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Pharmacokinetics and tolerability of lapatinib administered once daily in combination with tamoxifen

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Background: The pharmacokinetics (PK) and tolerability of daily oral dosing of lapatinib (LAP) and tamoxifen (TAM) in patients (pts) with advanced or metastatic breast cancer (MBC) were examined in this study. Optimal dose selection indeed requires characterization of PK to accommodate the potential for a bi-directional PK interaction involving LAP inhibition and TAM induction of CYP3A4 and P-glycoprotein (Pgp).
Methods: Previously treated pts with estrogen and/or progesterone positive MBC, whatever HER2 status, were randomly assigned to one of two groups, to separately assess each direction of the potential PK interaction at steady state during daily dosing of 1250 mg LAP and 20 mg TAM. In one group, the PK of LAP was assessed on the 14th day of dosing LAP alone, and again on the 28th day dosing of LAP and TAM together. In the other group, the PK of TAM was assessed on the 28th day of dosing TAM alone, and on the 7th day of dosing TAM and LAP together. LAP and TAM were dosed together throughout subsequent 28 day cycles.
Results: To date, 25 pts have been enrolled with a median age of 59 (39−83) and a median PS of 1. Preliminary PK data for LAP from six patients are summarized in the table below showing geometric median (95% confidence limits) parameters. They indicate that LAP plasma concentrations are decreased by TAM. Final PK analysis will be presented at the meeting. Most common adverse events for the combination were: fatigue grade (gr) 1/2 (76%), diarrhoea gr 1/2 (60%), pain gr 1/2 (60%), rash gr 1 (40%) and nausea gr 1/2 (32%). To date, best response observed was stable disease in 6/25 pts (24%). Ten pts progressed and 6 pts discontinued early.
Conclusions: These preliminary PK results are consistent with data indicating that TAM induces hepatic CYP3A, the primary route of LAP elimination. This key information may impact in ongoing adjuvant lapatinib studies.

Parameter (units)	LAP	LAP+TAM	Decrease in LAP+TAM vs LAP
LAP AUCtau (h × mg/L)	21.7 (13.8−51.3)	17.7 (10.3−29.6)	25% (18% to 46%)
LAP Cmax (mg/L)	1.42 (1.33−4.82)	1.19 (0.95−2.05)	32% (10 to 57%)
LAP Cmin (mg/L)	0.73 (0.23−1.23)	0.40 (0.22−0.61)	44% (3% to 58%)

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HER-2 positive locally advanced breast cancer: one or two entities?

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Background: Primary systemic chemotherapy is an established standard of care for LABC. Complete pathologic response (CpR) and minimal residual cancer burden (pT1a) are predictors for better disease free and overall survival.
This retrospective study evaluates the clinical activity of sequential AC followed by Docetaxel-Cisplatin (D-Cis) and Trastuzumab (T) in locally advanced HER-2 overexpressed breast cancer.
Methods: Non pretreated patients (pts), with invasive breast cancer, HER2 positive (IHC 3+), stage IIB-IIIB, with a baseline LVEF = 50% were eligible. The neo-adjuvant regimen consisted of 4 cycles of AC (60 mg/600 mg/m^2) followed by 4 cycles of D-Cis (75 mg/m^2 each) before surgery. T started with the first cycle of D-Cis at 8 mg/Kg loading dose then 6 mg/Kg for 1 year. Cycles were given every 3 weeks.
Results: Twenty four pts were reviewed. Median age: 49 years (28−64), premenopausal:14; median tumor size:7 cm (3−13) stage IIB: 3, IIIA: 8, IIIB: 13, ER/PR negative: 14. The toxicity related to AC was mild, with febrile neutropenia (FN) occurring in 3 pts and all pts completed the planned 4 cycles; while the second sequence with D-Cis was completed in 17 pts only. F.N, renal impairment, and hypersensitivity reaction were seen in 3, 1 and 1 pt respectively. An asymptomatic decline of 15 points in the LVEF occurred in 3 pts. Clinical evaluation of response by RECIST criteria pre surgery: OR: 23/24 (96%), CR (58%) and 1PD. The second sequence with D-Cis-T doubled the rate of clinical CR obtained with AC. All pts had surgery (except one with disease progression). Pathological assessment, (using NSABP criteria), revealed that 11 (47%) pts had no residual invasive carcinoma in the breast; 4 (17%) had residual occasional scattered tumor cells only (pT1a); 13 (56%) had negative nodes; 8 achieved CpR and 2 nCpR. 80% of the CpR/nCpR occurred in PR negative subset.
Conclusion: (1) The absence of progesterone receptor was associated with a high probability of CpR achievement suggesting 2 different entities within the all HER-2 positive breast cancer. (2) This high rate of CpR was obtained with a short exposure of 9 weeks to Trastuzumab raising the question of the optimal duration of anti her 2 therapy in the neoadjuvant setting.

