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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.

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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.