Conclusions: D demonstrates a significant improvement in objective RR at the doses used in routine clinical practice compared with N-P at the licensed dose. Overall the activity and toxicity profile in this retrospective analysis favour the use of D with GCSF over N-P as single agent therapy. Updated PFS data will be presented at the meeting.

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Comparison of True Recurrence Versus New Primary: an Analysis of Ipsilateral Breast Tumor Recurrences After Breast-Conserving Therapy

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Background: Ipsilateral breast tumor recurrence (IBTR) may develop in 5−20% of early breast cancer treated with breast-conserving therapy. Some prospective and retrospective studies had propounded that two classification of IBTR, true recurrence (TR), new primary (NP), would have a different features and outcomes. This study compared survival outcomes between two patient cohorts divided clinically as either TR or NP.

Materials and Methods: Between April 1991 and December 2009, a total of 5,888 patients who diagnosed breast malignancy were treated with breast-conserving therapy in the Gangnam Severance Hospital and the Asan Medical Center. Of 5,185 patients, after excluding ductal carcinoma in situ and no available data, 74 (15 in the Gangnam, 59 in the Asan) patients (1.4 %) had pathologically confirmed IBTR. If either within the same quadrant as index tumor or below 3cm distance between index tumor and IBTR lesion and the same estrogen receptor (ER) status and the same histologic type, that was defined as TR, and the others were defined as NP. According to the this criteria, of 74 patients, 45 (60.8 %) were classified as having TR and 29 (39.2 %) as having NP.

Results: The median follow up period after initial operation was 5.8 years, 5.8 years for TR and 5.9 years for NP. The median follow up period after IBTR was 2.3 years, 2.3 years for TR and 1.6 years for NP. There were no differences in the clinicopathologic features of initial tumor between TP and NP groups except location of initial tumor, more lateral in TR (88.9 %) than in NP (62.1 %) ($p = 0.023$), more negativity of ER in TR (70.5 %) than in NP (30.8 %) ($p = 0.002$), more triple negative breast cancer (TNBC) type in TR (44.7 %) than in NP (18.2 %) ($p = 0.007$). The median time to recurrence were shorter in TR group than in NP group, but no statistically significant (2.4 years vs. 3.1 years, $p = 0.132$). There was no difference for adjuvant treatment between the two groups, but in hormonal therapy, there was a trend for the difference between NP (64.3 %) and TR (42.2 %) ($p = 0.067$). In the TR and NP cohorts, breast cancer-specific survival was 78.3 % vs. 90.4 % ($p = 0.478$), and overall survival was 75.2 % vs. 84.7 % ($p = 0.655$), respectively.

Conclusions: With the limitation of patients number, the biologic behavior of NP seems to be different with that of TR. So when we consider the treatment of IBTR, the type of recurrence should be preferentially evaluated.

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Everolimus (EVE) for Postmenopausal Women with Advanced Breast Cancer (ABC) Refractory to Letrozole or Anastrozole: Long-term Efficacy and Safety Results of the BOLERO-2 Trial

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Background: Patients with hormone-resistant ABC show constitutive activation of the PI3K/Akt/mTOR pathway. In phase II studies, the oral mTOR inhibitor EVE has shown promising efficacy when used in combination with endocrine therapy in estrogen receptor-positive (ER+) ABC progressing during treatment with nonsteroidal aromatase inhibitors. BOLERO-2 is a multinational, double-blind, placebo-controlled, phase III study comparing EVE in combination with exemestane (EXE) with EXE alone in postmenopausal women with ER+ ABC refractory to letrozole or anastrozole.

Methods: Eligible patients were randomized (2:1) to EVE 10 mg/d or placebo (PBO) in combination with EXE 25 mg/d. Stratification criteria included sensitivity to prior hormonal therapy and the presence of visceral metastases. Study drugs were continued until disease progression or unacceptable toxicity. Primary outcome was investigator assessed progression-free survival (PFS). Adverse events (AEs) were monitored continuously.

Results: 724 patients were administered EVE+EXE (n = 485) or EXE (n = 239). Median age was 62 years; 56% had visceral involvement, and 84% were sensitive to prior hormone therapy. Current analysis is based on 457 events and a median follow-up of 12.5 months. Median investigator-assessed PFS was significantly longer at 7.4 months with EVE+EXE vs 3.2 months with EXE (HR=0.44; $P < 1 \times 10^{-16}$), and by central review at 11.0 vs 4.1 months, respectively (HR=0.36; $P < 1 \times 10^{-16}$). Response rates (RR) were also improved with EVE+EXE vs EXE (12.0% vs 1.3%; $P < 0.0001$) as well as clinical benefit rate (CBR) (50.5% vs 25.5%, respectively; $P < 0.0001$). Serious AEs occurred in 26.8% in the EVE+EXE arm and 13.9% in the EXE arm, including 11.2% (EVE+EXE) and 1.7% (EXE) attributed to study treatment. The most common grade 3/4 AEs (EVE+EXE vs EXE) were stomatitis (8% vs 1%), anemia (7% vs 1%), hyperglycemia (5% vs <1%), dyspnea (4% vs 1%), fatigue (4% vs 1%), and pneumonitis (3% vs 0%). At the current time, the overall survival is still immature because of the low number of events with 17.3% for the EVE+EXE arm and 22.6% for the EXE arm.

