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5-Year Results of TEAM Trial Show No Survival Differences Between Treatment Arms

Exemestane (E) is a steroidal aromatase inhibitor, structurally related to the natural substrate androstenedione. It binds irreversibly to and inactivates the enzyme aromatase, thereby blocking the aromatization of androgenic precursors into estrogens. The irreversible nature of the binding makes exemestane distinct from anastrozole and letrozole, whose action is reversible.

The Tamoxifen Exemestane Adjuvant Multinational (TEAM) study is a prospective, randomized, phase 3 trial designed to measure the efficacy of E as an initial adjuvant therapy compared with a sequential approach of tamoxifen (T) followed by E (T→E). On Thursday morning, Daniel Rea, MD, PhD, from the University of Birmingham in the United Kingdom, presented the 5-year results of the TEAM trial. A total of 9779 women were accrued and randomized to receive E for 5 years or T for about 2.5 years followed by E for a similar period. The primary end point was disease-free survival (DFS); secondary end points were remission-free survival, overall survival, and long-term safety and tolerability.

At a median follow-up of 5.1 years, 4868 patients in the T→E arm and 4898 patients in the E arm were available for efficacy analysis. There were no significant differences between treatment arms in DFS (HR=0.97, $P=0.604$), time to recurrences (HR= 0.94, $P=0.293$), or overall survival (HR=1.00, $P=0.99$). There was also no significant difference in DFS between treatment arms as a function of nodal status. Initial exemestane was associated with an increase in aromatase inhibitor-associated adverse events, including osteoporosis, fractures, arthralgia, nerve compression, vaginal dryness, hypertension, and hyperlipidemia. Tamoxifen followed by exemestane was associated with tamoxifen-related adverse events, including hot flashes, vaginal bleeding and discharges, endometrial pathology, venous thrombosis, and muscle cramps.

In response to a question from the audience, Dr Rea said it was unlikely that any significant difference between the treatment arms would be revealed over time. However, in response to another question, he agreed that exclusion of people who carry the CYP 2D6 mutation (rendering them resistant to tamoxifen) from the T→E treatment arm might increase the likelihood of seeing a treatment difference. He added that genetic data on these patients may be published in the future.

Modifiable Lifestyle Factors for Breast Cancer: Effects in Women With Existing Cancer

Numerous published studies have shown that various modifiable lifestyle factors significantly increase the risk of developing breast cancer. However, relatively few studies have examined the prognostic effect of such factors in women who already have cancer. Two abstracts presented on Thursday morning addressed the effects of alcohol consumption and obesity on recurrence and overall mortality in women with early-stage breast cancer.

Marilyn L. Kwan, PhD, from Kaiser Permanente in Oakland, California, presented results from the Life After Cancer Epidemiology (LACE) study. This prospective cohort study of 1897 early-stage breast cancer survivors examined the association of overall alcohol consumption and type of alcohol consumed with breast cancer recurrence and mortality. Frequency and serving size were assessed using a food frequency questionnaire. Delayed-entry Cox proportional hazards models were used, with all models adjusted for age at diagnosis, pre-diagnosis body mass index (BMI), folate intake, disease stage, hormone receptor status, treatment, and lymph node status. Alcohol consumption of ≥ 6 g/day (approximately half a mixed drink) significantly increased recurrence (HR=1.34, $P=.05$) and breast cancer death rates (HR=1.51, $P=.05$) compared with < 6 g/day. The elevated risk of recurrence was stronger in postmenopausal women (HR=1.51, $P=.03$) and in overweight/obese women (HR=1.58, $P=.03$). There was no significant association with overall mortality or estrogen receptor status.

