Final Analysis of NCIC CTG MA.27: A Randomized Phase III Trial of Exemestane Versus Anastrozole in Postmenopausal Women with Hormone Receptor Positive Primary Breast Cancer.

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Background: The non-steroidal reversible aromatase inhibitor (AI), anastrozole (A) is approved as adjuvant monotherapy in hormone receptor (HR) positive early breast cancer (EBC). The steroidal irreversible AI exemestane (E) is approved in sequence after an initial 2-3 years of tamoxifen. MA27 tested the hypothesis that exemestane would have greater efficacy and better end-organ safety than anastrozole for several reasons: E is an irreversible and more potent AI than A; unlike A, E does not induce intra-tumoral aromatase and; through its mild androgenic activity E may exert a second anti-tumor effect and a more favorable bone and lipid metabolism profile than A. Initially the study also tested the role of a cyclooxygenase-2 inhibitor, celecoxib, used in combination with an AI. However, celecoxib was discontinued early in MA27 following identification of cardiovascular toxicity with COX-2 inhibitors.

Methods: Postmenopausal women with hormone receptor positive primary breast cancer were randomized after adequate local treatment to 5 years of adjuvant A (1mg/day) or E (25mg/day) with or without celecoxib/placebo (400mg/plac twice daily for 3 years). The primary objective is the comparison of event free survival (EFS) between women treated with A or E. Secondary objectives include overall survival (OS), distant recurrence (DDFS), incidence of contralateral breast cancer (CBC) and safety. Quality of Life in a subset of women has been evaluated, and a very extensive tissue bank created. Stratification included: prior chemotherapy; lymph node status, celecoxib (during use), aspirin use (during randomization to celecoxib), and trastuzumab use (since November 2005). The primary endpoint (EFS) will look for an improvement from 87.5% to 89.9%; HR 0.80, 2-sided 5% level and 80% power, with 644 events required.

Results: 7576 women were randomized between June 2003 and July 2008. Celecoxib/placebo, was discontinued 2 years into the trial in December 2004 after 1635 patients had received celecoxib. The number of events required for final analysis was reached April 2010. Patient characteristics were balanced for age (median 64.1yrs); race; ECOG PS; mastectomy; TNM staging and; prior adjuvant chemotherapy. EFS, OS, DDFS, and CBC as well as clinical fractures, cardiovascular events and adverse events will be presented by arm in the final analysis.

Conclusions: NCIC CTG MA.27 is the first definitive EBC trial comparing a non-steroidal and steroidal AI as initial adjuvant therapy. Exemestane is not currently approved as initial adjuvant treatment and superiority or equivalence will lead to its inclusion as a first-line option for EBC in postmenopausal HR positive breast cancer. Efficacy, clinical fractures, cardiovascular events and AI related symptoms will help to define the cost-benefit ratios of these two AIs.
TAMRAD: A GINECO Randomized Phase II Trial of Everolimus in Combination with Tamoxifen Versus Tamoxifen Alone in Patients (pts) with Hormone-Receptor Positive, HER2 Negative Metastatic Breast Cancer (MBC) with Prior Exposure to Aromatase Inhibitors (AI).

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Background: Resistance to hormonal therapy may be associated with activation of the PI3K/AKT pathway. Preclinically, everolimus (RAD), an oral inhibitor of mTOR, has been shown to reverse resistance to tamoxifen (TAM). In a prior randomized phase II trial in estrogen-receptor positive operable breast cancer pts, RAD significantly increased neoadjuvant AI (letrozole) efficacy when given in combination. The objective of this randomized phase II study was to estimate the efficacy of the RAD+TAM combination in AI pretreated hormone-receptor positive/HER2 negative MBC pts based on the assumption that prior exposure to an AI might potentially enrich the proportion of pts whose tumor may be driven by an activation of the PI3K/AKT/mTOR pathway.

