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Sponsor/company: sanofi-aventis	clinicaltrials.gov Identifier: NCT00174707
	Study Code: TAX_IT1_302
Generic drug name: Docetaxel	Date: 28/Jul/2009

Title of the study:	A Phase III Randomized Study of Sequential Epidoxorubicin followed by CMF (Arm A) Versus Sequential Epidoxorubicin followed by Docetaxel followed by CMF (Arm B) Versus Sequential Intensified Epidoxorubicin followed by Docetaxel followed by High-Dose Cyclophosphamide (Arm C) in Early Breast Cancer Patients with Positive Axillary Lymph Nodes
Investigator(s):	Coordinating Investigator: Prof. Sabino De Placido, Cattedra di Oncologia Medica, Dipartimento di Endocrinologia ed Oncologia Molecolare e Clinica, Università degli Studi Federico II, Via S. Pansini 5, 80131 Naples Italy
Study center(s):	47 centers in Italy
Publications (reference):	De Laurentiis M. Sequential epirubicin-docetaxel-CMF regimen as adjuvant therapy of early breast cancer: Preliminary results of the Taxit-216 multicenter phase III trial. Proc Am Soc Clin Oncol 22: 2003 (abstr 115). Bianco AR, de Matteis A, Manzione L et al. Sequential epirubicin-docetaxel-CMF as adjuvant therapy of early breast cancer: results of the Taxit 216 multicentre phase III trial. Proc Am Soc Clin Oncol 2006; 24: 7S (Abstr 520).

Study period: Date first patient enrolled: 15-12-1997 Date last patient completed: 31-12-2007	Phase of development: III

Objectives:	Primary objective To compare the disease free survival (DFS) in patients treated with the sequential epidoxorubicin→CMF regimen to that in patients treated with the same treatment plus docetaxel given sequentially after epidoxorubicin. Secondary objectives • To compare the DFS in patients treated with sequential epidoxorubicin→ docetaxel →CMF (only patients with > 4 lymph nodes) regimen to that in patients treated with sequential intensified epidoxorubicin→docetaxel→high dose cyclophosphamide regimen. • To evaluate the overall survival in each arm. • To evaluate the tolerability of a sequential intensified epidoxorubicin→docetaxel→HD-cyclophosphamide (arm C). • To compare the safety of a sequential epidoxorubicin→docetaxel→CMF (arm B) regimen versus a standard sequential epidoxorubicin→CMFregimen (arm A).
Methodology:	Multicenter open-label phase III randomized study

Number of patients:	Planned: 914 pts (397 in Arm A, 397 in Arm B, and 120 in arm C)	Randomized: 998 pts (arm A 486; arm B 486; arm C 26)	Treated: 953 pts (arm A 478; arm B 475, arm C closed early, but 26 patients were treated).
Evaluated:	Efficacy: All subjects receiving at least one treatment dose were considered evaluable for efficacy analyses.	Safety: All patients who received some treatment were considered evaluable for toxicity analyses.	
Diagnosis and criteria for inclusion:	Node-positive breast cancer at first diagnosis. Age ≥ 18 years and ≤ 70 years. Mastectomy or breast conserving surgery, with axillary lymph node dissection for operable breast cancer (T1-3, N1, M0). Surgical procedures completed within 4-6 weeks before randomization. Normal left ventricular ejection fraction (LVEF).		
Investigational product: Dose:	Sequential Epidoxorubicin→Docetaxel→CMF (E → T →CMF) ± TAM (Arm B) Patients received epidoxorubicin 120 mg/m² every 3 weeks (for a total of 4 courses) followed by docetaxel 100 mg/m² one hour i.v. infusion every 3 weeks (for a total of 4 courses) followed by CMF i.v. d 1, 8 (for a total of 4 courses) every 4 weeks. After completion of chemotherapy, Tamoxifen was administered (dose: 20 mg os qd; duration: 5 years; patients: premenopausal ER+ or ER unknown; postmenopausal ER+, ER- or ER unknown).		
Duration of treatment: 40 weeks (arm B) and 28 weeks (arm A)		Duration of observation: 5 years	
Reference therapy:	Sequential Epidoxorubicin→CMF (E→CMF) ±TAM (Arm A) Patients received epidoxorubicin 120 mg/m² (for a total of 4 courses) every 3 weeks followed by CMF i.v. d 1, 8 (for a total of 4 courses) every 4 weeks. After completion of chemotherapy, Tamoxifen was administered (dose: 20 mg os qd; duration: 5 years; patients: premenopausal ER+ or ER unknown; postmenopausal ER+, ER- or ER unknown). Sequential Intensified Epidoxorubicin→Docetaxel →HD-Cyclophosphamide (E_i → T → C_{hd}) (± TAM) (Arm C)* Patients receive epidoxorubicin 120 mg/m² every 2 weeks (for a total of 4 courses) followed by docetaxel 100 mg/m² one hour i.v. infusion every 2 weeks (for a total of 4 courses) followed by cyclophosphamide 3000 mg/m² i.v. (for a total of 3 courses) every 3 weeks. After completion of chemotherapy, Tamoxifen was administered (dose: 20 mg os qd; duration: 5 years; patients: premenopausal ER+ or ER unknown; postmenopausal ER+, ER- or ER unknown). * Arm C was closed after recruitment of 26 patients because toxicity rules allowed by the protocol were exceeded.		