Conclusion: EVE+EXE significantly improved PFS, RR, and CBR compared with EXE. Side effects were manageable and consistent with previous reports of EVE in this patient population. These data support the use of EVE in combination with an aromatase inhibitor as a new therapeutic option for women with hormone therapy-refractory ABC.

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Oral Combination Chemotherapy with Capecitabine and Cyclophosphamide Showed Good Efficacy and Quality of Life for Metastatic Breast Cancer Patient

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Background: Anthracyclin and taxan-containing regimens are standard for first-line chemotherapy in metastatic breast cancer (MBC). However, increasing numbers of MBC patients have experienced the use of these agents with diminishing results, leading to the need for new regimens in treating MBC.

The combination of therapy with capecitabine (Xeroda®, X) and cyclophosphamide (C) which can be given orally and which have synergic effects with no cross-resistance to anthracycline and taxans was explored. As a complete cure is difficult for MBC, it is desirable that the treatment be continued while keeping the disease stable over a long period and simultaneously promoting a high quality of life (QOL).

We estimated efficacy and QOL as affected by treatment with the XC therapy.

Material and Methods: A phase II study of the XC combination therapy was conducted in patients with MBC. Twenty-four patients with the median age 54 (range 29−77 years) were registered. A dose of 1657 mg/m^2/day of capecitabine and 65 mg/m^2/day of cyclophosphamide were given orally for 2 weeks at 3-week intervals. We evaluated the effect of treatment, adverse events and the QOL after each cycle. The QOL was evaluated by QOL-ACD, QOL-ACD-B questionnaire surveys. The full score of the questionnaire is 5.0. The primary endpoint was the response rate. Progression-free survival, adverse events and the evaluation of QOL were investigated as secondary endpoints. Remission rates were compared using the χ^2 test.

Results: The metastatic sites of these patients were the lung, liver and bone. Fourteen patients (40%) had a single metastatic site, while 10 patients had multiple sites. The median dosing period was 16.8 (4−64) cycles. A complete response (CR) was obtained in four of 24 patients (17%), partial response (PR) in 5 (21%), stable disease (SD) in 11(45%) and progress disease (PD) in 4 (17%) resulting in a clinical benefit rate of 83%. The median progression-free-survival was 12.1 months. Adverse events occurred in 85% of these patients, but all of them were grade 2 or less. The QOL survey showed 4.0 in pre-treatment and 3.4 in 4 subsequent cycles; the QOL showed no significant statistical change pre- and post-treatment.

Conclusions: XC combination is useful in patients with MBC because it is no less effective than standard treatments and can be useful in maintaining the QOL of the patients.

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A Spanish Cost-utility Analysis of Nab-paclitaxel Compared to Conventional Paclitaxel Monotherapy for Pretreated Metastatic Breast Cancer: Results From the COSTABRAX Study

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Introduction: In the randomized controlled phase 3 trial CA012 demonstrated that a novel albumin-bound 130nm formulation of paclitaxel (nab®-paclitaxel, Abraxane®) had better efficacy than conventional paclitaxel in metastatic breast cancer (mBC) in patients who failed 1st-line treatment for metastatic disease and for whom standard anthracycline containing therapy is not indicated. The cost-effectiveness of nab®-paclitaxel versus conventional paclitaxel in the Spanish setting is analysed.

Patients and Methods: Clinical data for pretreated patients receiving nab®-paclitaxel 260 mg/m^2 3-weekly (q3w) and conventional paclitaxel 175 mg/m^2 q3w were taken from trial CA012. Since current conventional paclitaxel regimen has changed in Spain to 80 mg/m^2 weekly (q1w), an indirect comparison was carried out to compare nab®-paclitaxel q3w vs. conventional paclitaxel q1w in a secondary analysis. Drug costs, as well as administration, AEs and supportive care costs were taken from Spanish data sources. Long-term efficacy and costs of treatments were extrapolated up to 5 years by means of a Markov model. A panel of 18 Spanish oncologists validated the use of resources and the main model assumptions by completing a questionnaire and attending an in-person meeting. Results are shown as cost per life year gained (C/LYG) and cost per quality-adjusted life year (C/QALY). Costs and effects were discounted at a rate of 3%.

Results: The mean survival was 1.44 and 1.17 years for nab®-paclitaxel q3w and conventional paclitaxel q3w, with total costs of €15,972 and €13,483, respectively. The results of the cost-effectiveness analysis showed that nab®-paclitaxel q3w was associated with a C/LYG and a C/QALY of €9,387 and €15,085, respectively. The indirect comparison showed that nab®-paclitaxel q3w compared to conventional paclitaxel q1w have similar effectiveness and lower costs per patient (€15,972 and €17,146, respectively), which means nab®-paclitaxel has shown to be the most efficient option (dominant) compared to conventional paclitaxel q1w.