Methods: Eligible patients were stratified by time to progression after prior AI treatment and randomized 1:1 to receive either TAM (20mg/day) alone or RAD+TAM (RAD: 10 mg/d; TAM: 20mg/d). The primary objective was to estimate clinical benefit rate (CB) defined as the absence of progression at 6 months in the RAD+TAM arm. Using a Simon two-stage Minimax design, with alpha=5% and power=90%, considering a gain in CB of 20% as the minimum needed to warrant further study for the combination and assuming a CB of 50% in the TAM arm, 53 evaluable patients were needed in both arms. Secondary endpoints included safety and time to progression (TTP).

Results: In total, 111 pts (TAM: 57, RAD+TAM: 54) were randomized. Baseline characteristics were well balanced between the two treatment arms; median age was 64 years (range, 41-86); most pts were PS 0 (55 pts, 51%) or PS 1 (46 pts, 43%) Prior AI treatment had been given to 34 pts (31%) in the adjuvant setting; to 67 pts (60%) in the metastatic setting and 10 pts (9%) in both the adjuvant and metastatic setting. This population was poorly hormone sensitive as all but 10 pts (9%) had progressed either during AI or within 6 months after adjuvant AI. Furthermore, 57 pts (51%) and 28 pts (25%) had received prior chemotherapy in the adjuvant and/or metastatic setting, respectively. Efficacy: In an intent-to-treat analysis with a median follow-up of 13 months, CB was 42.1% (95% CI, 29.1-55.9) in the TAM arm and 61.1% (95% CI, 46.9-74.1) in the RAD+TAM arm. Median TTP was 4.5 months (95% CI, 3.7-8.7) with TAM and 8.5 months (95% CI, 6.01-13.9) with RAD+TAM (log-rank test: p=0.008, exploratory analysis). At the time of analysis, 17 pts had died in the TAM arm and 5 patients had died in the RAD+TAM arm (there was no toxic death). Safety: Safety data showed that toxicity was manageable in both groups. RAD had to be decreased to 5 mg/day for 15 pts (28%); 3 and 2 pts had to stop the treatment due to toxicities in the TAM and RAD+TAM arms respectively. Severe adverse events (G3-4) >10% were stomatitis (0/11%, TAM/RAD+TAM) and pain (19%/7%).

Conclusions: RAD combined with tamoxifen provides significant improvement in the 6 months clinical benefit rate compared to tamoxifen alone. Based on these promising results, this combination warrants further study in hormone-receptor positive/HER2 negative MBC after progression on AI.
Neoadjuvant Pertuzumab (P) and Trastuzumab (H): Antitumor and Safety Analysis of a Randomized Phase II Study ('NeoSphere').

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Background: P binds to HER2 and has complementary mechanisms of action with H. A clinical study of P+H showed meaningful activity in patients (pts) with metastatic HER2-positive breast cancer whose disease progressed on prior H therapy (Baselga et al. JCO 2010). NeoSphere is a Phase II randomized trial of preoperative systemic therapy comparing H and docetaxel (TH), THP, HP and TP to rank antitumor activity and tolerability.

Methods: 417 pts with centrally-confirmed HER2-positive (IHC 3+ or FISH positive) breast cancer (stage II or III including locally advanced) were randomized to receive 4 cycles of TH (n=107), THP (n=107), HP (n=107), or TP (n=96) before surgery. Cycles were given intravenously q3w: P, 840 mg loading dose and 420 mg maintenance; H 8 mg/kg loading dose and 6 mg/kg maintenance; T, 75 mg/m² with escalation to 100 mg/m² if the starting dose was well tolerated. After surgery all pts received H to 1 year and 3 cycles of FEC; in case of neoadjuvant HP they also received T before FEC. The primary endpoint was rate of pathological complete response (pCR) in the breast. For all patients, a tissue sample at baseline, as well as at surgery following 4 cycles of neoadjuvant therapy, was collected for biomarker analyses.

