Materials and Methods: Eligible pts have unresectable, HER2+, locally recurrent or MBC. The starting dose of oral SU was 37.5 mg/d (continuous daily dosing [CDD]). T was administered iv wkly (loading 4 mg/kg then wkly 2 mg/kg) or q3w (loading 8 mg/kg then q3w 6 mg/kg). Due to changes in standard of care, the trial was amended to allow inclusion of pts who had previously received chemotherapy in the 1st-line setting. Previous tx with T (± lapatinib) was also permitted. The primary endpoint was ORR and secondary endpoints included safety and pharmacokinetics (PK).
Results: A total of 60 pts have been enrolled in this ongoing trial (7 pts on the original protocol and 53 under the amendment [53 pts evaluable for safety and 51 pts evaluable for antitumor activity]). As of Oct 2008, 10 pts continue on study and 43 have discontinued, 9 due to AEs. Pts started a total of 259 cycles of tx with a median of 4 cycles/pt (range: 1−14). SU dose was reduced from 37.5 mg/d to 25 mg/d in 19/53 pts (36%). Most (70%) pts received SU + T as 1st-line tx. ORR was 24% and clinical benefit rate (CBR) was 39%. 2 (4%) pts achieved a CR, 10 (20%) pts had PRs and 21 (41%) had SD (5 unconfirmed PRs). The majority of responses (11/12 pts) occurred in pts who were tx-naïve or had received only adjuvant therapy (for this group: ORR = 32%; CBR = 44%). Median PFS was 26 wks (95% CI, 19.4−31.9). Most AEs were G1/2; G3 non-hematologic AEs (occurring in ⩾10% pts) were asthenia (13%) and hypertension (11%). G3/4 neutropenia occurred in 6 pts (12%). In total, 3 non-hematologic G4 AEs occurred (6%; all considered related to tx): LVEF decline, pulmonary embolism and pancreatitis. One G5 AE occurred (cardiogenic shock). LVEF decline was observed in 17/53 pts (32%) and all G1/2 cases (13 pts) were resolved with either no action or a temporary dose delay. PK data confirmed no significant drug–drug interactions.
Conclusions: The combination of SU (37.5 mg/d; CDD schedule) + T (wkly or q3w) showed acceptable tolerability and antitumor activity in HER2+ MBC pts.

5004 ORAL

Multicenter phase I clinical trial of daily and weekly everolimus (RAD001) in combination with vinorelbine and trastuzumab in patients with HER-2-overexpressing metastatic breast cancer (MBC) with prior resistance to trastuzumab

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Background: Resistance to trastuzumab (H) may be associated with loss/deregulation of PTEN or activating mutations in the PI3K/AKT pathway. Preclinically, everolimus (E), an oral inhibitor of the downstream factor mTOR, enhances efficacy and partially reverses resistance to H. The objective of this study was to establish the feasible dose/regimens of E in combination with vinorelbine (V) and H in heavily pretreated HER2+ MBC patients (pts).
Methods: A multicenter, Novartis sponsored, Phase I clinical trial (NCT00426530) was conducted using 2 regimens of a triple combination: V 25 mg/m^2, IV on days 1 and 8 q3w; H 4 mg/kg loading dose, followed by weekly 2 mg/kg IV; E either daily (d) (5 and 10 mg) or weekly (w) (20, 30, 50 and 70 mg).
Results: As of February 2009, 46 pts were enrolled: 26 in the E 5 mg/d cohort, 6 in the 20 mg/w and 14 in the 30 mg/w. Patient characteristics were: median age 49 y-o; visceral disease in 78% of pts; median number of prior chemo-regimens for metastatic disease 2 (range 0−10); H-resistance in 100% of pts; prior taxanes in 98% of pts, including 46% taxane-resistant; prior anthracyclines in 91% of pts; and 22% of pts refractory or resistant to lapatinib. Mean duration of study treatment, median V-RDI (relative-dose-intensity) and E-RDI, were: 26 wks, 77%, and 67%, respectively, in the 5 mg/d cohort; 29 wks, 85% and 78%, respectively in 20−30 mg/w cohorts. G3−4 neutropenia occurred in 22 (84%) and 18 (90%) of pts in the 5 mg/d and 20−30 mg/w cohorts, respectively, however it was considered manageable (G-CSF used in 1 patient). There was one case of febrile neutropenia. G3 stomatitis and G3 asthenia/fatigue were seen in 3 (12%) and 2 (8%) of pts in the 5 mg/d cohort, and in 1 (5%) and 3 (15%) of pts in the 20−30 mg/w cohorts. Forty-four pts were evaluable for efficacy (Table 1).
Conclusions: E in combination with V and H is well tolerated with neutropenia being the most relevant side effect. Promising anticancer activity was observed. The study is no longer recruiting and E 5 mg daily has been selected as the recommended dose and schedule for further development. Updated results, PK and biomarker data will be presented.

