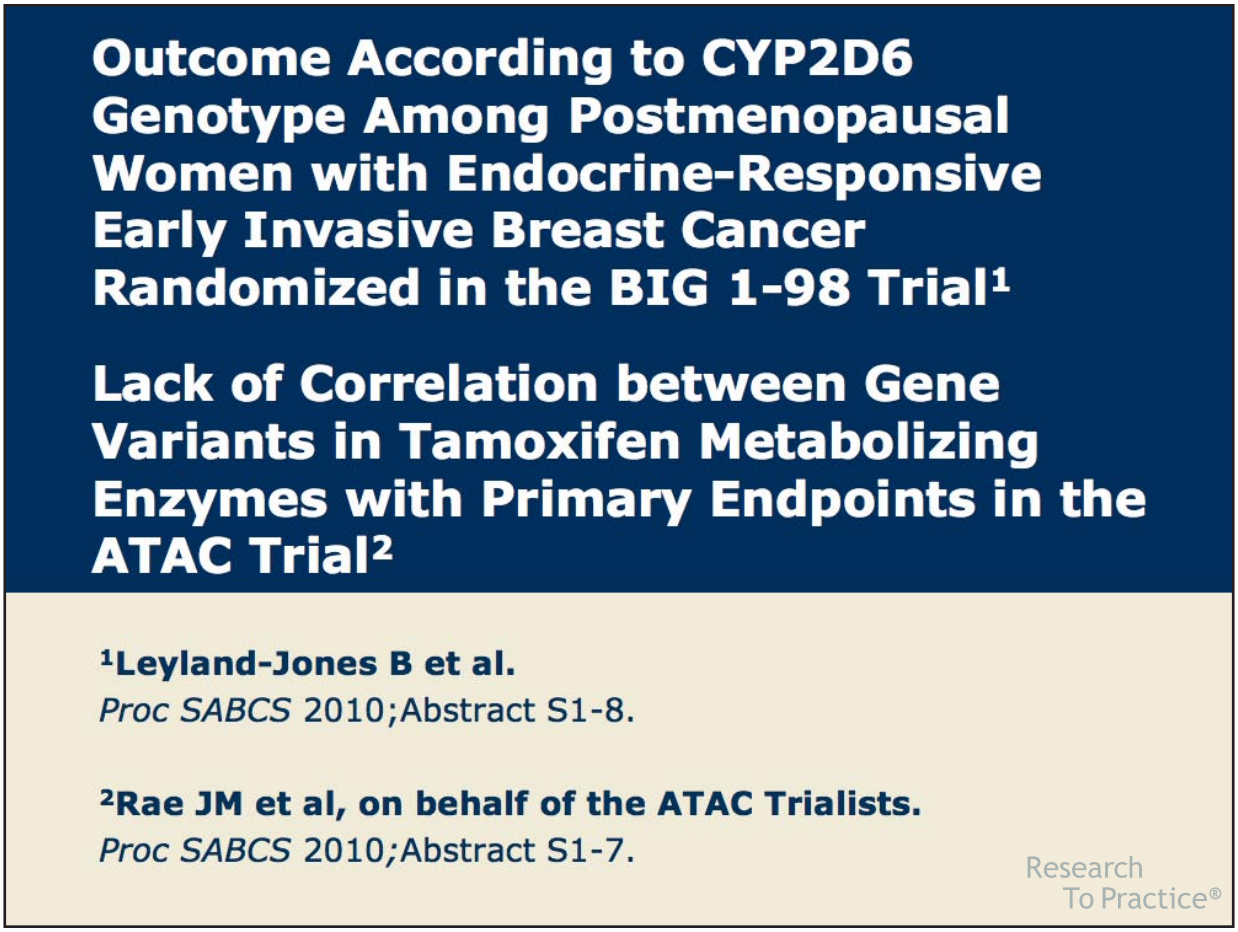
Correlation between Tamoxifen-Metabolizing Enzymes Genotypes/Phenotypes and Clinical Outcomes in Patients with Breast Cancer Treated with Tamoxifen

