Highlights of the 2010 Breast Cancer Symposium

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Breast Cancer In Focus

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91 ACOSOG Z1031: A Randomized Phase II Trial Comparing Exemestane, Letrozole, and Anastrozole in Postmenopausal Women With Clinical Stage II/III Estrogen Receptor-positive Breast Cancer

JA Olson, G Babiera, GW Unzeitig, PK Marcom, JM Guenther, K Deshryver, DC Allred, V Suman, K Hunt, MJ Ellis

In a randomized phase II study, Olson and colleagues evaluated the efficacy of neoadjuvant hormonal therapy with an aromatase inhibitor in 377 postmenopausal women with clinical stage II/III estrogen receptor–rich (Allred score 6–8) breast cancer. At baseline, participants were labeled marginal for breast conservation surgery, mastectomy candidate only, or inoperable. Median tumor size was 4.0 cm (range, 2–13 cm). Patients (N=374) received exemestane (25 mg/day), letrozole (2.5 mg/day), or anastrozole (1 mg/day) for 16 weeks prior to surgery. Progression was 6.5% for exemestane, 4.7% for letrozole, and 7.3% for anastrozole. Breast conservation surgery rate was 82% (163/199) in the group marginal for breast conservation surgery, 51% (77/152) in mastectomy candidates only, and 75% (3/4) in inoperable patients. Investigators concluded that patient selection for aromatase inhibitor therapy based on estrogen receptor expression can produce low rates of disease progression, high response, and breast conservation.

257 Eribulin Mesylate (E7389) Versus Treatment of Physician's Choice in Patients (pts) With Metastatic Breast Cancer (MBC): A Phase III Study (EMBRACE)

C Twelves, LT Vahdat, CE Akerele, J Wanders, J Cortes, on behalf of the Study 305 Investigators

Eribulin mesylate is a nontaxane microtubule dynamics inhibitor with a novel mode of action. Twelves and colleagues examined overall survival (OS) with eribulin mesylate as compared with traditional agents in heavily pretreated metastatic breast cancer patients (N=762). Secondary endpoints were objective response rate and progression-free survival (PFS). Patients had received 2–5 prior chemotherapy agents (≥2 for advanced disease), including an anthracycline and a taxane. The median age was 55 years. Patients were randomized 2:1 to receive eribulin mesylate (n=508; 1.4 mg/m^2 2–5 minute intravenous bolus on days 1 and 8 of a 21-day cycle) or physician's choice (n=254; any monotherapy or supportive care only). The median OS was 13.1 months for eribulin mesylate versus 10.7 months for physician's choice (P=.04). Eribulin mesylate showed objective response improvement (12.2% vs 4.7% in physician's choice [P=.002]) and increased PFS (median 3.7 months vs 2.2 months, respectively [P=.14]). Rates of grade 3/4 febrile neutropenia were more frequent in the eribulin mesylate group (4.6% vs 1.6%). Peripheral neuropathy caused 4.8% of patients to stop eribulin mesylate. Investigators concluded that in heavily pretreated MBC patients, eribulin mesylate provided a significant improvement in OS by a median of 2.5 months versus physician's choice and demonstrated a manageable toxicity profile.

284 Phase II Study of Trastuzumab, Docetaxel, and Bevacizumab as First-line Therapy in HER2-Positive Metastatic Breast Cancer

B Ramaswamy, S Viswanathan, S Carothers, L Wei, RM Layman, E Mrozek, S Puhalla, RR Tubbs, CL Shapiro

Data supports the use of vascular endothelial growth factor (VEGF)-targeted therapy with trastuzumab in human epidermal growth factor receptor 2 (HER2)-positive breast cancer. Ramaswamy and colleagues investigated the combination of trastuzumab, bevacizumab, and docetaxel as first-line therapy in HER2/neu-positive MBC patients. Eligible patients had HER2-positive MBC, no prior chemotherapy for MBC, and Eastern Cooperative Oncology Group (ECOG) performance status of 2 or lower. Fourteen patients were enrolled, with ongoing accrual. Study endpoints were safety and PFS. There were six 21-day cycles, with response assessments every 3 cycles. Circulating tumor and endothelial cells were measured at baseline and after cycle 1 to determine if they could be early predictors of response. On day 1 of each cycle, patients received 6 mg/kg of trastuzumab, 15 mg/kg of bevacizumab, and 100 mg/m^2 of docetaxel (later decreased to 75 mg/m^2). Patients benefiting from treatment were permitted to stop docetaxel and continue

on trastuzumab and bevacizumab. Results showed that 50% were estrogen/progesterone-receptor negative, and 93% had visceral involvement. The median PFS was 55.9 weeks (range, 1.1–109.4 weeks). Partial response occurred in 57%, and stable disease in 29% (including a duration of >1 year in 2 patients). Grade 3/4 toxicities were fatigue (36%) and nausea (14%). The combination of docetaxel, trastuzumab, and bevacizumab was active and well-tolerated in MBC.

