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Rechallenge With Docetaxel After a First Response in Metastatic Breast Cancer − a Significant Activity With Manageable Toxicity

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Background: Docetaxel (Dc) is a major drug in metastatic breast cancer (MBC). At progression, rechallenge with docetaxel can be discussed based on the previous efficacy and tolerance. No data on this pragmatic strategy are avalaible in MBC.
Methods: We identify 73 patients (pts) with the following criteria: (i) objective response or stable disease with a previous line of treatment with Dc in MBC, (ii) rechallenge with Dc (on a three weekly schedule) for progressive disease after a minimal Dc-free interval of 3 months. The main objectives were to evaluate the overall response, the time to progression (TTP) and toxicity at reintroduction of TXT.
Results: Median age was 57 years (34−84). Patients had already received 1, 2, 3, $\geqslant$ 4 lines of chemotherapy (including the first use of Dc) in 20%, 47%, 18% and 15% of cases, including capecitabine, anthracycline, and vinorelbine in 56%, 40% and 21% of cases, respectively. Visceral disease was described in 80% of cases. The median number of cycles was 6 (1−18). Overall, 57 pts (78%) obtained a symptomatic benefit from the treatment. Among the 32 pts (44%) with disease assessed according to RECIST criteria, 14 (44%) had a partial response and 11 (34%) had a stable disease >3 months. Among the 41 pts without an available evaluation according to RECIST, 22 (54%) experienced a biological partial response. The median TTP was 5.9 months (95% CI [4.9−6.9]). The median overall survival (OS) was 10.8 months (95% CI [9.1–12.5]). Toxicity was manageable. Forty seven pts (64%) reported grade 1/2 toxicity, mostly mucositis (37%), asthenia (34%) and nails toxicity (30%). Twenty six pts (36%) experienced grade 3/4 toxicity, mostly neutropenia (16%) and fluid retention (11%). Predictive factors of benefit at re-introduction of TXT are in progress.
Conclusion: This retrospective analysis supports the pragmatic strategy to retreat patients with MBC with Dc provided that this drug had shown previous activity and was stopped for other causes than progression.

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Improvement of Neoadjuvant Therapy Response by Using 4FE100C Vs 6FE100C in Locally Advanced Breast Cancer

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Background: Cytostatic agents such as antracyclines have showed to be effective in locally advanced breast cancer. Epirubicin used as a single agent or in combination can be used in higher dose without severe toxicity. Our main goal was to assess the difference between two schedule regimens based on $4FE_{100}C$ and $6FE_{100}C$.
Materials and Methods: Patients diagnosed with locally advanced breast cancer during 2003–2007 were included (n = 96). One group of patients (n = 48) received Cyclophosphamide 500 mg/m^2, Epirubicin 100 mg/m^2 and 5-Fluorouracil 500 mg/m^2 ($FE_{100}C$) during 4 cycles every 21 days. Other group of patients received 6 cycles of the same scheme. All patients were followed by surgery and radiotherapy.
Results: Objective Response (OR) was 62.5% for $4FE_{100}C$ group and 85.7% for $6FE_{100}C$ group ($p < 0.003$); we determined a complete response rate (CR) of 35.4% with $6FE_{100}C$ (CI 95%: 22−48%, n = 17) and complete pathologic response (pCR) for $6FE_{100}C$ was 20.8% vs 12.5% ($p = 0.04$; OR 1.57, CI 95%: 22−48%, n = 10). The toxicity by $6FE_{100}C$ was mild to moderate vomiting (52.4%, $p = 0.001$), hematologic toxicity was not significant ($p = 0.14$). There was not observed other toxicities.
Conclusions: In the analysis the clinical benefit was better in $6FE_{100}C$ group, the largest number of cycles was a predictor of OR. It was confirmed a significant improvement in the pCR and CR using intensified Epirubicin dose ($6FE_{100}C$). Surprisingly the toxicity in both schemes was similar and tolerable. Finally, we demonstrated that the use of $6FE_{100}C$ compare with $4FE_{100}C$ increase 1.6 folds the pCR in locally advanced breast cancer patients.