Results: Baseline characteristics were well balanced. About 40% of patients had locally advanced/inflammatory breast cancer. In the intent-to-treat analysis the rates of pCR and clinical objective response in the breast were:

<table>
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<tr>
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<th>TH (n=107)</th>
<th>THP (n=107)</th>
<th>HP (n=107)</th>
<th>TP (n=96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR</td>
<td>31 (29.0%)</td>
<td>49 (45.8%)</td>
<td>19 (17.8%)</td>
<td>23 (24.0%)</td>
</tr>
<tr>
<td>pCR + negative LN</td>
<td>23 (21.5%)</td>
<td>42 (39.3%)</td>
<td>12 (11.2%)</td>
<td>17 (17.7%)</td>
</tr>
<tr>
<td>Clinical CR+PR</td>
<td>80%</td>
<td>88%</td>
<td>68%</td>
<td>71%</td>
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pCR for THP was significantly higher (p=0.014) than TH which was significantly higher than HP (p=0.031). Clinical disease progression was reported in 1 patient on TH and 2 patients on HP. Feasibility was good for all T-containing arms. Adverse events of grade ≥3 were rare (<7%) with HP in sharp contrast with the >50% incidence in T-containing arms. One pt developed congestive heart failure with HP. Five more patients had asymptomatic decreased LVEF with TH (1), THP (3) and TP (1) that resolved at the subsequent assessment. Biomarker analysis is ongoing.

Conclusions: These data show the superior antitumor activity of THP and very favorable therapeutic ratio for HP that justify continuing study of the two monoclonals with and without docetaxel in women with HER2-positive early or metastatic breast cancer.
First Results of the NeoALTTO Trial (BIG 01-06 / EGF 106903): A Phase III, Randomized, Open Label, Neoadjuvant Study of Lapatinib, Trastuzumab, and Their Combination Plus Paclitaxel in Women with HER2-Positive Primary Breast Cancer.

Baselga J, Bradbury I, Eidtmann H, Di Cosimo S, Aura C, De Azambuja E, Gomez H, Dinh P, Fauria K, Van Dooren V, Paoletti P, Goldhirsh A, Chang T-W, Lang I, Untch M, Gelber RD, Piccart-Gebhart M, on Behalf of the NeoALTTO Study Team. Vall d’Hebron University Hospital, Barcelona, Spain; FSS Ltd, Kincraig, United Kingdom; University Hospital Kiel, Germany; Breast Cancer Center Vall d’Hebron University Hospital and SOLTI (Spanish Breast Cancer Research Group), Barcelona, Spain; Institut Jules Bordet and Breast European Adjuvant Study Team, Brussels, Belgium; Instituto Nacional de Enfermedades Neoplasicas, Lima, Peru; Breast International Group, Brussels, Belgium; SOLTI (Spanish Breast Cancer Research Group), Barcelona, Spain; Breast European Adjuvant Study Team, Brussels, Belgium; GlaxoSmithKline, Collegeville, PA; European Institute of Oncology, Milan, Italy; National Cheng Kung University Hospital, Tainan, Taiwan; National Institute of Oncology, Budapest, Hungary; Academic Hospital of the University Charite, Berlin, Germany; Dana-Farber Cancer Institute, Boston, MA; Institut Jules Bordet, Brussels, Belgium