261 Phase II Prospective Multicenter Study of Preoperative Paclitaxel, Gemcitabine, and Trastuzumab Combination Therapy in HER2-positive Stage II/III Breast Cancer: KCSG BR07-01

J Ro, S Im, KS Lee, E Lee, Y Kwon, D Noh, I Park, J Ahn, J Kim

Ro and colleagues studied the preoperative combination therapy of paclitaxel, gemcitabine, and trastuzumab in HER2-positive, clinical stage II/III breast cancer patients for efficacy and safety. Eligibility criteria included axillary lymph node involvement and sufficient organ function, with no prior hormone therapy, chemotherapy, surgery, or radiation. The primary endpoint was pathologic complete response in the breast and axillary lymph nodes. The 53 patients had a median age of 43 years and a median tumor size of 5.3 cm. They received weekly trastuzumab in combination with paclitaxel 80 mg/m^2 and gemcitabine 1,200 mg/m^2 on days 1 and 8 of each 21-day cycle for 6 cycles. Postoperative treatment included radiation therapy, and when indicated, 1 year of trastuzumab and 5 years of hormone therapy. Grade 3/4 adverse events were neutropenia (32%), transient elevation of aspartate aminotransferase/alanine aminotransferase (1.6%), and febrile neutropenia (0.6%). Two-year disease-free survival was 89%, distant disease-free survival was 96%, and OS was 100%. All patients maintained normal cardiac function.

230 Effect of Temsirolimus on the Growth Inhibitory Effect of Trastuzumab in HER2-positive Breast Cancer Cell Lines

E Kim, J Yang, H VanDusen, C Lobocki, L Dubay

The mammalian target of rapamycin (mTOR) plays a central role in regulating cellular protein synthesis. Temsirolimus is a novel mTOR inhibitor of cellular growth and survival. Trastuzumab, a monoclonal antibody that interferes with the HER2/neu receptor, suppresses the proliferation of HER2-overexpressing breast tumors. Kim and colleagues assessed the antiproliferative and apoptotic effect of temsirolimus and trastuzumab in breast cancer cell lines. In this study, increasing doses of temsirolimus (0.008–5 mM) and trastuzumab (0.008–5 nM) were tested alone and in combination against human breast cancer cell lines, including the amplified HER2 cell lines BT474 and SKBR3, and MB231, which expresses low levels of the receptor. The MTT colorimetric assay was used to evaluate cell growth inhibition after 5 days of treatment. Use of a fluorometric Caspase-3 activity assay revealed apoptosis after 24–48 hours. Trastuzumab (1 nM) suppressed growth in the BT474 and SKBR3 cell lines by 47.7% and 27.6%, respectively. Growth in the MB231 cell line was not inhibited. A dose-dependent response in all 3 cell lines was present with temsirolimus, which produced growth inhibition at the 1 mM dose ranging from 35–54%. The combination of drugs produced significant growth inhibition in only the HER2-positive cells due to an increase in apoptosis, as evidenced by an increase in Caspase-3 activity of 2.3- to 5-fold. This study suggests that the antiproliferative effect of trastuzumab in HER2-positive breast cancer cell lines is potentiated by the addition of temsirolimus, which may have clinical relevance in certain HER2-overexpressing breast cancers.

286 Evaluation of Trastuzumab Without Chemotherapy as a Postoperative Adjuvant Therapy in HER2-positive Elderly Breast Cancer Patients: Randomized Controlled Trial (RESPECT [N-SAS BC07])

M Sawaki, H Iwata, M Kashiwaba, N Taira, N Tokudome, T Nakayama, H Bando, T Mizuno, S Murakami, Y Yamamoto

Single-agent trastuzumab benefits HER2-positive breast cancer patients without chemotherapy-induced toxicity, especially in the elderly. Use of single-agent trastuzumab as an adjuvant treatment without concurrent or prior chemotherapy has not been investigated. In an ongoing randomized controlled trial in women ages 70–80 years with HER2-positive breast cancer, Sawaki and colleagues are comparing trastuzumab monotherapy with combination therapy of trastuzumab and chemotherapy. Eligible patients previously received curative surgery for primary breast cancer, and they will have stage I (tumor size [pT] ≥1 cm), IIA, IIB, or IIIA/M0 disease; baseline left ventricular ejection fraction greater than 55%; and sufficient organ function. Treatment includes either chemotherapy plus trastuzumab (8 mg/kg loading dose, 6 mg/kg every 3 weeks for 1 year) or trastuzumab monotherapy. Disease-free survival is the primary endpoint. Secondary endpoints include OS, relapse-free survival, and safety. The study began in October 2009. A 4-year registration period and 3-year follow-up period are part of the planned conclusion in October 2016.