Presentations discussed in this issue

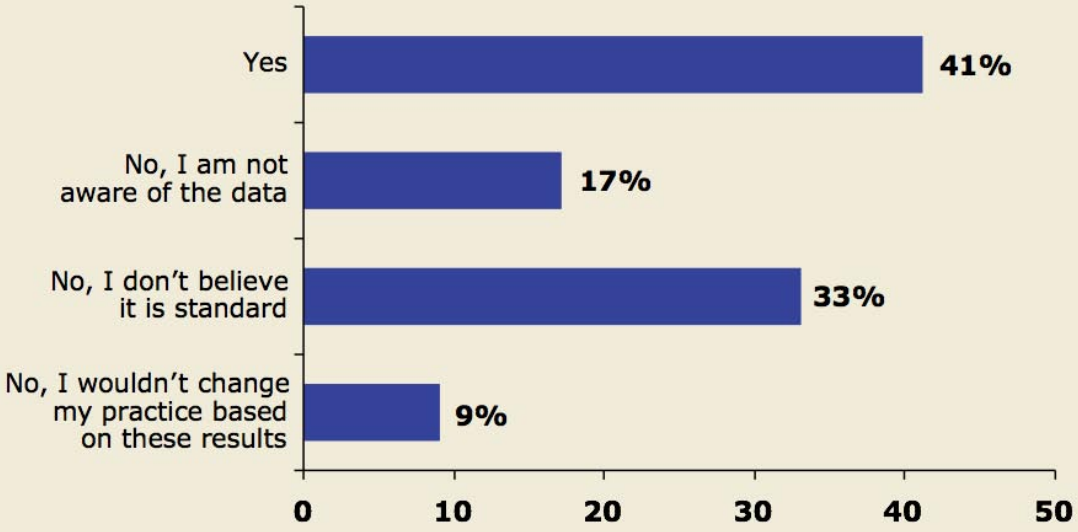
Leyland-Jones B et al. **Outcome according to CYP2D6 genotype among postmenopausal women with endocrine-responsive early invasive breast cancer randomized in the BIG 1-98 trial.** San Antonio Breast Cancer Symposium 2010;**Abstract S1-8**.

Rae JM et al. **Lack of correlation between gene variants in tamoxifen metabolizing enzymes with primary endpoints in the ATAC trial.** San Antonio Breast Cancer Symposium 2010;**Abstract S1-7**.

Slides from presentations at SABCS 2010 and transcribed comments from a recent interview with Clifford Hudis, MD (1/12/11)



Have You Ordered CYP2D6 Genotyping for Patients with ER-Positive Breast Cancer?



Patterns of Care in Breast Cancer, Research To Practice 2009.

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Outcome According to CYP2D6 Genotype Among Postmenopausal Women with Endocrine-Responsive Early Invasive Breast Cancer Randomized in the BIG 1-98 Trial

Leyland-Jones B et al.

Proc SABCS 2010;Abstract S1-8.

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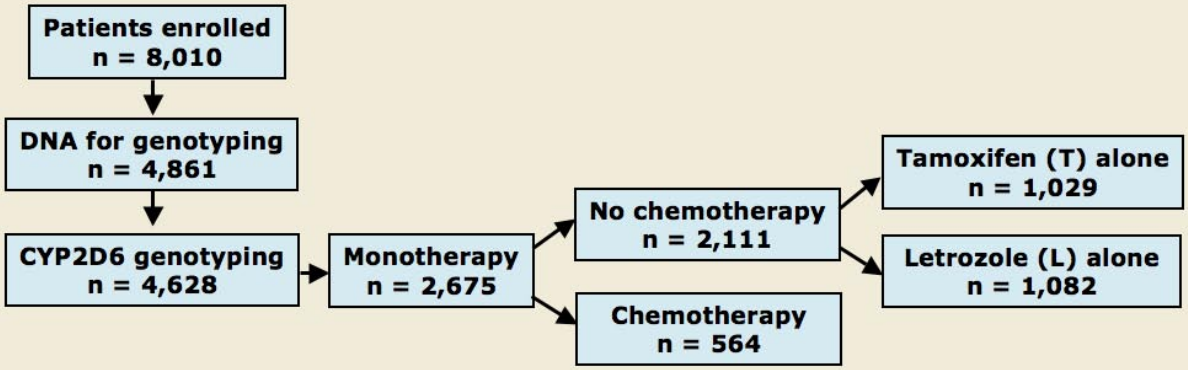
BIG 1-98: Analytic Cohort