Marianne Ewertz, MD, from Odense University Hospital in Denmark, reported the results of a study analyzing the effects of obesity on early-stage breast cancer prognosis. The study was designed to determine if obesity increased the risk of recurrence or death independently of other prognostic factors or affected the response to adjuvant treatment. The study population included 18,967 patients with early breast cancer whose height and weight were available from the Danish Breast Cancer Cooperative Group. Women with a higher BMI (≥ 30) tended to be older and postmenopausal and to have larger tumors and more positive lymph nodes. Analysis of cumulative incidence showed no association between BMI and locoregional recurrence up to 10 years after diagnosis. There was a significant effect of elevated BMI on distant metastasis and on breast cancer-specific survival—women with a BMI ≥ 25 had a 42% to 46% increased risk of developing distant metastases within 10 years, and a 26% to 38% increased risk of dying from breast cancer 10 or more years after diagnosis. In addition, patients with a BMI ≥ 30 showed a poorer response to treatment with chemotherapy or endocrine therapy than patients with a lower BMI.

In both of these papers, questions arise about confounding factors affecting the results. Several attendees questioned whether the effects of alcohol reported by Dr Kwan could be discriminated from the effects of other factors, such as depression, obesity, quality of diet, and exercise. An additional cautionary issue mentioned in the morning plenary session by Valerie Beral, MD, from the University of Oxford, is that the contribution of all of these modifiable lifestyle factors to the overall risk and prognosis of breast cancer may be quite small compared with reproductive history.

Bisphosphonates: Multiple Layers of Efficacy?

Bisphosphonates are used for the prevention and treatment of osteoporosis and the skeletal lesions of malignant metastatic disease. Recent data have suggested that they might also have a direct effect on cancer. Papers presented last year at SABCs and at the annual meeting of the American Society of Clinical Oncology indicated that the bisphosphonate zoledronic acid may be effective in reducing tumor burden or relapse rate in early breast cancer. Two papers presented on Thursday afternoon discussed this new application of bisphosphonates. A third assessed the bone-preserving efficacy of zoledronic acid compared with the investigational monoclonal antibody denosumab, which inhibits RANKL, a key mediator of osteoclast activity.

Rowan Chlebowski, MD, PhD, Professor in Residence and Chief of the Medical Oncology/Hematology Department at the University of California, Los Angeles, presented data from an observational cohort study designed to evaluate the association between oral bisphosphonate use and breast cancer incidence in the Women's Health Initiative cohort of 154,768 postmenopausal women. The main analyses considered baseline information on bisphosphonate use, collected by questionnaire or interview. A conceptual problem in the analysis was that, while women with low bone mineral density (BMD) have a lower risk of breast cancer, low BMD is an indication for bisphosphonate use. To correct for this, an algorithm-designed hip fracture risk score was used to adjust for potential BMD differences between women who used bisphosphonates and those who did not, while Cox proportional hazards models that accounted for factors known to affect breast cancer risk were used to compute hazard ratios for breast cancer. This analysis showed a significant reduction in breast cancer incidence in bisphosphonate users vs nonusers (HR=0.68, $P<.01$). This advantage was not affected by differences in cancer stage or grade. Dr Chlebowski pointed out that use of bisphosphonates has been increasing while the use of hormone replacement therapy has been decreasing, suggesting that the lower incidence of breast cancer seen during this time may be influenced by both factors. Interestingly, the incidence of ductal carcinoma in situ (DCIS) was *increased* in bisphosphonate users compared with nonusers (HR=1.59; $P=.002$). In the discussion following the presentation, it was suggested that this phenomenon, also seen in the STAR trial with raloxifene, may mean that in situ lesions are being arrested, preventing them from developing into invasive disease.