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Breast Cancer Subtype and Survival in Metastatic Patients Treated With Bevacizumab

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Background: HER2 negative breast cancer is classified into 3 distinct subtypes known as triple negative, luminal A and luminal B, which differ for gene expression profile, prognosis and treatment outcome. Patients with luminal B early breast cancer weakly respond to primary hormono- and chemo-therapy and present poor clinical outcome. This study aimed to analyze the implication of breast cancer subtype on survival of HER2 negative metastatic breast cancer (MBC) patients treated with bevacizumab at any time.
Methods: Retrospective survival analyses were performed in HER2 negative MBC patients treated with bevacizumab between July 2005 and June 2010, according to clinical characteristics and breast cancer subtypes. Patients were classified as triple negative (ER and PR negative), luminal A (ER and/or PR positive and Ki67 < 14%) and luminal B (ER positive and PR negative or Ki67 >14% or grade III). Survival estimates were analyzed according to each breast cancer subtype.
Results: A total of 132 patients were identified. Six patients were excluded for incomplete information. Median age at diagnosis was 48 years (range, 27−79 years). Median overall survival (OS) was 41.8 months (CI 95%: 36.62–46.98). According to breast cancer subtype, OS was 32.38 months (CI 95%: 24.23–41.43), 40.8 months (CI 95%: 33.11–48.49), and 48.27 months (CI 95%: 37.47–59.06) in patients with triple negative (n = 39), luminal B (n = 45) and luminal A (n = 42) MBC, respectively. A trend toward worse survival was observed for triple negative breast cancer patients ($p = 0.06$).
Conclusions: This analysis on the use of bevacizumab in a daily clinical practice setting shows high OS rate across all breast cancer subtype. These findings might help on the design of future studies with antiangiogenics in breast cancer treatment.

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Trastuzumab Responder Will Show Good Repose to Lapatinib

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Background: Combination of Lapatinib (L) plus capecitabine (C) is commonly used in patients (pts) with trastuzumab (T)-pretreated HER2-positive metastatic breast cancer (HER2+MBC), although, it is difficult to estimate one's response to L+C therapy in practice.
Materials and Methods: HER2+MBC pts resistant to T-based regimen(s) received L+C. L was administered 1250 mg/body daily and C was given 2000 mg/m^2/day from day 1 to 14 in a 3-week cycle. Clinical efficacy was assessed by 2 (or 3) courses.
Results: Thirty-two female, T-resistant HER2+MBC pts (31 immunohistochemically HER2-positive, 1 FISH-positive), median age of 57 (range 33−72) were treated with L+C. Twenty-six pts (81.3%) had visceral lesion(s) and 8 pts (25.0%) had histories of central nervous system involvement. Median T-based regimens pts received prior to L+C was 2 (range 1−7), and 15 pts (46.9%) were heavily (>2) pretreated. Of 28 pts who have complete history of previous therapies, exposed to T from 56 to 2226 (median 837) days prior to L+C. Twenty-three pts discontinued therapy because of disease-progression (21 pts) or toxicity (2 pts). Of 21 resistant pts, 9 re-challenged T-based therapies, 3 received HER2-nonspecific regimens including clinical trials and 9 underwent supportive care. Of 29 evaluable pts, 1 (3.1%) achieved complete response (CR), 3 (9.4%) showed partial response (PR) and 15 (46.9%) maintained stable disease (SD) for more than 16 weeks. Median progression-free (PF) was 154.0 days (95% confidence interval 103.9–204.1), and median overall survival (OS) was 426.0 days (95% CI 305.5–546.5). Pts heavily pretreated (2 > T-based regimens) showed a trend of inferior PF (202.0 vs. 151.0), although, it was not statistically significant ($p = 0.23$). Furthermore, numbers of prior T-based regimens did not affect OS ($p = 0.72$). Interestingly, pts who showed a minor response, less than 360 days of treatment duration, to prior T-based regimen(s) had a trend of inferior PF (median 108.0 vs. 161.0, $P = 0.18$) and OS (337.0 vs. 448.0, $P = 0.01$).
Conclusions: Within our observation, lapatinib plus capecitabine showed a clinical effectiveness against patients with trastuzumab-pretreated

HER2+MBC both in early and late phase of their clinical course. Treatment duration to trastuzumab may be one of a marker to predict a response to lapatinib.