Patient characteristics: Caucasian: 98%, ER-positive: 100%, Node-negative: 57%, No chemotherapy (Chemo) received: 77%

Current analysis objectives:

- To investigate the association of CYP2D6 variants with breast cancer-free interval (BCFI) and onset of hot flashes/night sweats.
- To evaluate the role of adjuvant chemotherapy, which was administered in about one third of trial patients prior to randomization to adjuvant endocrine therapy.

Leyland-Jones B et al. *Proc SABCS* 2010;Abstract S1-8.

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CYP2D6 Phenotype

- **Poor metabolizers (PM):**
  - Homozygous or compound heterozygous for null alleles (*3, *4, *6 or *7)
- **Intermediate metabolizers (IM):**
  - Homozygous for reduced-function alleles (*41) or heterozygous for reduced- and null-function alleles
  - hetEM: Heterozygous for one reduced- or null-function allele
- **Extensive metabolizers (EM):**
  - Absence of reduced- or null-function alleles

Leyland-Jones B et al. *Proc SABCS* 2010;Abstract S1-8.

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CYP2D6 Phenotype is Not Associated with BCFI in Patients Treated with Tamoxifen +/- Chemo

Tamoxifen Alone				
CYP2D6 Phenotype	**Patients (n)**	**Events (n)**	**Adjusted HR (95% CI)**	***p*-value**
Poor metabolizers (PM)	86	8	0.58 (0.28-1.21)	0.35
Intermediate metabolizers (IM)	277	40	0.95 (0.50-1.40)	
Extensive metabolizers (EM)	610	75	Reference	

Chemotherapy plus Tamoxifen				
CYP2D6 Phenotype	**Patients (n)**	**Events (n)**	**Adjusted HR (95% CI)**	***p*-value**
PM	26	3	0.76 (0.23-2.48)	0.23
IM	77	12	0.57 (0.29-1.10)	
EM	167	37	Reference	

Leyland-Jones B et al. *Proc SABCS* 2010;Abstract S1-8.

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CYP2D6 Phenotype is Not Associated with BCFI in Patients Treated with Letrozole +/- Chemo

Letrozole Alone				
CYP2D6 Phenotype	**Patients (n)**	**Events (n)**	**Adjusted HR (95% CI)**	***p*-value**
PM	99	11	0.95 (0.50-1.80)	0.98
IM	296	37	1.02 (0.69-1.53)	
EM	639	72	Reference	

Chemotherapy plus Letrozole				
CYP2D6 Phenotype	**Patients (n)**	**Events (n)**	**Adjusted HR (95% CI)**	***p*-value**
PM	25	3	1.00 (0.30-3.35)	0.34
IM	66	12	1.68 (0.83-3.39)	
EM	169	23	Reference	

Leyland-Jones B et al. *Proc SABCS* 2010;Abstract S1-8.

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Author Conclusions and Clinical Implications

- Genotype analysis of postmenopausal women with endocrine-responsive early breast cancer (EBC) treated on the BIG 1-98 trial found CPY2D6 phenotypes of reduced enzyme activity (PM, IM) were:
  - NOT associated with worse disease control
  - NOT associated with reduced hot flashes (data not shown)
- For postmenopausal women with endocrine-responsive EBC:
  - CYP2D6 pharmacogenetics testing *is not* justified to determine whether to administer tamoxifen
  - Presence or absence of hot flashes *should not be used* as an indicator of tamoxifen efficacy

Leyland-Jones B et al. *Proc SABCS* 2010;Abstract S1-8.