	PR−	PR+
CpR/nCpR	8/15 (53%)	2/8 (25%)

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Brain metastasis from triple negative breast cancer

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Background: Brain metastasis in patients with breast cancer is a clinical dilemma with few effective therapeutic options. There is a compelling clinical need to identify patients who are at high risk of developing this disastrous event, so that early detection and early treatment could be considered.
Aims of the study: To characterize the receptor profile (ER, PR and HER2) of patients with brain metastasis from breast cancer. To assess the prognosis of patients with brain metastasis with respect to receptor status, focussing on patients with triple negative breast cancer.
Materials and Methods: 62 consecutive patients with brain metastasis from 2003 to 2008 were included in this retrospective study. The receptor status was assessed and compared to that of a control population of 631 breast cancer patients diagnosed during the same period. The survival of patients with triple negative disease was compared to other subsets of patients with brain metastasis.
Results: 17 (27.4%) of the 62 patients with brain metastasis had triple negative breast cancer, compared to 104 (16.48%) of the 631 control patients (p = 0.047). The proportion of patients who were ER negative (48.4% Vs 24.2%; p = 0.001) and HER2 positive (40% Vs 14%; p = 0.001) was also higher in the study population. Patients with triple negative tumors had a shorter overall survival (3.0 years Vs 4.4 years; p = 0.041) compared to other patients. These patients had a shorter time to development of brain metastasis after diagnosis, though not statistically significant (2.3 years Vs 3.9 years; p = 0.107). Patients with triple negative breast cancer had shorter survival after the development of brain metastasis, compared to patients with receptor positive cancer (2.4 months Vs 6.2 months; p = 0.0086).
Conclusion: Patients with triple negative breast cancer are at a high risk of developing brain metastasis and have a poor survival. There may be case for screening for brain metastasis and even prophylactic treatment in this subset of patients.

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New isolated mediastinal lymph node or pulmonary nodule during surveillance of breast cancer: clinical factors to differentiate metastasis from benign lesion

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Background: New isolated mediastinal lymph node (LN) or pulmonary nodule during surveillance of breast cancer is not always possible to be pathologically diagnosed. We conducted this study to reveal clinical factors which are useful to differentiate metastasis from benign lesion in this situation.
Material and Methods: We consecutively enrolled breast cancer patients who presented new isolated mediastinal LN or pulmonary nodule during surveillance, and whose lesions were pathologically confirmed, between 1995 and 2008 at Seoul National University Hospital. Tissue diagnosis was made by mediastinoscopy, video-assisted thoracic surgery (VATS) or thoracotomy. Clinical factors including initial TMN stage, biologic subtype, lesion size, total number of lesions and maximal standardized uptake value (SUV) of positron-emission tomography (PET) were retrospectively analyzed between malignant and benign group.

Results: A total 43 patients were enrolled (isolated mediastinal LN:13 patients, isolated pulmonary nodule: 30 patients). Eighteen patients (42%) were confirmed to have benign lesion (group A) and 25 patients (58%) confirmed to have metastasis (group B). The disease free interval (median duration from initial operation of breast cancer to the detection of mediastinal LN or lung nodules) was similar between two groups (7.8 months (A) vs 9.5 months (B), p = 0.386). Between two groups, initial T stage (p = 0.145) and N stage (p = 0.749) was not different. Hormone receptor positivity was more prevalent in group A (72.2% vs 40.9%, p = 0.048) and triple-negativity was more prevalent in group B (16.7% vs 40%, p = 0.113). The mean size of the largest lesion was bigger in group B than in group A (20.8 mm vs 14.4 mm, p = 0.024). There was no difference in the number of lesions between two groups (2.17 (A) vs 2.76 (B), p = 0.361). PET was performed in 29 patients (67%). Metastatic lesions had significantly higher maximal SUV than that of benign lesions (6.42 vs 3.41, p = 0.021). mSUV more than 6.0 could define the lesion to be metastasis with the sensitivity of 50% and the specificity of 92% by ROC curve.
Conclusions: The biologic subtype, size of lesion and maximal SUV on PET could help physician to differentiate metastasis from benign lesion in breast cancer patients who present new isolated mediastinal LN or pulmonary nodule during surveillance.

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Analysis of factors predicting response to second-line trastuzumab-based therapy in patients (pts) with Her2-positive advanced breast cancer (ABC)

