cytochrome P450 2D6, an enzyme known for 30 years to be genetically polymorphic. Endoxifen concentrations associate with CYP2D6 genotype and studies conducted in the prevention, adjuvant and metastatic settings suggest that patients with the CYP2D6 poor metabolizer genotype respond less well to tamoxifen treatment. There is a clear alternative to tamoxifen for these patients: the aromatase inhibitor class of drugs.

Despite the fact that aromatase inhibitors (AIs) appear slightly but definitively superior to tamoxifen as adjuvant therapy in postmenopausal women, the relatively low cost of tamoxifen makes it the only viable oral therapy in many countries, and the AIs are ineffective, monotherapy in premenopausal women. It is possible that the relative benefit of tamoxifen in extensive metabolizers of CYP2D6 may render the drug more effective than AIs in this group of patients. Recent data indicate that patients who are poor metabolizers of tamoxifen drop out of trials and from therapy at a notably lower rate.

A key recent trial (E-2100) demonstrated that the anti-VEGF antibody bevacizumab combined with paclitaxel showed greater reductions in DFS survival than paclitaxel alone, but the combination did not alter overall mortality. We have recently demonstrated that germline genetic variability in the VEGF receptor associated with outcomes in this trial which hada group that experienced overall survival benefits not different from placebo, and a group that survived on average a year longer. It is of note that variants in the same gene are also associated with risk for toxicity from bevacizumab therapy: hypertension.

Conclusions: These data suggest that germline genomic variability in candidate genes, but also in pharmacologic and physiologic pathways may be valuable approaches to further refining the targeting of patients with breast cancer to maximize efficacy, but also to reduce toxicity and thus to optimize the overall risk:benefit ratio of therapy for breast cancer.

21 Proffered Paper Oral

Genetic polymorphism of CYP2D6: a critical factor for early metastatic relapse in patients treated with adjuvant tamoxifen

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Current adjuvant hormonal therapy in postmenopausal women with breast cancer is debatable between upfront aromatase inhibitors and sequential treatment initiated with tamoxifen. We previously reported a retrospective analysis in order to identify risk factors of early systemic relapse among postmenopausal women treated with tamoxifen for an hormone-positive carcinoma in adjuvant setting (Debled, Cancer 2007). A distant recurrence occurred in 5.3% within the first 3 years of tamoxifen. Lymph node involvement and modified SBR grade were identified as independent predictive factors of early recurrence. Exploratory immunohistochemical analyses performed on tumors that subsequently recurred did not reveal any unusual expression of EGFR, HER2, or VEGF-R2 that could have suggested a role in tamoxifen resistance.

As genetic variation in tamoxifen-metabolizing enzymes may be another factor to consider, we examined the frequency of germline cytochrome P450 (CYP)2D6*4 variant genotype from normal tissue of early relapse patients. Results were compared to frequency of this variant in South-west French healthy people.

Materials and Methods: DNA was isolated from paraffin-embedded normal tissue from 22 patients having subsequently relapsed within 3-years adjuvant tamoxifen. After PCR amplification of CYP2D6 gene, the CYP 2D6*4 polymorphism was detected using restriction enzymes as previously described (Jin, JNCI 2005). Frequency of CYP2D6*4 variant was simultaneously determined by analysis of DNA from 100 local healthy blood donors.

Results: CYP 2D6*4 heterozygotes were in 14 among 22 relapsed patients (64%) compared to 40 among 100 healthy people. Difference is statistically significant (Chi-2 test, $p = 0.04$). No CYP 2D6*4 homozygote variant was observed.

Conclusion: As CYP 2D6 polymorphism does not appear to increase breast cancer risk, these results confirm a clinical relevant association between genetic variation in tamoxifen-metabolizing enzyme CYP2D6 and early relapse. Analyses of a larger number of relapsed patients are in progress. Results of a cohort of patients treated with adjuvant tamoxifen who did not relapse despite adverse prognostic factors (grade III and N+ >1) will also be available. Individual analysis of CYP2D6 genetic variant may be in the future an important factor to be considered for selection of patients who should receive upfront aromatase inhibitor treatment.

22 Proffered Paper Oral

Clinical implications of CYP2D6 genotyping on tamoxifen treatment in breast cancer

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Background: In October 2006 the FDA recommended an update in the tamoxifen label to reflect the increased risk for breast cancer recurrence in postmenopausal ER-positive patients who are CYP2D6 poor metabolizers. This recommendation however was based on only few studies at that time. More clinical studies addressing the relation between CYP2D6 genotype and tamoxifen efficacy have been performed and published since. An updated analysis of the literature is presented.

Methods: Searches were conducted of Medline, Embase, Web of Science, scientific meeting proceedings and manual review of references from eligible publications.

Results: 8 eligible studies were evaluated, 7 of which were retrospective analyses and one was published as abstract. One study investigated the effect in metastatic breast cancer in a small partially prospective cohort. Another study investigated the effect on prophylactic tamoxifen use. Five studies were in line with the FDA advice, however 3 studies (including the largest study) showed contradictory results. Possible explanations for the conflicting results are the inability to adjust for possible confounders – especially CYP2D6 inhibitor use – and the comparison of different groups of combined genotypes (*4/*4 + *1/*4 vs *1/*1 or *4/*4 vs *1/*1 + *1/*4). The 3 studies showing no or even an opposite effect were unable to account for some important confounders. Still, confounding bias is expected to be limited because of the influence of Mendelian randomization. Furthermore, mostly only the *4 allele has been investigated whereas other CYP2D6 variant alleles (e.g. *5, *9 and *41) may also modify the effect.

Conclusions: The clinical relevance of CYP2D6 genotyping to tailor tamoxifen therapy has not been fully clarified as present study results are inconsistent. In a small majority of studies an increased risk in poor and intermediate metabolizers is reported. The biological activity of tamoxifen is possibly modified by other factors, some influencing the major metabolite endoxifen (e.g. CYP2D6 inhibitor use). Therefore, at the Leiden University Medical Center, the Netherlands, a prospective study is started to associate complete CYP2D6 genotype by SNP array and endoxifen plasma concentration with breast cancer recurrence and survival, powered to detect a doubled risk of recurrence in poor CYP2D6 metabolizers ($n = 650$).

Wednesday, 16 April 2008 12:30–14:30

POSTER SESSION

Advocacy and education

23 Poster

Informational and supportive needs of women considering extended hormonal adjuvant treatment (ExHAT) – a Canadian survey conducted by SOLARIS (Summit of Opinion Leaders – Advocacy, Research, Information and Support)

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Background: The results of NCIC MA-17 led to the need to inform women of the potential benefits of ExHAT with Letrozole (L) following 5 years of adjuvant (adj) tamoxifen (T).

Method: In 02/2007, we convened a meeting of 30 key advocates/survivors in Canada (SOLARIS) to discuss this issue. Under the auspices of the Canadian Breast Cancer Network (CBCN), we conducted a 43 question National Survey addressing the informational and supportive needs of women who had completed at least 4 years of adjT. The survey was completed online or by mail through CBCN and Ipsos Reid between 12/04−28/05, 2007.

Results: There were 230 respondents (CI:+/-6.5%)-the vast majority responded through mail/website. Median age was 61.5 years (range