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A Clinical Study to Assess Pharmacokinetics and Safety of Neratinib in Subjects With Chronic Hepatic Impairment and Matched Healthy Subjects

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Background: Neratinib (NER; HKI-272) is a potent, low molecular weight, orally administered, irreversible pan-ErbB receptor tyrosine kinase inhibitor in development for the treatment of erbB-2-positive breast cancer. The objective of this study was to evaluate the pharmacokinetics (PK) and safety of NER in subjects with chronic hepatic impairment (HI) and in matched healthy subjects.
Materials and Methods: This was an open-label, single-dose, parallel-group study (NCT00781430, completed, Pfizer) conducted in subjects with chronic HI (Child-Pugh classes A, B, and C; n = 6 each) and healthy subjects (n = 9) matched by sex, age, BMI and, if possible, smoking habit. All subjects received a single oral dose of NER 120 mg immediately after a standard breakfast. Plasma samples obtained through 72 hours postdose were analyzed for NER by liquid chromatography/tandem mass spectrometry.
Results: 27 subjects aged 37−65 years enrolled and completed. Following oral administration of NER 120 mg, mean (CV%) C_{max} and AUC were 18.5 ng/mL (65%) and 296 ng·h/mL (61%) in healthy subjects, 31.2 ng/mL (66%) and 394 ng·h/mL (83%) in Child-Pugh A subjects, 17.1 ng/mL (58%) and 286 ng·h/mL (78%) in Child-Pugh B subjects, and 47.0 ng/mL (59%) and 767 ng·h/mL (46%) in Child-Pugh C subjects, respectively. NER oral clearance decreased in Child-Pugh C subjects compared with healthy subjects. There were no effects of body weight on the oral clearance or apparent volume of distribution of NER in either HI or healthy subjects. The elimination half life of NER in Child-Pugh C subjects increased 3-fold compared to healthy subjects. Adverse events (AEs) were reported by 7 subjects (25.9%), and all were treatment emergent AEs (Child-Pugh B group, n = 2 [33.3%]; Child-Pugh C group, n = 3 [50.0%]; healthy subjects, n = 2 [22.2%]). The most commonly reported AEs were mild diarrhea and hematuria and were reported by Child-Pugh C subjects (n = 2 [33.3%] each). There were no reports of serious AEs, or AE-related discontinuations during the study.
Conclusions: Following a single oral dose of NER 120 mg in subjects with HI, NER exposures (C_{max} and AUC) and oral clearance in the Child-Pugh A and B groups were similar to those in healthy subjects; in the Child-Pugh C group, the exposure was approximately 3-fold higher and the oral clearance was approximately 36% lower than in healthy subjects. A single oral dose of NER 120 mg is safe and generally well tolerated in both hepatically impaired and healthy subjects.

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A Phase 1 Study of Neratinib in Combination With Vinorelbine in Japanese Patients With Advanced or Metastatic Solid Tumours