Table 1: Overall response and time to progression (K-M based)

Best Response	5 mg/d n = 25	20 mg/w n = 6	30 mg/w n = 13
CR (%)	1 (4)	–	–
PR (%)	4 (16)	1 (17)	2 (15)
SD (%)	15 (60)	3 (50)	9 (60)
PD (%)	5 (20)	2 (33)	2 (15)
Time to progression, median (wks)	32	33	29

5005 ORAL

Surgical resection of the primary tumour is associated with improved survival in patients with distant metastatic breast cancer at diagnosis

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Background: In the Netherlands approximately one out of nine women are diagnosed with breast cancer annually. 3−10% of them have distant metastatic disease at initial presentation (stage IV disease). Because this is considered to be an incurable disease, it is treated palliatively. Local treatment of the primary tumor is only recommended if the primary tumor is symptomatic. Recent studies indicate that removal of the primary tumor may have a beneficial effect on mortality risk of patients with primary distant metastatic breast cancer. This retrospective study analysis the impact of surgical resection of the primary tumor on the survival of patients with primary distant metastatic disease is investigated, taking into account the presence of co-morbidity and other potential confounders.
Methods: In the period 1993 till 2004, 15 769 patients with breast cancer were diagnosed in the south of the Netherlands. This study included the 728 patients with distant metastatic disease at initial presentation, which was 5% of all patients. Of them, 40% had surgery of the primary tumor. Stratified analyses were performed to compare surgically and non-surgically treated patients in subgroups defined by age, T-classification, number of metastatic sites and co-morbidity. To examine the independent contribution of surgery of the primary tumor, a multivariable analysis was performed. Follow-up was carried out until 1 July 2006.
In addition, the medical charts of a selection of all patients have been reviewed. Type of surgical treatment and information about the surgical resection margins are studied as well as whether or not an axillary lymph node dissection had taken place.
Results: Median survival of the patients who had surgery of their primary tumor was significantly longer than for the patients who did not have surgery (31 vs. 14 months). The 5-year survival rates were 24.5% and 13.1%, respectively ($p < 0.0001$). In a multivariable analysis, adjusting for age, period of diagnosis, T-classification, number of metastatic sites, co-morbidity, use of loco-regional radiotherapy and use of systemic therapy, surgery appeared to be an independent prognostic factor for overall survival (HR 0.62; 95% CI 0.51−0.76). Results of the medical chart review are expected before September 2009.
Conclusion: Removal of the primary tumor in patients with primary distant metastatic disease was associated with a reduction of the mortality risk of around 40%. The association was independent of age, presence of co-morbidity and other potential confounders. In order to find a biological explanation for the improvement in overall survival, the effect of type of surgery and the impact of tumor free resection margins are investigated.

5006 ORAL

15-year trends in metastatic breast cancer (MBC) survival in Greece – a meta-analysis of ten Hellenic Cooperative Oncology Group (HeCOG) clinical trials

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Background: In the metastatic setting a detected time trend to improved prognosis could be attributed to the corresponding recent advances in the therapeutic approaches. The aim of the current study was first to assess, in a large cohort of well over a thousand patients, the time trends in survival

in MBC for the last fifteen years and second to explore its association to prognostic factors affecting outcome including therapeutic regimen.
Material and Methods: This meta-analysis uses individual patient data collected from all ten trials on MBC (6 non randomized, 4 randomized) conducted by HeCOG from 1991 through 2006. Four 4-year time periods (1991–1994, 1995–1998, 1999–2002 and 2003–2006) were constructed for exploration of time trends in survival according to the patient's date of metastatic diagnosis. Different first line regimens in the 10 trials include anthracycline monotherapy (epirubicin, in the early 90s) and taxane-containing regimens either as monotherapy or in different combinations with anthracyclines or other drugs. In two phase II studies and the last randomized study, trastuzumab was administered in all patients with HER2 overexpressing tumors.
Results: Information is based on a total of 1365 patients with a median follow up of 3.7 years and median survival of 1.9 years (median survival 1.3, 1.7, 2.2 and 2.6 years for 1991–1994, 1995–1998, 1999–2002, and 2003–2006, respectively). Survival improved significantly across diagnosis time periods, by 26%, 44% and 52% respectively in each time period as compared to the first (1991–1994), (1995–1998: HR = 0.74, p = 0.002; 1999–2002: HR = 0.56, p < 0.001; 2003–2006: HR = 0.48, p < 0.001). The effect of metastatic diagnosis time period remains almost unchanged in the presence of the following significant prognostic factors: performance status, hormonal receptor status, previous adjuvant treatment, visceral metastasis at entry and number of metastatic sites. When exploring the effect of new treatment introduction, taking into account the same significant prognostic factors, the effect of time period disappears and the same effect magnitude is explained directly by the introduction of taxanes or trastuzumab (taxanes at 1st line: yes vs. no: HR = 0.73, p = 0.004; trastuzumab at 1st line: yes vs. no: HR = 0.64, p < 0.001).
Conclusions: The results provide significant evidence of improvement in prognosis of MBC patients within the last 15 years, taking into account all important significant prognostic factors, and this improvement could be explained almost fully by the use of new agents in the management of the disease.