Conclusions: The COSTABRAX study performed from the Spanish health perspective showed that nab®-paclitaxel q3w was more effective and a cost-effective option compared to conventional paclitaxel q3w in the treatment of mBC with a C/QALY ratio lower than the generally accepted threshold of 30.000 € by health authorities. Compared to conventional paclitaxel q1w regimen, nab®-paclitaxel q3w was the most efficient option with lower total costs.

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Change of Biomarker Status in Recurrent Breast Cancer

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Background: Breast cancer is a heterogeneous disease and management is based on the disease status and tumor biology. In each patient treatment is tailored considering the factors to drug response mainly Hormonal and Her 2 neu status. Historically the trend has been to continue with hormonal therapy for years if patient's primary tumor is hormone positive. After adequate therapy once a tumor recurs, it was assumed that no change in biological features would occur in the recurrent disease compared to the primary. Studies comparing samples from primary tumor with recurrent loco regional and metastatic disease have demonstrated change in ER, PR and Her 2 neu status. Recurrent disease is a challenge to treat after the exhaustion of first line management. It is important to be sure that patient responds to the treatment given after the recurrence. The aim of this study is to quantify the percentage of tumor that changes receptors for ER, PR and Her 2 neu between original and recurrent disease.

Materials and Methods: Patients with recurrent breast disease presenting to the Breast Unit of Liaquat National Hospital from January 2004–January 2011 were included in this study and were analyzed for biomarker status. Outcome of interest was any change in the biomarker status (ER, PR, Her 2 neu) with respect to primary status.

Results: A total of 58 female patients with biopsy proven recurrent breast carcinoma were included in the study. The mean age was 46 years, with a period of two years and three months as mean time to recurrence. Invasive Ductal carcinoma was the most prevalent recurrent tumor among the study population. There was a change of 25% in ER status (p-value <0.01), change of 36% in PR status (p-value 0.036) and Her 2 neu status changed in 22%(p-value <0.01) which was statistically significant. Of the 42 patients who were triple negative at presentation, 30 patients remained triple negative on recurrence (p-value 0.02). Six of the 16 patients became triple negative upon recurrence(p-value <0.01).

Conclusions: Our study demonstrated that there is indeed a change in biomarker status of patients presenting with recurrent breast carcinoma. There is a need for clinicians to check biomarker status of recurrent breast cancer patients as this may aid in the shift in management plan.

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Design of RESILIENCE: a Phase 3 TRial Comparing CapecitabinE in Combination with SorafenIb or PLacebo for Treatment of Locally Advanced or MetastatIc HER2-Negative Breast CancEr

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Background: Sorafenib is an oral multikinase inhibitor with antiangiogenic and antiproliferative activity. Sorafenib is currently indicated for renal cell and hepatocellular carcinoma, with activity in other tumor types being explored. A double-blind, randomized, phase 2b screening trial (SOLTI-0701) of sorafenib in patients with HER2-negative advanced breast cancer (BC) showed a statistically significant improvement in progression-free survival (PFS) in the sorafenib+capecitabine arm vs the placebo+capecitabine arm: 6.4 vs 4.1 months (hazard ratio = 0.58; 1-sided $P = 0.0006$). Grade 3/4 toxicities were comparable except G3 hand-foot skin reaction/syndrome (HFSR/HFS) (44% vs 14%). These results support a phase 3 trial of sorafenib+capecitabine in advanced BC.

Methods: RESILIENCE is an ongoing multinational, double-blind, placebo-controlled, phase 3 trial designed to assess sorafenib + capecitabine as first- or second-line therapy in advanced HER2-negative BC (ClinicalTrials.gov, NCT01234337). Eligibility criteria include: $\geqslant$18 years of age; $\leqslant$1 prior chemotherapy regimen for advanced BC; resistant to/failed taxane and anthracycline or no indication for further anthracycline; no prior VEGF treatment. Patients are randomized to capecitabine (1000 mg/m^2 PO twice daily [BID], days 1−14 of 21) with sorafenib (PO BID, days 1−21, total dose 600 mg/day) or placebo. Sorafenib 600 mg/day corresponds to the average daily dose during SOLTI-0701 that was effective and had manageable toxicity. Capecitabine and sorafenib/placebo doses can be escalated to 1250 mg/m^2 BID and 800 mg/day, respectively, as tolerated. The protocol outlines strategies to manage toxicities with dose interruption and reduction. Dose re-escalation after reduction is only allowed for sorafenib/placebo. Guidelines detail prophylactic and symptomatic therapy for HFSR/HFS. Radiographic assessment is Q6 weeks for 36 weeks, then Q9 weeks. Primary endpoint is PFS. Secondary endpoints include overall survival, time to progression, overall response rate, and duration of response. Enrollment began in November 2010 and targeted enrollment is ~519 patients.

Conclusions: RESILIENCE will provide definitive PFS data for sorafenib+capecitabine as first- or second-line therapy in HER2-negative advanced BC and will better characterize the benefit-to-risk profile of this regimen.