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Background: Upfront use of trastuzumab (T), either alone or in combination with chemotherapy or aromatase inhibitors, is well established in Her2-positive ABC. Upon disease progression, pts may be switched to lapatinib plus capecitabine. Others however may be candidates for continued antibody therapy. Finding the optimal treatment approach therefore is pertinent. We tried to identify factors predicting efficacy of second-line T-based therapy.
Methods: 97 pts treated with >1 line of T-based therapy were identified from a breast cancer database. Her2-status was determined by immunohistochemistry and re-analyzed by FISH if a score of 2+ was gained. Time to progression (TTP) on second-line therapy was defined as primary study endpoint. Secondary endpoints consisted of response rate (RR), clinical benefit rate (CBR; CR+PR+SD >6 months), overall survival (OS), development of brain metastases, and cardiac toxicity.
Response was evaluated every three months (m) using UICC criteria. TTP and OS were estimated using the Kaplan-Meier product limit method. Multivariate analyses (Cox proportional hazards model, multinomial logistic regression) were applied in order to identify factors associated with TTP and RR.
The following variables were included: age, initial tumor stage, grading, endocrine receptor status, prior non T-containing palliative chemotherapy, metastatic sites, and clinical benefit from T-based first-line therapy. *p* values <0.05 were considered to indicate statistical significance.
Results: Second-line TTP was median 7 m (95% CI 5.74−8.26) and first-line 8 m (95% CI 6.25−9.74) (n.s.). RR on second-line was 30.9% (44.3% first-line). In the multivariate models, none of the factors included could independently predict for activity of second-line treatment. OS was 43 months (95% CI 37.92−48.09).
A significant deterioration of cardiac function was observed in three patients; 40.2% developed brain metastases on second-line T or during follow-up after a median 21 m (95% CI 13.86−28.14).
Conclusions: Trastuzumab in multiple lines showed considerable activity. None of the variables investigated correlated with activity of second-line therapy. In order to predict for activity of second-line T, evaluation of other factors known to confer trastuzumab-resistance (p95Her2, PTEN-loss) appears necessary.

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Shorter Overall Survival (OS) in HER2-positive (HER2+) metastatic breast cancer (MBC) patients (pts) treated with trastuzumab (T) ± chemotherapy (CT) and overexpressing HER3 by immunohistochemistry (IHC)

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Background: Mechanisms of resistance to T in HER2+ MBC pts are still poorly understood. Both EGFR and HER3 form heterodimers with HER2. We investigated the role of HER3 protein expression by IHC in HER2+ MBC pts treated with T ± CT.
Material and Methods: From 04/99 and 03/06, 76 consecutive HER2+ MBC pts were treated at our institution but tumor tissue was available, for this analysis, from 42 pts. HER2 was evaluated by IHC (MoAb CB11) and scored according to DAKO Herceptest. HER3 status was evaluated by IHC on 3.5 μm section of formalin-fixed, paraffin embedded tissue using a mouse MoAb (clone RTJ1; Novocastra United Kingdom; used at 1:20). The immunostaining reactivity was citoplasmatic. Tumors were considered HER3+ if >50% of tumor cells were positive.
Results: At median follow up of 26.5 months (3.7−99.6) from the start of T, 42 pts were evaluable for OS and incidence of CNS metastases and 40 for response to T and TTP. Median age of pts was 53 years (23−77). We observed 25/40 responses (CR+PR) to T ± CT (62.5%) and CNS metastases in 20/42 pts (47.6%); median TTP from the start of T was 9.6 months (1.3−80+). Median OS from the start of T was 29.6 months (3.7−99.6+). Twenty-one pts were HER3+ with a cut-off of 50%. HER3 overexpression was not significantly correlated with response to T, TTP, incidence of CNS metastases; OS from start of T was shorter in HER3+ tumors compared to HER3 tumors (28.2 vs 42.7 months; p = 0.152). These data confirm the notion that HER2/HER3 heterodimer is the major oncogenic unit in HER2+ MBC.
Conclusions: In this limited series of pts, a worse OS was observed in HER2+ MBC with HER3+ status by IHC. Approaches to target HER2/HER3 signaling may be warranted.

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Micrometastatic tumor cells in blood and bone marrow of patients with primary breast cancer: extended surrogate marker-panel for multi-gene expression analysis

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Background: We have validated a new preanalytical enrichment and molecular detection method using embedded tumor cell calibrators (ETC) for quantitative gene expression analysis of circulating tumor cells (CTC) and bone marrow tumor cells (DTC). Here we present results of an extended surrogate marker panel.
Methods: Samples from patients were divided in native probes and matched calibrator probes containing either 2 or 10 breast carcinoma tumor cells (ETC). The high affinity antibodies BM7 (MUC-1) and VU1D9 (EpCAM) coupled to 4 μm dynabeads (Invitrogen®) were used for immunomagnetic tumor cell enrichment from $1x10^7$ bone marrow (BM) cells and 10 ml peripheral EDTA-blood of patients with primary breast cancer and metastatic disease. Separated cells were lysed and used for mRNA isolation and c-DNA synthesis. We used end point RT-PCR (Adnagen®) and real-time quantitative RT-PCR approaches with the epithelial markers cytokeratin19 (CK19), mammaglobin1 (MG1), MUC1 and EpCAM for tumor cell identification. The phenotype of micrometastatic cells was determined by expression analysis of the markers ALDH1, TKTL1, Survivin, CXCR4, HIF-1, HER2 and CD276 (B7-H3).
Results: Positivity rate of ETC controlled RT-PCR on the basis of CK19, MG1, and EpCAM was 8.6% in 16/187 patients with primary breast cancer, 24% for DTC analysis in BM and 61.1% in patients with metastatic disease. During a 12 to 24 months follow-up of 114 patients of the primary breast cancer group CTC positivity was determined in 9.6% of the patients, however only one of these had been positive before operation. In three patients with multimarker expression early metastasis was clinically confirmed later. Progressive disease in metastatic breast cancer patients was characterized by elevated marker levels of CXCR4 (86%), survivin (58%) and CD276 (50%).