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Treatment of locally recurrent, unresectable or metastatic breast cancer with AMG 706 plus paclitaxel or docetaxel: results from a phase 1b study

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Background: AMG 706 is an oral, investigational inhibitor of angiogenesis with direct antitumor activity, achieved by selectively targeting VEGF, PDGF and Kit receptors. Inhibition of the VEGF pathway in combination with chemotherapy has shown promising activity in the treatment of advanced breast cancer.

Materials and Methods: This is an ongoing phase 1b, open-label, dose-finding study of AMG 706 with paclitaxel or docetaxel in patients (pts) with advanced breast cancer. Objectives are to establish the maximum tolerated dose (MTD); evaluate pharmacokinetics (PK); and assess safety and efficacy of AMG 706. Eligible pts are female $\geqslant$18 years with confirmed locally recurrent or metastatic breast cancer, ECOG 0 or 1, and $\leqslant$1 prior chemotherapy regimen for advanced breast cancer. Pts received escalating doses of AMG 706 (50 mg or 125 mg QD) continuously from day 3 of cycle 1 onward, plus (Arm A) paclitaxel (90 mg/m^2) on days 1, 8, and 15 of each 28-day cycle (Cohorts 1 and 2); or (Arm B) docetaxel on day 1 of each 21-day cycle (100 mg/m^2 [Cohorts 1 and 2] or 125 mg QD AMG 706 plus 75 mg/m^2 docetaxel [Cohort 3]). Assessments included safety, dose-limiting toxicities (DLT), PK, and objective response (OR) every 8 weeks (Arm A) or 6 weeks (Arm B).

Results: At the time of the data cut-off, 25 pts had received $\geqslant$1 dose of AMG 706 (Arm A/B, n = 8/17). The median age (range) was 52 (28–66) years. There was 1 DLT of grade 3 migraine: Arm B, Cohort 2. The MTD has not been reached. AMG 706 treatment-related adverse events (AE) were: any AE, Arm A/B 75/82% of pts (grade 3, 13/29%; there were no grade 4/5 AEs). Specific AEs included diarrhea 50/59% (grade 3, 0/6%), fatigue 25/24% (no grade 3), nausea 13/24% (no grade 3), anorexia 0/18% (no grade 3), headache 13/12% (no grade 3), and hypertension 13/12% (grade 3, 13/6%). Preliminary data showed that PK profiles for AMG 706, paclitaxel, and docetaxel were generally within the expected range. In pts evaluable for tumor response (Arm A/B n = 2/9), best OR was: PR n = 1/4; SD n = 1/5; durable SD $\geqslant$24 weeks n = 0/1; PD n = 0/0.

Conclusions: In this study of pts with advanced breast cancer, combination therapy of AMG 706 plus paclitaxel or docetaxel resulted in drug exposures that were within the expected range, and therapy was tolerable. Updated safety and efficacy data will be presented for all cohorts. A randomized phase 2 study of paclitaxel with or without AMG 706 is ongoing.

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The level of HER2/neu gene amplification as predictive factor in patients with metastatic breast cancer treated with a trastuzumab-based therapy

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Background: Trastuzumab (Herceptin®, Roche, Basel Switzerland, T), a humanized monoclonal antibody which selectively targets the HER2 protein extracellular domain, is the mainstay of treatment for patients (pts) with HER2-positive metastatic breast cancer (MBC). Fluorescence in-situ hybridization (FISH) is used to detect HER2 gene amplification and is considered the most reliable predictive factor to a T-based treatment. The FDA-approved PathVysion test for HER2 assessment is positive when HER-2/CEP17 ratio is >2 but in clinical practice it can be observed a wide variability in the ratio of amplification, whom clinicial significance is still unknown. To further investigate the clinical significance of different HER-2/CEP17 ratio, we performed FISH analysis, using PathVysion kit of all patients treated at our Institute with a trastuzumab-based regimen for HER-2 positive metastatic breast cancer.

Materials and Methods: We prospectively performed a FISH test using PathVysion® kit in all available tumor samples from the primary tumor or a metastatic lesion of pts treated at Istituto Clinico Humanitas and Cliniche Gavazzeni Oncology Departments from October 2001 to June 2006 with a T-based regimen for MBC. PathVysion FISH test includes a second probe for the centromeric region of chromosome 17 (CEP17) and allows a correction of the HER2 gene copy number to the number of copies of chromosome 17 (HER-2/CEP17 ratio). We further correlated the HER-2/CEP17 ratio obtained for each pt with some clinical outcome variables (TTP, time to CNS progression TTCNS, OS).

Results: Thirty-three pts with MBC were included in this study. Pts characteristics were: median age: 60 (range: 27–73); invasive ductal carcinoma: 31 (94%), visceral disease: 21 (67%). T was given in association with chemotherapy in 27 (82%) pts. Our results show that the number of HER2 gene copies increased the risk of disease progression with a correlation at limits of statistical significance, no significant correlation was observed with OS. In detail, at a median follow-up of 25 months, median TTP and OS were 10.3 and 20.3 months, respectively. Progression at CNS during T therapy was observed in 7 patients (21%), whereas 13 patients (39%) had a CNS progression during the entire course of disease with a median TTCNS progression of 9 months.

Conclusions: This is the first observation of a correlation between the level of HER2 amplification and TTP in pts treated with a trastuzumab-based therapy for MBC. If confirmed in larger cohorts of patients, HER-2/CEP17 ratio could represent a reliable, manageable and economical predictor of response to trastuzumab therapy.

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Breast cancer Disease Specific Array (DSA) – a platform for discovery of biomarkers from breast cancer derived FFPE tissue

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Background: Breast cancer is the second leading cause of cancer deaths in women today. It is the most common cancer among women, excluding nonmelanoma skin cancers. It is therefore a subject of extensive research focused on identification of reliable genomics biomarkers to aid in accurate classification of the disease, predicting its progression and patients' response to both available therapies and those in development. DNA microarrays are a powerful tool for global analysis of gene transcript expression and they have in recent years become, one of the key elements of biological research. Currently available commercial microarray design tends to focus on the best-categorised and most commonly known genes from all body tissues. Therefore these powerful genomic tools are lacking in disease focus, and only a subset of genes on a generic array will yield biologically meaningful results in any given tissue specific study, potentially missing vital information contained in patients samples.

Materials and Methods: Through a combination of large-scale in-house sequencing, gene expression profiling and public sequence and gene expression data mining we have characterised the transcriptome of breast cancer and used this information to create a unique disease focused microarray – the Breast Cancer DSA™. It has been designed and manufactured using the microarray technology of the Affymetrix GeneChip™ platform.

Results: The Breast Cancer DSA™ allows for interrogation of ~60,000 transcripts relevant to breast cancer, tens of thousands of which are unavailable on leading commercial microarrays. In addition to the unique content, this high density DSA™ is designed to focus on interrogating sequences located close to the 3′ end of the transcript, which enables the optimised determination of gene expression from FFPE tissue. Presented here are the array design process and the results of experiments carried out to demonstrate the array's utility in identification of transcripts that are important diagnostically

Conclusion: The Breast Cancer DSA™ research tool is an innovative microarray platform that represents the transcriptome in both normal and cancerous tissues that has been optimized for analysis of FFPE samples enabling the use of these valuable archived tissue banks.