Background: The addition of trastuzumab to neoadjuvant chemotherapy has significantly improved pathological complete response (pCR) in patients with HER2-positive early breast cancer (BC). Lapatinib, a dual HER2/EGFR tyrosine kinase inhibitor, combined with chemotherapy has significantly improved progression free survival in patients with metastatic HER2-positive BC. Additionally, lapatinib combined with trastuzumab improved disease-free and overall survival in patients with metastatic HER2-positive BC. The NeoALTTO trial is testing the efficacy of lapatinib, trastuzumab or their combination together with paclitaxel when given as neoadjuvant therapy in patients with HER2-positive BC. Material and Methods: NeoALTTO is an international, multicenter, randomized study comparing the efficacy of lapatinib plus paclitaxel, versus trastuzumab plus paclitaxel, versus concomitant lapatinib and trastuzumab plus paclitaxel given as neoadjuvant treatment for HER2-positive primary BC. From January, 2008, to December, 2009, 455 patients from 99 participating sites were randomized to receive either lapatinib 1500 mg/d (154 pts), or trastuzumab 4 mg/kg IV loading dose followed by 2 mg/kg IV weekly (149 pts), or lapatinib 1000 mg/d with trastuzumab for a total of 6 weeks (152 pts). After this biological window, patients continued on the same targeted therapy plus weekly paclitaxel 80 mg/m² for a further 12 weeks, until definitive surgery (total neoadjuvant therapy duration of 18 weeks). After surgery, patients received 3 cycles of adjuvant FEC followed by the same targeted therapy as in the biological window of the neoadjuvant phase for a further 34 weeks (to complete 52 weeks of anti-HER2 therapy). The primary objective of the study is to evaluate and compare among the three arms the rate of pCR, defined as the absence of invasive cancer in the breast at the time of surgery. Secondary objectives include objective response rate, safety, pathologic node-negative status, rate of conversion to breast conservation, disease-free survival and overall survival. All patients underwent tumor biopsies for comparative pharmacodynamic analyses before beginning therapy and on day 15 of the biological therapy window. A subset of patients also participated in PET/CT and circulating tumor cells substudies. Results: pCR was significantly higher in the combination arm (lapatinib plus trastuzumab) compared with either trastuzumab or lapatinib alone (51.3% vs. 29.5% vs. 24.7%, respectively; p < 0.01 for both). Corresponding objective (clinical) response rates at 6 weeks (biological window) were 67.1%, 30.2% and 52.6%, and those at surgery were 80.3%, 70.5% and 74.0%. There were neither major cardiac dysfunctions nor any toxic deaths during the neoadjuvant phase. There was increased, but manageable, toxicity (mainly diarrhea and liver enzyme alterations) in the lapatinib arms. Conclusions: The primary objective of NeoALTTO was achieved for the combination. Dual blockade of HER2 pathway is a valid concept. Data for correlation between pCR and DFS and/or OS will be available in the future.
First Efficacy Results of a Randomized, Open-Label, Phase III Study of Adjuvant Doxorubicin Plus Cyclophosphamide, Followed by Docetaxel with or without Capecitabine, in High-Risk Early Breast Cancer.

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Background: Combination regimens incorporating anthracyclines and taxanes are among the most effective for EBC and are particularly suitable for pts with high-risk disease. Significant efficacy benefit has been shown in phase III trials integrating capecitabine (X) into anthracycline/taxane-containing (neo)adjuvant regimens (Joensuu H, et al. Lancet Oncol 2009; Steger G, et al. ASCO 2010). We present first efficacy results of a large, randomized, multicenter phase III study comparing adjuvant doxorubicin plus cyclophosphamide (AC) followed by docetaxel (T) with or without X in high-risk early stage BC.

Methods: Pts aged 18-70 years, with high-risk, histologically-confirmed BC were eligible. High risk was defined as ≥1 positive lymph node, T1-3, and M0; or node negative with tumors >2 cm and M0; or node negative with tumors >1 cm, both ER and PgR negative, and M0. Treatment comprised four 3-weekly cycles of AC (A: 60mg/m2, C: 600mg/m2, both day 1) followed by four 3-weekly cycles of T (100mg/m2 day 1) or XT (X: 825mg/m2 b.i.d., days 1-14; T: 75mg/m2 day 1). Pts with hormone receptor-positive disease received tamoxifen or aromatase inhibitor for 5 years, and after 2005, pts with HER2-positive disease were offered 1-yr of concurrent or poststudy trastuzumab. Primary endpoint: DFS (518 events were expected at 5 years); secondary endpoints: OS; safety; delivered dose intensity.

