**422** POSTER

**Phase I study of lapatinib (GW572016) in combination with letrozole in cancer patients**

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**Background:** Lapatinib is an oral, selective and highly potent competitive tyrosine kinase inhibitor of both ErbB1 and ErbB2. Coexpression of both estrogen receptor (ER) and ErbB2 is associated with inferior survival (versus ER+ alone) and tamoxifen resistance in breast cancer patients (pts). Clinical advantages may be observed by simultaneously blocking both ER and ErbB pathways.
**Material and methods:** Patients (pts) with ER+ or progesterone receptor (PR)+ advanced breast cancer or other tumors likely to respond to this combination (eg, ovarian cancer) were enrolled. Lapatinib was administered orally in escalating doses (1250 mg-1500 mg/day) in combination with letrozole 2.5 mg/day. Three pts were treated at each dose cohort, with expansion to 6 if a dose-limiting toxicity (DLT) was observed. Once optimally tolerated regimen (OTR) was determined, pharmacokinetic (PK) parameters of lapatinib and letrozole alone and in combination were studied. Clinical response assessments by RECIST criteria were performed every 8 weeks.
**Results:** A total of 39 pts were enrolled in the trial (n = 18 breast cancer; n = 16 ovarian cancer; n = 5 other). Median age was 56 years (range 31–73). A median of 3 treatment periods (1 treatment period = 4 weeks) was administered (range 1–14). Toxicities in 35 assessable pts (1250 mg = 4; 1500 mg = 31) included grades 1–2 diarrhea, fatigue, nausea, anorexia, rash, and vomiting. 15% of pts had grade 3 diarrhea, and 1 pt had grade 3 rash. All clinical activity was observed at the 1500 mg lapatinib+letrozole 2.5 mg/day dose level. Three of 18 breast cancer pts had SD for $\geqslant$ 6 months (treatment duration 6–8 mo). These 3 pts had ErbB2+ and ER/PR+ disease, with 2 having received prior aromatase inhibitor (AI) and all received prior chemotherapy (3–5 regimens). One of 2 endometrial cancer pts had a PR (treatment duration 13+ mo), and 1 of 16 ovarian cancer pts had SD for $\geqslant$ 6 months (treatment duration 8 mo).
**Conclusions:** Lapatinib 1500 mg/day plus letrozole 2.5 mg/day was determined as the OTR. The combination of lapatinib and letrozole was well tolerated and showed preliminary signs of clinical activity, primarily long-term stable disease. Phase III studies are under way to further test this and other lapatinib-endocrine therapy combinations in advanced breast cancer and endocrine-resistant populations.

**423** POSTER

**A markov model to evaluate the cost effectiveness of five bisphosphonate therapies in the prevention of bone complications in breast cancer patients with bone metastases: a German outpatient perspective**

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**Background:** Oral and IV bisphosphonate agents are effective in reducing skeletal related events (SREs) and alleviating bone pain in breast cancer patients with bone metastasis. However, these agents are characterized by different efficacy, administration time, and costs. We conducted an economic analysis to compare cost-effectiveness of these agents from a German outpatient perspective.
**Methods:** A Markov model was developed to simulate survival and incidence of SREs for a hypothetical cohort of patients receiving no treatment (NT), monthly injections of ibandronate (IBN), generic pamidronate (PA) or zoledronic acid (ZA), or daily oral therapy with clodronate (CL) or ibandronate (OI). Probabilities of SREs and mortality data were obtained from published clinical trials of each agent. The risk reduction in SREs with therapy was estimated using the Anderson Gill method. Costs of drugs and administrations, cost of SREs, and utility values were estimated from published sources. Utilities were applied to time with and without SREs to capture the impact on quality of life. All outcomes were discounted at 5%.
**Results:** The cumulative number of SREs over the lifetime of the patients was lowest for ZA (3.95 per patient), followed by IBN (4.44), PA (4.55), OI (4.55), OC (4.59) and NT (5.62). Total costs per patient of were lowest for NT (*17,348), followed by ZA (*18,534), PA (*19,177), OC (*19,508), IBN (*20,174), and OI (*21,173). Per-patient quality-adjusted life years (QALY) was highest with ZA (0.781), followed by IBN (0.776), PA (0.775), OC (0.773), OI (0.761) and NT (0.737). Compared to NT, ZA cost *26,795 per QALY gained and was less costly and more effective than all other bisphosphonates.
**Conclusions:** Zoledronic acid appears to be the most cost-effective bisphosphonate therapy and is also highly cost effective compared to no therapy.

