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Tolerability of lapatinib in combination with taxanes (T) in 507 patients with breast cancer (BC)

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Background: This analysis presents tolerability data for combination of Lapatinib (Tyverb®/Tykerb®) (L), an oral, dual ErbB1/B2 tyrosine kinase inhibitor and taxanes (T), the most frequently used cytotoxic in BC treatment. The side-effects observed with EGFR inhibitors (erlotinib, gefitinib) in combination with T were neutropenia, diarrhea and rash. Data from a range of clinical studies with L and paclitaxel (P) or docetaxel (D) are presented.

Methods: Pharmacokinetics (PK) and preliminary safety data from 507 patients are summarised.

Results: PK analysis from study EGF10009 (q3w), show systemic exposure was increased for both L (21%) and P (23%) at doses of 1500 mg daily and 175 mg/m^2/q3w, respectively. PK analysis from study EGF10021, (L 1250 mg & D 75 mg/m^2 with prophylactic pegfilgrastim) indicated no significant effect on systemic exposure of either agent.

Toxicities $\geqslant$ grade 3, across all studies for all patients include, neutropenia (15%), diarrhea (18%), rash (5%), febrile neutropenia (3%), neuropathy (4%), and LVEF decrease (0.6%). The rate of neutropenia, rash and neuropathy were similar in combination to each agent alone, however diarrhea was more common. The frequency and severity of diarrhea was increased in studies EGF10009 and EGF102580 where no proactive treatment of diarrhea was introduced, whereas in study EGF105764, with proactive treatment, a lower incidence of $\geqslant$grade 3 diarrhea was reported (5%). For study EGF30001 and the overall diarrhea in this pooled analysis, the $\geqslant$ grade 3 diarrhea observed is similar to what is seen with lapatinib monotherapy clinical studies. The incidence of $\geqslant$ grade 3 LVEF decrease was low (0.6%) compared with reports of docetaxel plus trastuzumab (TRZ) combinations.

Conclusions: T plus L combinations have significant activity in HER2+ BC (60−70% RR reported in EGF102580 and EGF30001) and have a predictable and manageable safety profile. Proactive diarrhea management is essential for these combinations and dose adjustments should be considered in patients with persistent or severe diarrhea.

Study	Phase/L+T	Dose L mg/d T mg/m^2	Tumor	N	Diarrhea $\geqslant$G3 (%)
EGF10009	I/L+P	1250–1500/135–225 q3w	Refractory	44	7
EGF10009	I/L+P	1500/80 qw	Refractory	12	50
EGF105764	II/L+P	1500/80 qw	1L MBC	57	5
EGF102580	II/L+P	1500/80 qw	IBC	49	61
EGF10021	I/L+D	1000–1500/50−75 q3w	Refractory	52	10
EGF30001	III/L+P	1500/175 q3w	1L MBC	293	15

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Severe skin toxicity observed in patients (pts) treated with capecitabine (CAP) and weekly paclitaxel (PACLI) for metastatic breast cancer (MBC)

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Introduction: Skin toxicity has recently been recognized as an important toxicity of antineoplastic drugs. We report the incidence of skin toxicity in MBC treated with innovative regimen of CAP and weekly PACLI.

Patients and Methods: Eleven MBC patients were included into phase I study with the combination of CAP 2000 mg/m^2 daily (DI−D14) and escalating doses (60 mg/m^2, 75 mg/m^2 and 90 mg/m^2) of weekly PACLI (DI, D8, D15) and 15 MBC patients proceeded into phase II study of CAP 2000 mg/m^2 daily (DI−D14) combined with weekly administered PACLI 60 mg/m^2 (DI and D8). Regimens were repeated every 3 weeks. Adverse events were graded according to Common Terminology Criteria for Adverse Events, version 3.0.

Results: All 26 patients were evaluable for toxicity. Two patients in phase I receiving PACLI 75 mg/m^2 in combination with CAP experienced grade 3 nail toxicity, with grade 3 hand-foot syndrome (HFS) in one patient and grade 2 dermatitis in the other, which were deemed as dose-limited toxicity. Based on this, weekly PACLI dose of 60 mg/m^2, was selected for phase II study. The total of 18 patients received CAP 2000 mg/m^2 daily (DI−D14) and 60 mg/m^2 weekly PACLI combination. Toxicity of this regimen was mild without grade 3/4 adverse events. Skin toxicity was as follows: grade 1/2 HFS in 11/18 pts, grade 1/2 rash/desquamation in 8/18 pts and grade 1/2 nail toxicity in 4/18 pts. Due to repeat grade 2 HFS, despite CAP dose reduction, 1/18 pts went off therapy.

Conclusion: According to our findings the combination of CAP 2000 mg/m^2 daily (DI−DI4) and with weekly PACLI 75 mg/m^2 is not feasible due to severe skin toxicity.

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Effects of chemotherapy on olfactory function in breast cancer patients

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Background: Disorders of olfaction have a negative impact on quality of life and nutrition and are frequent complaints in patients undergoing chemotherapy. This prospective study investigates the olfactory function of breast cancer patients receiving chemotherapy.

Material and Methods: The olfactory function was tested 4 times in 63 previously chemo-naïve breast cancer patients: Before, in the midth, directly after, and 3 months after chemotherapy. Olfactory testing was performed by means of "Sniffin' Sticks", a validated instrument containing separate tests for odor tresholds, odor discrimination, and odor identification. Seven patients received Carboplatin, 56 patients received combination chemotherapy consisting of 5-Fluorouracil, Epirubicin, Cyclophosphamid, or Docetaxel and Adriamycin. The data were analyzed using the variance analysis.

Results: During chemotherapy, the olfactory function decreased. Three months after chemotherapy, the olfactory function recovered almost back to baseline. This change was significant for the score of odor thresholds (8.5$\pm$2.3 – 6.5$\pm$1.9 – 4.9$\pm$1.5 – 7.5$\pm$1.9), odor discrimination (13.8$\pm$1.9 – 12.4$\pm$1.9 – 11.6$\pm$2.2 – 13.7$\pm$1.5), and odor identification (14.3$\pm$1.9 – 13.8$\pm$1.9 – 13.3$\pm$2.2 – 14.1$\pm$1.8). There was no significant difference between patients receiving Carboplatin or any other chemotherapy.

Conclusions: Chemotherapies in patients suffering from breast cancer have a significant effect on olfactory function. Odor threshold is reduced more than odor discrimination and odor identification. Reduced olfactory function is one reason of reduced appetite leading to lower energy intake and weight loss during chemotherapy. Additional flavoring during chemotherapy may compensate the diminished chemosensory function, reduce weight loss and thus improve quality of life of breast cancer patients.

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Clinical characteristics of bone fractures in breast cancer women receiving adjuvant aromatase inhibitors

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Background: The evidence exists that non-steroidal aromatase inhibitors (AI) therapies used in adjuvant setting carry an increased risk of bone fractures. Before the clinical value of preventive measures for that events (such as bisphosphonates, life-style changes, etc.) will be clearly established, the careful identification of patients' subgroup with the highest fracture risk might be helpful in making decision regarding the most optimal sequence of endocrine therapy and supportive care.

Material and Methods: Data on skeletal adverse events and predictive factors of fracture risk were collected during the questionnaire-based interview from 96% patients treated with adjuvant AI in three separate institutions between 01.01.2002 – 31.12.2007. Adjuvant anastrozole (N = 288) or letrozole (N = 43) was given to 331 postmenopausal breast