Results: Between Aug 2002 and Feb 2006, 2,611 pts were randomized to AC→T (n=1,304) or AC→XT (n=1,307). The treatment arms were well balanced at baseline: median age was 51 yrs (range 26-72) and most pts had ECOG PS 0 (91%). The study failed to meet its primary endpoint of DFS (HR 0.84, 95% CI: 0.67-1.05; p=0.125) after a median follow-up of 5 years, with 304 events. However, a statistically significant improvement in OS was seen in pts receiving AC→XT vs AC→T (HR 0.68, 95% CI: 0.51 - 0.92; p=0.011), with 183 events. Subgroup analyses of DFS and OS appeared to favor the AC→XT arm over the AC→T arm, with few exceptions. The frequency of AEs was similar in both arms: 99.8% AC→T (n=1,305) vs 100% AC→XT (n=1,283), as was the incidence of serious AEs: 20.2% vs 15.6%, respectively. Differences were noted between the AC→T and AC→XT arms, respectively, in terms of the incidence of grade 3 hand-foot syndrome (3.8% vs 18.1%), and grade 3/4 stomatitis (4.5% vs 9.1%), diarrhea (2.9% vs 5.1%) and febrile neutropenia (13.1% vs 9.4%). Median dose intensity of T was 0.97 (range: 0.08-1.41) in the AC→T arm and 0.96 (range: 0.03-1.45) in the AC→XT arm; the corresponding value for X was 0.67 (range: 0.00-1.20), which is lower than reported with XT in MBC.

Conclusions: Although this pivotal study failed to meet its primary endpoint of DFS, improvements in OS were seen with the addition of X to a standard anthracycline/taxane-containing adjuvant regimen. These results must be interpreted with caution due to the lower than expected event rate at 5 years. No new safety signals were detected, but the incidence of grade 3/4 stomatitis in the AC→XT arm was higher than previously reported with XT in the metastatic setting.
Updated Survival Analysis of a Phase III Study (EMBRACE) of Eribulin Mesylate Versus Treatment of Physician’s Choice in Subjects with Locally Recurrent or Metastatic Breast Cancer Previously Treated with an Anthracycline and a Taxane.

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Background: Eribulin mesylate (E7389) is a non-taxane microtubule dynamics inhibitor with a novel mode of action. EMBRACE was the first trial to compare overall survival (OS) of this new chemotherapeutic agent to real-life treatment choices (treatment of physician’s choice; TPC) in heavily pretreated subjects with advanced breast cancer. TPC was any monotherapy (cytotoxic, hormonal, biologic) or supportive care only. It was previously reported that the study met its primary endpoint with a significant improvement in OS by a median of 2.5 months with eribulin vs. TPC. That primary analysis was based on 422 of 762 events that occurred by May 12, 2009; here we present an updated survival analysis requested by the FDA of the pivotal Phase 3 study through March 3, 2010.

Methods: This report is an updated survival analysis based on 589 of 762 (77.3%) events that occurred by March 3, 2010. Data were censored for subjects who were still alive, lost to follow-up, or withdrew consent on or before the date of data cut-off (March 3, 2010). A treatment arm comparison of OS was performed (with geographic region, HER2/neu status and prior capecitabine use as stratification factors for randomization) using a stratified log-rank test. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated to assess the magnitude of the treatment benefit.

Results: Seven hundred sixty two women were randomized in the study; 508 to the eribulin arm and 254 to the TPC arm. 386 (76.0%) events occurred in the eribulin-treated arm while 203 (79.9%) events were recorded in the TPC-treated group. Nine (1.8%) eribulin and 5 (2.0%) TPC patients were lost to follow-up or withdrew consent. OS was significantly longer in the eribulin treatment arm as compared with the TPC treated arm. (p=0.014; HR 0.805; 95% CI 0.677, 0.958). Median OS was 403 days (13.2 months) compared with 321 days (10.5 months) for TPC. A sensitivity analysis in the following 3 populations showed that the HR was similar to the primary (intent to treat) analysis and the treatment difference was statistically different: population of subjects treated (p = 0.016; HR 0.806; 95% CI 0.676, 0.960), at the cut-off of 572 (75%) deaths (p=0.008; HR 0.787; 95% CI 0.660, 0.939) and with no stratification terms (p=0.024; HR 0.822; 95% CI 0.694, 0.975). Based on the Kaplan-Meier analysis, eribulin-treated subjects had a 1-yr and 2-yr survival rate estimate of 54.5 and 21.9% compared with 42.8 and 19.2% for TPC, respectively.

Conclusions: The OS advantage associated with eribulin treatment reported in the primary analysis was maintained throughout the observation period. The results of this OS-updated analysis support the initial OS analysis of the pivotal trial EMBRACE, demonstrating the superiority of eribulin over TPC in heavily pretreated women with advanced breast cancer.