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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.

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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.

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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.

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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

treatment were predictive factors in a multivariate analysis. The 2 years incidence of brain metastasis in patients with visceral metastasis treated by trastuzumab as frontline therapy was 45%.
Conclusions: This study suggests that patients with Her2-overexpressing metastatic breast cancer with visceral involvement treated with trastuzumab present a high risk of brain metastasis.

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Value of tumour markers CA 15–3 and CEA in predicting response and progression during fulvestrant treatment

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Background: Tumour markers are often used to monitor response to therapy in patients with metastatic breast cancer (MBC) and an increase in tumour markers after 3 months of treatment may be a sign of *de novo* disease progression (PD). Here we assessed the prognostic value of tumour markers at predicting response and secondary PD in patients receiving fulvestrant ('Faslodex') therapy.
Methods: Postmenopausal women who had received prior endocrine therapy for MBC were treated with fulvestrant 250 mg/month as part of a Compassionate Use Programme (CUP). Changes in cancer antigen 15–3 (CA 15–3) and carcinoembryonic antigen (CEA) were prospectively monitored on a monthly basis in patients experiencing a partial response (PR), stable disease (SD) $\geqslant$ 6 months and *de novo* PD. Levels of these markers were also evaluated for the 3 months preceding secondary PD in patients who had previously experienced clinical benefit (CB) with fulvestrant.
Results: Tumour marker data from 67 patients participating in the CUP were analysed; seven patients (10.4%) had a PR, 28 patients (41.8%) had SD $\geqslant$ 6 months and 32 patients (47.8%) had *de novo* PD. Tumour marker data for the first 4 months of treatment are presented in the table.

Patients response	Median marker levels				P-value
	Month 1	Month 2	Month 3	Month 4	
PR (n = 7)					
CA 15–3 (U/mL)	67.0	83.0	84.0	84.0	NS
CEA (ng/L)	5.5	4.0	4.0	4.1	NS
SD $\geqslant$ 6 months (n = 28)					
CA 15–3 (U/mL)	110.0	109.0	143.0	147.0	0.0023
CEA (ng/L)	7.2	7.0	7.4	6.3	NS
De novo PD (n = 32)					
CA 15–3 (U/mL)	95.5	103.5	139.0	191.0	0.0214
CEA (ng/L)	10.6	12.7	15.5	17.0	NS
Secondary PD (n = 28)					
CA 15–3 (U/mL)	258.5[a]	311.5[b]	389.0[c]	388.5[d]	0.0016
CEA (ng/L)	6.6[a]	7.4[b]	7.3[c]	8.1[d]	NS

[a]2 months before PD; [b]1 month before PD; [c]PD; [d]1 month after PD

Conclusions: Patients experiencing *de novo* PD or secondary PD with fulvestrant show significantly increasing CA 15–3 levels. However, those experiencing SD $\geqslant$ 6 months and even those with a PR may also show an initial increase in CA 15–3 levels; this should not be taken as a sign of PD without radiological verification. CEA was a poor prognostic marker for response in patients receiving fulvestrant.

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The TEXAS trial – mature results of activity/toxicity of Taxotere given with anthracyclines in a community setting, as first line therapy for metastatic breast cancer

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The TAX 306 Phase III study demonstrated that doxorubicin plus docetaxel (AT) is more effective than doxorubicin plus cyclophosphamide. Between 1999 and 2001, 470 patients were registered in an open evaluation study at UK Cancer Centres.136 patients had 3 weekly AT (A – 50 mg/m^2), 333 ET (E – 75 mg/m^2), each with T – 75 mg/m^2. Median cumulative dose of T was 420 mg/m^2. 152 patients discontinued treatment, for disease progression (67, 14%), adverse events (63, 13%) and withdrawal of consent (11, 2%). ORR (ITT), was 61% (n = 66) for AT, and 62% (n = 182) ET, similar to AT in TAX 306 (ORR 59%).
At a median follow up of 72 weeks, 433 (92%) had progressed following first line therapy and 401 (85.5%) had died. Overall median time to progression was nearly 37 weeks, (37.8 weeks ET, 35.4 AT). Both groups in TAX306 and in TEXAS compared favourably, in terms of response rates and TTP, with single-agent chemotherapy.
The main toxicity was neutropenia, with 75 patients (55%) on AT and 203 (61%) on ET with NCI grade 3/4 neutropenia. Febrile neutropenia or neutropenic sepsis was reported for 32 (24%) of the AT arm and 78 (23%) of the ET arm. There were 3 (0.9%) deaths from neutropenic sepsis in the ET arm and 2 (1.5%) in the AT arm, non-hematologic toxicities were diarrhea, nausea, vomiting, and pyrexia. 38 (11%) of patients on ET and 22 (16%) on AT withdrew from the treatment due to an adverse event. One patient in the ET arm had CHF after 6 cycles and 3 patients were withdrawn after cycle 1 or 2 due to cardiac dysrhythmia.
AT or ET are effective for patients with rapidly progressive visceral disease. Myelosuppression is manageable and long-term toxicity not a major issue. AT or ET represent useful options for first-line therapy for MBC.

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Application of the rough sets theory to evaluate prognostic factors in breast cancer patients subjected to mastectomy

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Background: the paper presents analysis of relationship between variables describing breast cancer patients and therapy results. The method based on the rough sets theory and induction of decision rules is applied to perform the analysis. Rough sets are a method of dealing with domains characterized by inconsistent and incomplete information. Proceeding in this way, they formulate some indications, which may be helpful in making decisions referring to the treatment of breast cancer patients.
Material and methods: the data set contains 718 breast cancer patients described by 21 variables (factors) and divided into two classes: patients who did not experience cancer recurrence and patients who had cancer recurrence. In the years 1992–1994, those patients were subjected to mastectomy and underwent chemotherapy at the Chemotherapy Ward of the Wielkopolska Oncology Centre in Poznan. The observation period was equal to 10 years (2002–2004). The whole group of patients was divided into two sets: a learning set and a testing one.
Results: in the first phase of the analysis, the rough sets based approach was applied to determine variable importance for the patients' classification. The set of selected variables, which ensured high quality of the classification, was obtained. Then, the decision rules were generated from the learning set by means of the algorithm inducting the minimal cover of the learning examples. The testing set was a base to evaluate prognostic potential of the generated decision rules. Total accuracy of prognosis (classification) for the decision rules was equal to 70.3%. In the case of the patients who had had cancer recurrence the prognosis accuracy was 76.3%, and for the patients who had had no recurrence of cancer it was 60.7%. The prognosis accuracy is described as a ratio of number of test cases for which the rules correctly indicated cancer recurrence or lack of recurrence to the total number of test cases.
Conclusions: the obtained decision rules provide guidelines which may be helpful in making decisions referring to treatment of breast cancer patients as well as evaluating their prognosis.
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Advanced stage breast cancer treatment: a survey of European opinion leaders

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Background: The purpose of this study was to determine physician preferences for treatment of women with advanced stage breast cancer.
Material and methods: The study was conducted in 5 countries. A patient scenario was used to guide the reader throughout the survey: postmenopausal woman diagnosed with stage IV breast cancer, with a