5007 ORAL

MicroRNA profiling of circulating tumor cells (CTC) present in large quantities of leukocytes

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Background: The CellSearch Circulating Tumor Cell Test (Veridex) is the only FDA approved diagnostic test for the detection and enumeration of CTCs. CTC enumeration by this technique has proven clinical relevance in metastatic prostate, colorectal and breast cancer. Next to enumeration, there is great interest in the molecular characterization of CTCs, which may yield better prognostic and predictive factors and models. Although this system allows capture of CTCs in blood of cancer patients by selectively isolating EpCAM-positive cells followed by visual quantification of DAPI- and CK-8/18/19-positive cells [1], there are still considerable quantities of contaminating leukocytes (DAPI+/CD45+) present after enrichment. Previously, we optimized a method to determine mRNA expression of up to 96 genes in as little as a single breast cancer cell [2]. By using a set of genes with no or minor expression by leukocytes, we succeeded to specifically determine gene expression profiling in a small number (frequently less than 5) of CTCs present in a CTC-enriched blood sample typically containing over 800 contaminating leukocytes. In this study we set out to similarly characterize these CTCs at the miRNA level. MiRNAs are naturally occurring non-coding RNAs that play a role in gene regulation. Expression of various miRNAs have been associated with outcome in breast cancer.
Methods: We screened healthy blood donors (HBDs), breast cancer tissues, breast cancer cell lines spiked in blood from HBDs, and breast cancer patients for miRNA expression specific for breast cancer tumor cells with the TaqMan human MicroRNA assay v1 set (Applied Biosystems) containing 446 miRNAs.
Results: Of the 446 miRNAs, ~300 could be measured reliable in human breast cancer tissue specimens. Out of these, 60 appeared to be specific for the breast cancer tumor cells, i.e expression was over 10-fold higher when compared with the levels measured in the healthy blood donors. Next, the potential clinical applicability of these 60 differentially expressed miRNAs was validated on CTCs from a cohort of breast cancer patients with metastatic disease as detected by the CellSearch CTC test.
Conclusion: We consider our approach of great interest for the further characterization of CTCs, thereby improving insight into biological processes involved in cancer progression and ultimately patient management.

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Oral presentations (Tue, 22 Sep, 09:00−11:00)
Breast cancer II − Early disease

5008 ORAL

Minimal axillary lymph node involvement in breast cancer has different prognostic implications according to the staging procedure

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Purpose: It is still controversial whether the identification of micrometastases and isolated tumor cells in the axillary lymph nodes of patients with breast cancer has any prognostic value.
Patients and Methods: We evaluated the prognostic role of isolated tumor cells and micrometastases in the axillary lymph nodes in 3,158 consecutive patients (pT1−2 pN0-N1mi (with a single involved lymph node) and M0, referred to the Division of Medical Oncology after surgery performed at the European Institute of Oncology from April 1997 to December 2002. Median follow-up was 6.3 years (range 0.1−11 years).
Results: Sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND) were performed in 2,087 and 1,071 patients respectively. A worse metastasis-free survival (MFS) was observed for patients with micrometastatic disease compared to node negative patients, if staged with ALND (log-rank p < 0.0001; HR 3.17; 95% CI: 1.72−5.83 at multivariate analysis), but not for patients who underwent SLNB (log-rank p = 0.36).
Conclusion: The presence of a single micrometastatic lymph node is associated with a higher risk of distant recurrence as compared to node negative disease only for patients undergoing ALND for staging purposes. Treatment recommendations for systemic therapy should not take into account the presence of a single micrometastatic lymph node identified during complete serial sectioning of sentinel node(s).

5009 ORAL

Influence of isolated tumor cells in sentinel nodes on outcome in early pT1N0M0 breast cancer

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Aim: The aim of the study was to evaluate the prognostic significance of isolated tumor cells found in a sentinel node biopsy.
Patients and Methods: The study is based on a prospectively followed-up cohort of 1,865 consecutive patients diagnosed with invasive pT1 (tumor size $\leqslant$20 mm) breast cancer in one university breast unit between February 2001 and August 2005. Of the 1,390 patients who had received no neoadjuvant therapy and who underwent a sentinel node biopsy, 63 had isolated tumor cells in the sentinel nodes (stage pT1N0i+M0, verified by axillary node dissection), and 868 had not (pT1N0i-M0). The median follow-up time was 55 months.
Results: Patients with pN0i+ disease were treated more often with systemic adjuvant therapy than those with pN0i-disease (87% vs. 51%; $P < 0.0001$). There was no significant difference between the groups in 5-year recurrence-free survival (90.3% vs. 93.2%, respectively; $P = 0.32$) or overall survival, but patients with pN0i+ cancer had less favorable 5-year breast cancer-specific survival (95.2% vs. 98.4%; $P = 0.035$), and they were more frequently diagnosed with distant metastases from breast cancer (8.1% vs. 1.9%) during the first 5 years of follow-up ($P = 0.001$). Several