**424** POSTER

**The influence of trastuzumab and non-anthracycline chemotherapy combined treatment on valvular, systolic and diastolic cardiac function in metastatic breast cancer patients – 4 years follow up**

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**Purpose:** to asses long-time cardiotoxic risk of treatment with trastuzumab and chemotherapy in metastatic breast cancer patients.
**Patients and methods:** 66 patients treated with combination of trastuzumab 2 mg/kg 1-weekly and chemotherapy consisting of docetaxel 75 mg/m$^2$ and cisplatin 75 mg/m$^2$ every 3 weeks or cisplatin or vinorelbine or capecitabine in monotherapy at standard doses were evaluated clinically, by ECG and by Doppler echocardiography at baseline (I), in 2nd (II), 4th (III), 6th (IV) month of chemotherapy and every 3 months up to 4 year follow-up (V) thereafter. Valvular function, resting left ventricular ejection fraction (LVEF), Left ventricle (LV) and left atrium (LA) diameters, diastolic and systolic LV function were determined. 51/66 patients were anthracycline pre-treated to median cumulative dose 380 mg/m$^2$, 33/66 of patients were irradiated to chest wall.
**Results:** during treatment there was progression of mitral insufficiency in 7/66 patients. No statistically significant changes were found for mean left ventricular ejection fraction (LVEF): I – 66%, II – 65%, III – 64%, IV – 63%, V – 66%, mean LV end-diastolic diameter (LVED) I – 47 mm, II – 48 mm, III – 48 mm, IV – 50 mm, V – 49 mm, mean isovolumetric relaxation time (IVRT) I – 94 ms, II – 84 ms, III – 90 ms, IV – 98 ms, V – 84 ms, mean LA diastolic dimension: I – 36 mm, II – 35 mm, III – 35 mm, IV – 35 mm, V – 35 mm. In nine cases asymptomatic moderate global hypokinesis was observed (EF: 49–59%), in five cases asymptomatic segmental hypokinesis was seen. All but one (13/66) of these patients were treated previously with anthracycline containing chemotherapy. Median cumulative dose of doxorubicin was 540 mg/m$^2$.
**Conclusion:** echo-doppler imaging during trastuzumab and chemotherapy combination treatment revealed progression of mitral regurgitation in some patients. The incidence of asymptomatic impaired systolic cardiac function was frequent (21% of patients). Most important risk factor for trastuzumab cardiotoxicity seems to be a high cumulative dose of doxorubicin given as a previous line of chemotherapy.

**425** POSTER

**Influence of trastuzumab on the incidence of brain metastasis in patients with Her2-overexpressing metastatic breast cancer**

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**Background:** It has been reported in several studies that patients with Her2-overexpressing metastatic breast cancer present a high risk of brain metastasis. The identification of predictive factors for brain metastasis in this subset of patients could allow to develop strategies for early detection or prevention.
**Patients and methods:** Patients were selected from two institutions to have presented a Her2-overexpressing metastatic breast cancer between 2000 and 2004. Predictive factors for brain metastasis were determined by multivariate analysis using Cox model.
**Results:** 147 patients have been included in the present study. 57%, 55%, 77% of patients presented a hormone receptor negative tumour, a high grade tumour and a visceral metastasis respectively. 26% of patients have been treated by trastuzumab on frontline treatment. 29% of patients have developed brain metastasis. The 2 years incidence of brain metastasis was 33%. Visceral metastasis and treatment with trastuzumab on frontline