The Breast Cancer in Northern Israel Study (BCINIS) is a population-based, case control study of breast cancer cases and age/clinic/ethnic/resident group-matched controls. Gad Rennert, MD, PhD, from the Technion-Israel Institute of Technology, used subjects from this study to examine the association between bisphosphonate use and the risk of developing breast cancer. Bisphosphonate use was determined by patient report or by pharmacy record. Data were available for 2368 cases and 2207 controls. There was a $\approx 30\%$ reduction in breast cancer incidence in patients who self-reported using bisphosphonates for 5 or more years (OR=0.66); this result was confirmed by pharmacy records of bisphosphonate prescriptions (OR=0.72). Bisphosphonate use for < 1 year was not associated with a change in breast cancer risk; the reduced risk started in year 2 and persisted over longer periods, reflecting the stability of the drug in the body. Considering the results of the study presented by Dr Chlebowski, it is interesting that Dr Rennert and colleagues observed no increase in rates of DCIS in patients receiving bisphosphonates. A limiting factor in interpreting these analyses is that breast cancers detected in bisphosphonate users had better prognostic markers, with a significantly higher proportion of strongly ER-positive tumors, a significantly lower proportion of poorly differentiated tumors, and a lower (but not significant) proportion of HER2-positive tumors. As in the previous study, it is difficult to separate the drug effects from baseline patient conditions.

RANKL is the primary mediator of osteoclast formation, function, and survival and plays a vital role in physiologic and cancer-induced bone resorption. Metastatic tumor cells stimulate RANKL activity, leading to a self-reinforcing cycle of bone destruction. Denosumab is a fully human monoclonal antibody administered by monthly subcutaneous injection that binds and inhibits RANKL, interfering with bone resorption. Alison Stopeck, MD, from the University of Arizona, presented the results of a study comparing denosumab with zoledronic acid for the prevention of skeletal-related events (SREs) in patients with advanced breast cancer with bone metastases. At the primary analysis cutoff date, 1020 patients in the zoledronic acid arm and 1026 patients in the denosumab arm remained in the study and were available for analysis. Denosumab use resulted in an 18% reduction in the time to first on-study SRE (HR=0.82, $P=.01$), an 18% reduction in the time to first on-study SRE or hypercalcemia (HR=0.82, $P=.007$), and a 23% reduction in the time to first and subsequent on-study SREs (rate ratio=0.77, $P=.001$) compared with zoledronic acid.

use. Skeletal morbidity rate (number of SREs per subject divided by time at risk) showed a relative reduction of 22% in the denosumab arm ($P=.004$). Other end points (time to first radiation to bone, time to experiencing moderate or severe pain) showed a similar benefit for denosumab use. However, there was no difference in overall survival or overall disease progression between the treatment arms. Denosumab was also associated with fewer side effects: of 20 selected adverse events, 18 were less likely in patients receiving denosumab, including a significant reduction in adverse events related to renal toxicity. Rates of osteonecrosis of the jaw were similarly low in patients receiving either zoledronic acid or denosumab (1.4% and 2.0%, respectively).

Robert Weinberg, PhD: AACR Distinguished Lecturer for 2009

The AACR Distinguished Lectureship in Breast Cancer Research was established to recognize outstanding science that has inspired or has the potential to inspire new perspectives on the etiology, diagnosis, treatment, or prevention of breast cancer. This year's awardee is Robert A. Weinberg, PhD, the Daniel K. Ludwig Professor for Cancer Research at the Massachusetts Institute of Technology and a founding member of the Whitehead Institute for Biomedical Research. Dr Weinberg won the National Medal of Science in 1997, the Wolf Prize in Medicine in 2004 (shared with Roger Y. Tsien), and is a member of the US National Academy of Sciences. He is the author of more than 325 articles and 6 books, including a comprehensive cancer textbook entitled *The Biology of Cancer*.

Dr Weinberg is most widely known for his discoveries of the first human oncogene, *ras*, and the first tumor suppressor gene, *Rb*. His laboratory is currently pursuing research in 3 main areas: the collaborative interactions between epithelial and mesenchymal cells that result in the formation of carcinomas; how human cancer cells acquire the ability to invade and metastasize; and the molecular mechanisms of cellular senescence and its effects on cell proliferation in vitro and in vivo.

Dr Weinberg's lecture, "Breast Cancer Stem Cells and the Epithelial-Mesenchymal Transition," will be presented this morning at 11:30 AM.

