2. Synopsis

Abbreviated Clinical Study Report Synopsis: Study H3E-MC-S080(a)

Title of Study: A Randomized Phase 2 Trial of Doxorubicin plus Pemetrexed followed by Docetaxel, versus Doxorubicin plus Cyclophosphamide followed by Docetaxel, as Neoadjuvant Treatment for Early Breast Cancer	
Investigator(s): This multicenter study included 12 principal investigators and 17 enrolling sites including subinvestigators.	
Study Center(s): This study was conducted at 17 study center(s) in four countries.	
Publication(s) Based on the Study: Schneeweiss A, Lauschner I, Ruiz A, Sánchez-Rovira P, Segui M, Goerke K, Wolf M, Manikhas A, Wacker J, Marmé F, Lichter P, Sinn H, Sohn C, Mansouri K, Bauknecht T, Hahn M: Doxorubicin/Pemetrexed Followed by Docetaxel Versus Doxorubicin/Cyclophosphamide Followed by Docetaxel as Neoadjuvant Treatment for Early-Stage Breast Cancer: A Randomized Phase II Trial, Clinical Breast Cancer, April 2007: 555-558. Schneeweiss A, Ruiz A, Rovira P, Bottini A, Manikhas A, Wacker J, Schumacher T, Wolf M, Segui M, Sinn P, Kennedy L, Mansouri K, Bauknecht T. 2009. Results of clinical endpoints of a randomized phase II trial with doxorubicin + pemetrexed followed by docetaxel versus doxorubicin + cyclophosphamide followed by docetaxel as primary systemic therapy for early breast cancer. The Breast, Vol 18, Suppl 1, March 2009, p S63. Abstract nr. 0178	
Length of Study: Date of first patient enrolled: 08. September 2005 Date of last required visit for the main analysis: 11. February 2008	**Phase of Development:** 2
Objectives: Primary Objective: The primary objective of the study is to assess the antitumor activity, as measured by the pathologic complete response (pCR) rate in the breast, of neoadjuvant treatment with two different sequential treatment regimens (AP-Doc, AC-Doc) in female patients with early breast cancer (T2-T4/N0-N2/M0). Secondary Objectives: • To assess the clinical response rates after the first and second sequence of chemotherapy in both treatment arms in this patient population. • To assess the rate of histologically negative axillary lymph node status in both treatment arms. • To assess disease-free survival in both treatment arms. • To characterize the quantitative and qualitative toxicities of both treatment arms in this patient population.	
Study Design: This is an open-label, randomized, multicenter trial to evaluate two different sequential neoadjuvant combination treatments administered every 21 days in female in- and outpatients with primary, operable breast cancer (T2-4/N0-2/M0).	

Number of Patients:
Planned: 128 per treatment group
Entered: 276
Randomized: 135 AP-Doc (experimental arm), 122 AC-Doc (standard arm)
Treated 134 AP-Doc (experimental arm, 123 AC-Doc (standard arm)
Completed 8 cycles: 110 AP-Doc, 107 AC-Doc

Diagnosis and Main Criteria for Inclusion:
Female patients having a histologically confirmed diagnosis of primary invasive early breast cancer, with a tumor size ≥ 2 cm of stages T2-T4, N0-N2, and M0, at least 18 years but no more than 70 years of age.

Test Product, Dose, and Mode of Administration: Doxorubicin 60 mg/m^2, pemetrexed 500 mg/m^2, given on day 1 of 4 three-weekly cycles as intravenous infusion, followed by 4 three-weekly cycles of docetaxel 100 mg/m^2 (AP-Doc).

Duration of Treatment: 24 weeks

Reference Therapy, Dose, and Mode of Administration: Doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2, given on day 1 of 4 three-weekly cycles as intravenous infusion, followed by 4 three-weekly cycles of docetaxel 100 mg/m^2 (AC-Doc).