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Lack of Correlation between Gene Variants in Tamoxifen Metabolizing Enzymes with Primary Endpoints in the ATAC Trial

Rae JM et al, on behalf of the ATAC Trialists.
Proc SABCS 2010;Abstract S1-7.

Objective and Methods

- **Study Objective:**
  - Determine whether a correlation exists between single nucleotide polymorphisms (SNPs) in tamoxifen metabolizing enzymes and clinical outcomes in the ATAC trial of adjuvant anastrozole vs tamoxifen for five years.
- **Genetic Analysis in the ATAC Trial:**
  - Genotypes determined from leukocytic DNA present in formalin-fixed paraffin-embedded tumor samples
    - **CYP2D6 gene** - seven most common SNPs in Caucasians were genotyped and entered into the establishment of a CYP2D6 scoring system for predicting CYP2D6 phenotype, based on predicted allele activities: *1, *2, *3, *4, *6, *10, *41
    - **UGT2B7 gene** - common functional SNP in Caucasians was genotyped: *2

Rae JM et al. *Proc SABCS* 2010;Abstract S1-7.

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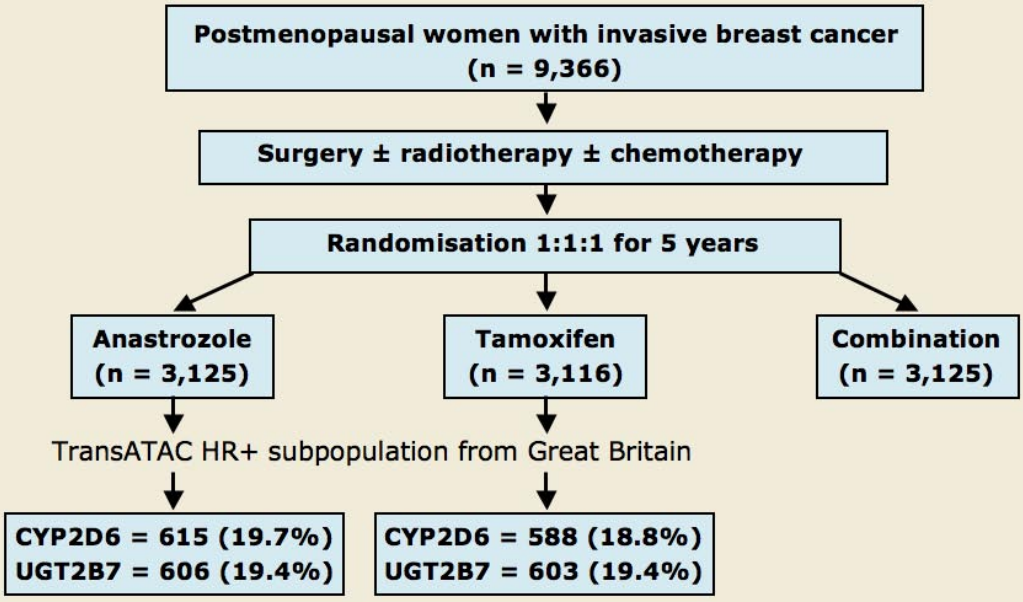
ATAC Trial Design



Rae JM et al. *Proc SABCS* 2010;Abstract S1-7.

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CYP2D6*4 Gene Variant Does Not Predict Recurrence in Patients Treated with Tamoxifen or Anastrozole

Tamoxifen Arm				
CYP2D6 Genotype	**Hazard Ratio**	**95% CI**	***p*-value**	**Overall *p* for Trend**
Wt/Wt (n = 402)	Ref	—	—	0.688
*4/Wt (n = 149)	1.19	0.79-1.80	0.397	
*4/*4 (n = 37)	0.98	0.45-2.14	0.972	

Anastrozole Arm				
Wt/Wt (n = 430)	Ref	—	—	0.22
*4/Wt (n = 146)	0.66	0.38-1.13	0.130	
*4/*4 (n = 39)	0.61	0.22-1.66	0.332	

Wt = wild type; the CYP2D6*4 variant is the most common and is associated with decreased tamoxifen activation.

