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CIRG/TORI 010: first analysis of a randomized phase II trial of motesanib plus weekly paclitaxel (P) as first line therapy in HER2-negative metastatic breast cancer (MBC)

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Background: Motesanib (M) is an oral tyrosine kinase inhibitor of VEGF, PDGF and Kit receptors. We assessed, in an ongoing double-blinded placebo-controlled trial, the effect of adding M to P as first line treatment of patients (pts) with MBC. A P plus bevacizumab (B) arm was included. The CIRG/TORI 010 study was supported by Amgen.
Methods: 282 pts with HER2-negative and measurable MBC were randomly assigned treatment with P 90 mg/m^2 on days 1, 8 and 15 in combination with blinded placebo (P: arm A), blinded M 125 mg once daily (PM: arm B) or open label B 10 mg/kg on days 1 and 15 (PB: arm C). Treatment was administered in 28-day cycles until disease progression, toxicity or consent withdrawal. The primary objective was to determine the difference in response rate (RR) between P and PM. Treatment efficacy was assessed every 8 weeks according to RECIST and scans were independently centrally reviewed.
Results: 277 pts received the assigned treatment. Pts characteristics at entry were balanced: median age was 55, 80% had hormone receptor positive tumors and 66% had received prior chemotherapy with curative intent. At the first planned analysis, 16 weeks after last patient enrolment, the median treatment duration was 6 cycles. The median cumulative dose of P was similar across the arms: 1328, 1282 and 1438 mg/m^2 in arm A, B and C, respectively. Pts received a median cumulative dose of B=133 mg/kg (arm C) and an averaged daily dose of M = 111 mg (arm B). The table displays the efficacy results and relevant differences in toxicities incidences (all grade).

	Arm A (P)	Arm B (PM)	Arm C (PB)
Efficacy (all pts)	**n = 94**	**n = 91**	**n = 97**
RR (95% CI)	35% (26−46)	48% (38−59)	45% (35−56)
Progression-Free Survival (95% CI)	8.0 mo (6.6−9.6)	9.1 mo (8.1−11.6)	10.1 mo (9.0−15.3)
Toxicity Incidence (% treated pts)	**n = 90**	**n = 91**	**n = 96**
Nausea	44	60	48
Diarrhea	33	69	42
Vomiting	24	40	23
Abdominal Pain	21	44	16
Stomatitis	11	15	29
Alopecia	63	59	71
Infections	54	55	66
Hypertension	13	57	30
Anorexia	16	35	25
Left Ventricular dysfunction	1	8	3
Hepatobiliary disorders	6	17	3
Back Pain	1415	23	
Peripheral Neuropathy	42	48	54

The RR favored PM and PB as compared with P but the differences were not statistically significant (p = 0.09, adjusting for stratification factors). The distributions of times to progression or death did not significantly differ between the three arms.
Conclusion: The administration of M in combination with weekly P is feasible with no unexpected toxicities. This regimen is efficacious in the treatment of pts with Her2-negative MBC.

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MoniCa: A multicenter phase II study to determine the efficacy of capecitabine as first line monochemotherapy in patients with HER2 negative, medium-risk, metastatic breast cancer (GBG39)

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Background: Monotherapy as first-line treatment in metastatic breast cancer (MBC) is indicated in patients (pts) with low-risk metastases e.g. without liver involvement, bone and lymph node metastasis only. The disease should be slowly progressing and not life threatening. So far, there are only limited data available on capecitabine (X) at a daily dose of 2000 mg/m^2 as first-line treatment in MBC.
Material and Methods: Pts with HER2-negative MBC without previous chemotherapy for metastatic disease, good performance status, and measurable disease according to WHO criteria could be enrolled. X was given intermittently at 1000 mg/m^2 bid on days 1−14 q3w. Treatment was continued until disease progression (PD), unacceptable toxicity, patients request or withdrawal from study. The primary endpoint was time to disease progression (TTP); secondary endpoints were objective response rate (ORR), duration of response, overall survival (OS), clinical benefit rate (CB, defined as CR, PR, or stable disease [SD] $\geqslant$24 weeks), safety and toxicity, and ORR in male pts. X was assumed to give median TTP of 30 weeks. To exclude a median TTP of $\leqslant$25 weeks with α=0.05, the total number of pts required was 200 assuming a dropout rate of 5%.
Results: From July 2005 to March 2008, 165 pts were recruited in 35 centres. The median age was 65 years (range 37−90). 53% of pts had hormone receptor-positive disease and 93% had HER2-negative disease. One male pt was included. The median number of cycles was 7 (range 1−39) with a medium follow up of 16 months. Seven pts are still receiving treatment. In 93 pts (56%) the dose was reduced or interrupted at least once. The median dose of X was 3500 mg per day (range 1594 to 4500 mg). The main reason for dose reduction or discontinuation was PD (71%). 69 SAEs were reported, the majority (33/69) due to underlying disease, including three fatal SAEs (myocardial infarction, cerebral bleeding and liver failure). The median TTP was 32.2 weeks (95% CI 29.58, 34.81). The best ORR was CR in 7.9%, PR in 17.6%, SD in 37% and PD in 27.9%. 3.6% of pts withdrew consent and in 6.1%, study therapy was discontinued at the investigator's decision.
Conclusion: This is the largest study investigating X with an up-to-date dosage as 1st-line monotherapy in MBC demonstrating an excellent safety and high efficacy profile despite the dose of 2000 mg/m^2. This seems especially attractive for elderly pts.

5003 ORAL

Phase II study of sunitinib in combination with trastuzumab for the treatment of metastatic breast cancer: activity and safety results

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Background: Sunitinib (SU) is an oral, multitargeted tyrosine kinase inhibitor of VEGFRs, PDGFRs, KIT, RET, FLT3, and CSF-1R, with proven single-agent activity in heavily pretreated metastatic breast cancer (MBC) pts. Trastuzumab (T) is approved as monotherapy for 2nd-line treatment (tx) and in combination with taxane-based therapies for 1st-line tx of MBC. This study [NCT00243503; Pfizer] investigates the combination of SU + T in HER2+ MBC pts.

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.

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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

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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.

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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