New Poster Session Topic: Research Resources

A new category in the poster sessions this year is worthy of particular note: *Research Resources*, posters 3074-3076 this afternoon, will highlight the availability of 2 large tumor and tissue banks and their associated data, as well as presenting the Love/Avon Army of Women as a novel and creative mechanism for quickly locating willing and appropriate women (with or without breast cancer) for specific studies. These valuable resources are open to qualified investigators from around the world.

Program Updates Corrections

In issue #1 of the newsletter, AstraZeneca was mistakenly listed as a Patron Plus donor. They are in fact an Angel Plus donor to SABCS. We thank them for their generous support.

The following abstract was erroneously listed as withdrawn in the SABCS Pocket Program and the program portion of the abstract book. The abstract is published in the abstract book on page 516s. The poster will be presented during Poster Discussion 4, this morning at 7:00 AM.

402. Complete IGF signaling blockade by the dual-kinase inhibitor, BMS-754807, is sufficient to overcome tamoxifen and letrozole resistance in vitro and in vivo

Haluska P, Hou X, Huang F, Harrington SC, Greer A, Macedo LF, Brodie A, Evans DB, Carboni JM, Gottardis MM. Mayo Clinic, Rochester, MN; Bristol-Myers Squibb Co., Princeton, NJ; University of Maryland, Baltimore, MD; Novartis Pharma AG, Basel, Switzerland

Revised Abstract

Abstract 17

Alcohol consumption and breast cancer recurrence and survival among women with early-stage breast cancer

Kwan ML, Kushi LH, Weltzen E, Castillo A, Caan BJ. Kaiser Permanente, Oakland, CA

Purpose: To describe alcohol consumption and examine its association with breast cancer recurrence and mortality in the Life After Cancer Epidemiology (LACE) study, a prospective cohort study of early-stage breast cancer survivors.

Methods: Patients included 1897 participants diagnosed with early-stage breast cancer between 1997 and 2000 and recruited primarily from the Kaiser Permanente Northern California Cancer Registry. Alcohol consumption (beer, wine, and liquor) was assessed at cohort entry using a food frequency questionnaire. A total of 349 breast cancer recurrences and 332 overall deaths were ascertained after an average follow-up of 5.93 years. Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals.

Results: A total of 958 women (51%) were considered drinkers (>0.5 g of alcohol per day), and the majority drank wine (90%), followed by liquor (43%), and beer (36%). Drinking ≥ 6 g/day of alcohol compared to minimal or no drinking (≤ 0.5 g/day) was associated with an increased risk of breast cancer recurrence (HR = 1.34; 95% CI: 1.00, 1.82) and death (HR = 1.51; 95% CI: 1.00, 2.28). The increased risk of recurrence appeared to be greater among postmenopausal (P for trend = .03) and overweight or obese women (P for trend = .03). No associations were observed for risk of overall mortality and alcohol use.

Conclusions: Consuming 3 to 4 alcoholic drinks or more per week might be related to an increased risk of breast cancer recurrence, particularly among postmenopausal and heavier women, regardless of other prognostic factors. While additional prospective studies are needed, these observations suggest that after a breast cancer diagnosis, women should consider limiting their consumption of alcohol.

Contributing Faculty Editor:
Gary C. Chamness, PhD



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The 2009 San Antonio Breast Cancer Symposium (SABCS) is presented by the CTRC, AACR, and the Baylor College of Medicine. The driving force behind this collaboration is the shared mission of the organizations to advance progress against breast cancer. By combining their respective strengths, the San Antonio Breast Cancer Symposium encompasses the full spectrum of breast cancer research and facilitates the rapid transition of new knowledge into improved care for breast cancer patients.



Poster Added

This abstract has been added as #3183. The poster will be included in Poster Session 3, today at 5:30–7:30 PM.