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Background: Neratinib (NER) is an orally administered, small-molecule, irreversible pan-erbB receptor inhibitor that is being evaluated in the treatment of breast cancer and other solid tumours. The primary objective was to confirm the safety and tolerability of NER in combination with vinorelbine (VIN) at the maximally tolerated dose (MTD) as determined in an earlier study. Secondary objectives were to obtain preliminary antitumour activity and pharmacokinetic (PK) data in Japanese patients (pts).
Materials and Methods: This was an open-label, phase 1 study of multiple oral doses of NER in combination with intravenous VIN in pts with advanced or metastatic solid tumours (NCT00958724; completed; Pfizer). Pts received NER 240 mg/day starting Day 2 of 1st cycle and then daily at each subsequent 3-wk cycle and VIN 25 mg/m^2 on Days 1 and 8 q3w. Adverse events (AEs) and dose-limiting toxicities (DLTs) were assessed, anti-tumour activity was measured every 6 wks, and PK analyses were conducted for VIN alone (Day 1/Cycle 1) and NER + VIN (Day 8/Cycle 1).
Results: 6 pts (breast cancer, n = 3; head/neck cancer, n = 3) were enrolled, received study drug, and were included in safety and efficacy evaluations. The median duration of treatment for NER was 18.5 wks and 17.1 wks for VIN; median total exposure was 30,240 mg for NER and 299.9 mg/m^2 for VIN. One DLT was reported (grade 3 blood sodium level decreased). The most common treatment-emergent AEs (any grade/grade $\geqslant$3) were neutropenia (100%/67%), leukopenia (100%/50%), and diarrhea (100%/33%); no pt withdrew because of an AE and no deaths were reported. The overall response rate was 16.7% (95% confidence interval [CI], 0.4%, 64.1%); 1 pt with breast cancer (baseline HER2 status of 3+) had a partial response with duration of 12.0 weeks. 5 pts had stable disease (SD) with a median duration of 18.3 (95% CI, 18.0, 30.0) wks, and 1 of 5 pt had SD $\geqslant$24 wks. Median progression-free survival was 18.2 (95% CI, 18.0, 24.1) wks. There were no obvious differences between VIN concentration-time profiles following administration of VIN alone and NER + VIN. VIN C_{max} was decreased upon concomitant administration with NER (mean ratio [VIN:NER + VIN], 0.682); there were no remarkable change in AUC (mean ratio, 0.925). NER exposures were comparable to previous studies.
Conclusions: NER was well tolerated at oral doses of 240 mg daily in combination with VIN in Japanese pts with advanced or metastatic solid tumours.

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Chemosensitivity to Neoadjuvant Chemotherapy of Breast Cancer Subtypes

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Background: Human breast tumours are diverse in their natural history and in their responsiveness to treatment. We examined the relationship of neoadjuvant chemotherapy response to outcome among these breast cancer subtypes.
Materials and Methods: We used immunohistochemical markers [(1) HER2+/HR− for HER2+/ER−, (2) HR−/HER2− for basal-like, (3) HER2−/HR+ for luminal A and (4) HER2+/HR+ for luminal B] to subtype a prospectively maintained data set of patients with breast cancer treated with neoadjuvant docetaxel and doxorubicin chemotherapy. Patients received neoadjuvant docetaxel/doxorubicin chemotherapy were enrolled in this study. We analyzed each subtype for clinical and pathologic response to neoadjuvant chemotherapy and examined the relationship of response to disease free survival and overall survival.
Results: Of the 110 patients tested, 31 (28.2%) were basal-like, 19 (17.3%) were HER2+/ER−, 12 (10.9%) were luminal A, and 48 (43.6%) were luminal B. Pathologic complete response rate occurred in 7 (6.4%) of basal-like, 1 (0.9%) of luminal B and 3 (2.7%) of luminal A subtypes (p = 0.04). Patients with the HER2+/ER− and luminal B subtypes had worse disease-free survival and overall survival than those with the luminal A and basal-like subtypes.
Conclusions: Luminal B and HER2+/ER− subtypes are more sensitive to docetaxel/doxorubicin neoadjuvant chemotherapy than luminal A and basal like subtypes. HER2+ phenotype was associated with shorter survival, even though it was associated with a higher response rate to neoadjuvant chemotherapy.

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Phase II Study Assessing Lapatinib Added to Letrozole in Patients With Progressive Disease Under Aromatase Inhibitor in Metastatic Breast Cancer − Study BES 06

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Purpose: The role of type I receptors epidermalgrowth factor receptor (EGFR) and human epidermal growth factor receptor 2(HER2) in cross-talk with estrogen receptor signaling pathway has been demonstrated in pre-clinical studies. This cross-talk may cause endocrine resistance in breast cancer. On the other hand various inhibitors of such HER1/HER2receptors have yielded additive or synergistic effects when combined with endocrine agents. This trial evaluated the effect of adding lapatinib, a dual tyrosine kinase inhibitor blocking EGFR and HER2, to letrozole after a clinical