Rae JM et al. *Proc SABCS* 2010;Abstract S1-7.

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UGT2B7*2 Gene Variant Does Not Predict Recurrence in Patients Treated with Tamoxifen or Anastrozole

Tamoxifen Arm				
UGT2B7 Genotype	**Hazard Ratio**	**95% CI**	***p*-value**	**Overall *p* for Trend**
Wt/Wt	Ref	—	—	0.549
*2/Wt	1.29	0.79-2.09	0.310	
*2/*2	1.11	0.65-1.90	0.709	

Anastrozole Arm				
Wt/Wt	Ref	—	—	0.845
*2/Wt	0.88	0.52-1.49	0.640	
*2/*2	0.85	0.47-1.52	0.640	

The UGT2B7*2 variant is associated with decreased tamoxifen inactivation.

Rae JM et al. *Proc SABCS* 2010;Abstract S1-7.

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Author Conclusions and Clinical Implications

- The genotypes of CYP2D6 and UGT2B7 tamoxifen metabolizing enzymes were not associated with clinical outcomes in the ATAC trial.
- Use of concomitant CYP2D6 inhibitors (SSRI) does not affect outcomes.
- For adjuvant tamoxifen or anastrozole treatment, the evidence is NOT sufficient to recommend:
  - Genotyping for CYP2D6 and UGT2B7
  - Avoidance of the use of CYP2D6 inhibitors

Rae JM et al. *Proc SABCS* 2010;Abstract S1-7.

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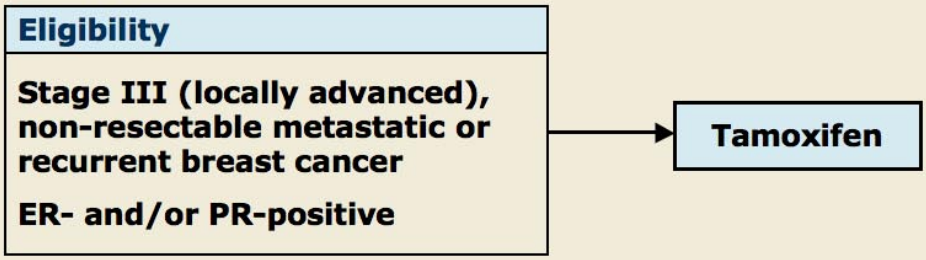
ECOG-E3108: A Phase II Multicenter Trial Correlating Progression-Free Survival and CYP2D6 Activity

Target Accrual: 240 (Open)
Trial Identifier: NCT01124695



Primary Objective: To correlate CYP2D6 score (0 vs 1-2) and progression-free survival in patients treated with tamoxifen

www.ClinicalTrials.gov, February 2011.

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Investigator Commentary: CYP2D6 Genotyping and Clinical Outcome in Postmenopausal Women with Early BC

This has been an area of controversy as there has been mixed evidence on the use of CYP2D6 testing to make treatment decisions. The hypothesis that CYP2D6 genotype could predict response to tamoxifen was sound, but some past studies were positive and others were negative. This left us scratching our heads and sometimes left clinicians crossing within databases the writing of prescriptions for SSRIs that inhibit CYP2D6 against the tamoxifen prescriptions to see whether they were going to predict rates of recurrence.

Retrospective reanalysis of two large randomized trials — BIG 1-98 and ATAC — which evaluated tamoxifen versus aromatase inhibitors were presented at SABCS 2010. Investigators looked specifically at tamoxifen itself or tamoxifen relative to the aromatase inhibitors and attempted to determine whether germline CYP2D6 status had any bearing on the relative benefits of tamoxifen. CYP2D6 status did not allow clinicians to predict with any accuracy which patients did or did not benefit from tamoxifen.

These were clean data sets and well-studied, prospectively followed patient populations. This is likely the highest level of evidence we're ever going to get, and this is nearly a unique resource at this point. I believe this story is over.

Interview with Clifford Hudis, MD, January 12, 2011