Abstract 3183

Interim analysis of a randomized phase 2 study of the novel li-Key hybrid HER2/neu peptide (AE37) vaccine to prevent breast cancer recurrence: United States Military Cancer Institute Clinical Trials Group Study I-05

Peoples GE, Perez SA, Clifton GT, Holmes JP, Georgakopoulou K, Benavides LC, Gates JD, von Hofe E, Baxevasis C, Mittendorf EA, Ardavanis A, Ponniah S, Papamichail M

Background: CD4+ T helper peptides from HER2/neu have been evaluated in vaccine trials. The li-Key addition, a 4-amino-acid (LRMK) modification, increases vaccine potency when compared to unmodified class II epitopes. We present results of a prospective, randomized, single-blinded phase 2 clinical trial of the li-Key hybrid HER2/neu peptide (AE37) + GM-CSF immunoadjuvant vaccine vs GM-CSF alone in the adjuvant setting in disease-free, high-risk breast cancer (BCa) patients to prevent recurrence.

Methods: Disease-free, high-risk BCa patients who have completed standard adjuvant therapy were enrolled and randomized to receive 6 monthly inoculations of either 500 µg of AE37 with 62.5 or 125 µg of GM-CSF (peptide group; PG) or 62.5 or 125 µg of GM-CSF alone (adjuvant group; AG). Toxicity was assessed after each inoculation using National Cancer Institute Common Terminology Criteria for Adverse Events v3. Immunologic response was monitored using delayed-type hypersensitivity (DTH) reactions and 3H-thymidine proliferative assays for both hybrid AE37 (LRMK+HER2/neu 776-790) and AE36 (unmodified HER2/neu 776-790) peptides. Patients were clinically, radiographically, and pathologically monitored for recurrence of BCa.

Results: Thus far, 120 (49 PG, 71 AG) of the planned 200 patients have completed the primary series. The PG and AG have similar demographic/prognostic characteristics (Table). Toxicity profiles in the PG and AG were almost identical with no grade 4-5 local toxicities and no grade 3-5 systemic toxicities in either arm. Median DTH reaction to AE36 and AE37 increased significantly from baseline at 1 month after completion of the primary series in the PG group (AE36: 0.0±0.8 cm to 15.3±2.1 cm; AE37: 0.0±0.7 cm to 24.5±2.6 cm; $P \leq 0.0001$) and did not change in the AG group (AE36: 0.0±0.5 cm to 0.0±1.4 cm; AE37: 0.0±0.7 cm to 0.0±1.6 cm; $P > .05$). Median proliferation response to AE36 and AE37 increased significantly from baseline at 3, 6, and 12 months after the start of the vaccine series in the PG ($P < .015$) and did not change significantly in the AG. At a median follow-up of 13 months, there have been no (0.0%) recurrences in the PG (0/49) compared to 7.0% (5/71) in the AG ($P = .08$).

Conclusions: The modified peptide AE37 is safe with mild toxicities observed primarily due to the GM-CSF immunoadjuvant. AE37 elicits a strong HER2/neu-specific in vivo and ex vivo immune response to the modified and unmodified peptides. Importantly, the AE37 peptide vaccine may protect against BCa recurrences.

| | Peptide | Adjuvant | P Value |
|--------------------|---------|----------|---------|
| n= | 49 | 71 | |
| Age, median | 49 | 52 | .06 |
| Node-positive | 75.5% | 62.1% | .16 |
| Grade 3 | 48.9% | 57.8% | .44 |
| Tumor ≥2 cm | 55.1% | 56.1% | 1 |
| ER/PR-negative | 38.8% | 40.9% | .84 |
| HER2 overexpressor | 59.2% | 60.6% | 1 |

Posters Withdrawn

1055, 3108, 4027, 4147, 6028, 6164

Cancellation

Due to speaker illness, the Basic Science Forum "Can We Measure Tumor Dormancy and Does It Matter?" scheduled for Saturday, December 12, 12:30–1:35 PM in Ballroom B, is cancelled.

Disclosures

Dr Debra Ikeda has disclosed that she is the recipient of grant support from Spectros Inc., ART, Inc, and Sidney B. Frank Foundation. Dr David Mankoff has disclosed that he is a consultant for Pfizer and has received scientific study/trial support from Merck and Pfizer. Dr Hilde Schulte has disclosed that she is a consultant for Krebs, Bundesverband e.V.