Methods:
Statistical: The primary objective of this clinical trial is to estimate the antitumor activity, as measured by the pathological complete response (pCR) rate, of neoadjuvant treatment with either doxorubicin + pemetrexed followed by docetaxel (regimen A), or doxorubicin + cyclophosphamide (AC) followed by docetaxel (regimen B). This is a randomized, two-stage sequential open-label treatment phase 2 study. All confidence intervals for parameters to be estimated will be constructed with a significance level of $\alpha = 0.05$.
A two-stage design was employed independently for each of the both arms, with the possibility of stopping each treatment early for lack of efficacy (Simon 1989). For the first stage, 42 protocol-qualified patients were evaluated per treatment arm immediately after pCR data had been available for these patients. Enrollment continued without interruption until the first-stage evaluation. If fewer than or equal to 4 out of the 42 patients showed pCR to the investigational regimen, the accrual for this regimen would have been stopped and the conclusion would have been drawn that this regimen is not worthy of further study in this tumor type, unless other tumor-specific clinical considerations suggest otherwise. If more than 4 patients responded, accrual would continue until 121 qualified patients would have been enrolled. If, at the end of stage 2, fewer than or equal to 17 out of 121 patients responded, this regimen would be deemed not worthy of any further investigation in this patient population, unless clinical considerations suggest otherwise.
Bioanalytical: Results on a companion protocol for pharmacogenomic analysis of tumor tissue samples will be reported separately.

Summary:
257 female patients with histologically confirmed diagnosis of primary invasive early breast cancer in stages T2-T4 (tumor size ≥2 cm), N0-N2 and M0 were included into this trial. They were at least 18 years but no more than 70 years of age.
The pCR rate in the qualified patients (N = 246) was **16.5%** (95% CI: 10.5–24.2) in AP-Doc (N = 127) and **20.2%** (95% CI: 13.4–28.5) in the AC-Doc (N = 119). As for secondary objectives, results are presented in table S080.2.1.

Table S080.2.1. Results of Secondary Study Objectives

	AP-Doc (n/N, %)	AC-Doc (n/N; %)
Clinical response rate (CR+PR) at cycle 4	53/131 (40.5%)	52/119 (43.7%)
Clinical response rate (CR+PR) at cycle 8	78/131 (59.5%)	81/119 (68.1%)
CR	19/131 (14.5%)	21/119 (17.6%)
PR	59/131 (45.0%)	60/119 (50.4%)
Histologically negative axillary lymphnodes	67/127 (52.8%)	63/119 (52.9%)
Disease-free survival	Censoring rate 91.1% (Min 8.1, Max 107 weeks)	Censoring rate 92.6% (Min 10.1, Max 132 weeks)

The overall safety profile of both treatment arms was predictable and corresponded to the known profile of the applied compounds. No death occurred. Serious adverse events occured in more patients receiving AC-Doc (24/123; 19.5%) than in AP-Doc (15/134; 11.2%). Most common SAEs experienced by number of patients in each treatment arms were leukopenia, febrile neutropenia and pyrexia. Twelve patients in AP-Doc (9.0%) discontinued treatment due to adverse events, for 11 patients (8.2%) these AEs were judged as possibly study drug related. Nine patients in AC-Doc discontinued treatment due to adverse events (7.3%), for 7 patients (5.7%) AEs were seen as possibly study drug related. No clinically relevant or significant changes in laboratory values occurred.

Conclusions:

Primary Endpoint:

- AP-Doc and AC-Doc were active and showed a pCR rate comparable to pCR rates of other published neoadjuvant regimen.

Secondary Endpoints:

- Clinical Response Rates after first and second sequence showed comparable data to other neoadjuvant regimen.
- Histologically negative axillary lymph node status was similar in both arms.
- Data on disease-free survival are not mature yet.
- AP-Doc seems to be a safe combination chemotherapy with a low incidence of clinically significant side effects in the neoadjuvant setting in early breast cancer patients, overall showing comparable results to AC-Doc.

Of note, in the hormone receptor positive subgroup of patients, AP-Doc seems to be of advantage according to a published meta-analysis in neoadjuvant chemotherapy treatments. This interesting finding should be further evaluated in a phase 3 trial covering an unmet medical need to improve the outcome of chemotherapy in hormone receptor positive early breast cancer.