Criteria for evaluation:	
Efficacy	Primary endpoint: Invasive disease free survival (IDFS) Secondary endpoints: Overall survival (OS), and recurrence-free survival (RFS)
Safety:	Occurrence of hematological and non hematological toxicities graded according to NCI criteria, from mild to life threatening. Adverse events reported by the patient or noted by the investigator.
Statistical methods:	All efficacy analyses were done on an 'as randomized' basis (intent-to-treat strategy). All subjects receiving at least one treatment dose were considered evaluable for efficacy analyses. Efficacy results were reported for IDFS, OS and RFS according to the Standardized Definitions for Efficacy End Points (STEEP) system. According to the data archive structure, the following hierarchical strategy was applied to derive the censoring times when the main endpoint was not observed: Date to loss to follow-up or withdrawal, if available, otherwise Date to last assessment, if available, otherwise Date to last available cycle of therapy, if available, otherwise Date of randomization All time-to-events curves were estimated with Kaplan-Meier (K-M) product limit, and statistical significance was assessed with 2-sided log-rank test. Adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) were estimated using a Cox proportional hazards model that included treatment, lymph node metastases (1-3, 4-9, 10+), ER status (negative, positive, unknown) and menopausal status (pre/post) as covariates. Although originally scheduled, interim analyses were in fact not performed. Toxicity analyses were done on an 'as treated' basis. All patients who received some treatment were considered evaluable for toxicity analyses. Statistical analysis of toxicity was done in two ways. First, an exact linear permutation test was applied to acknowledge the ordinal nature of toxicity grades (Cytel 7 software). Second, an exact chi-square test was applied comparing severe (grades 3 to 4) versus not severe (grades 0 to 2) toxicity. Compliance to treatment was reported both on a per patient and on a per cycle basis, according to treatment actually received, and the analysis was only descriptive.
Summary:	Between December 1997 and July 2002, 972 patients were randomized (486 in arm A and 486 in arm B). After inclusion of 26 patients in arm C, a planned safety analysis was conducted to evaluate the feasibility of the dose-intensified treatment. All feasibility rules were met except for grade 4 skin toxicity in two patients, which led to early closure of arm C. Consequently, no efficacy results are reported for this arm.

Efficacy results:

At the date of conclusion of this study, 142 patients had died and the median follow-up was 62 months. A total of 278 IDFS events had occurred (see Table). IDFS was better in the experimental arm (B), although the difference did not reach statistical significance (log-rank *P* = .134). The estimated probability of not having any IDFS event at 5 years was 74% for arm B and 68% for arm A (HR = 0.82, 95% CI = 0.64 to 1.03; *P* = .1337). The estimated probability of being recurrence-free at 5 years was significantly better for arm B than for arm A (76% *vs* 69%, respectively; HR = 0.75, 95% CI = 0.59 to 0.96; *P* = .0332). There was a statistically significant improvement of OS, with an estimated probability of being alive at 5 years of 90% for arm B and 85% for arm A (HR = 0.67, 95% CI = 0.48 to 0.94; *P* = .0168). Multivariate analyses that included treatment, lymph node metastases, ER status and menopausal status as covariates confirmed these results.

Patients with first invasive disease-free survival events

	Arm A E →CMF (total 486) n. (%)	Arm B E → T →CMF (total 486) n. (%)
Breast cancer relapse	139 (28.6)	108 (22.2)
Loco\regional	25 (5.1)	19 (3.9)
Distant	114 (23.5)	89 (18.3)
Death	5 (1.0)	7 (1.4)
Second primary cancer	5 (1.0)	14 (2.9)
Breast	1 (0.2)	3 (0.6)
Other	4 (0.8)	11 (2.3)
Total IDFS events	149 (30.7)	129 (26.5)
None (event-free patients)	337 (69.3)	357 (73.5)

Safety results:

As shown in the Table below, in both arms, grade 3-4 neutropenia rates were higher than usually reported in similar studies (84.4% and 90.2% in arms A and B, respectively; *P* = .009). However, when the analysis of neutropenia was limited to laboratory values recorded on the day of chemotherapy (day 21 for epirubicin and docetaxel, and day 28 for CMF), grade 3-4 neutropenia rates decreased to 10.4% and 12.4% in arms A and B, respectively, and the difference was no longer significant (*P* = .42). The rate of febrile neutropenia was significantly higher in the experimental arm (11.6% *vs* 6.2%). Severe anemia and thrombocytopenia were uncommon.

Hematological toxicity: grade 3-4 events according to treatment arm

	Arm A E→CMF n. (%)	Arm B E→T→CMF n. (%)	*P**
Neutropenia at nadir	406 (84.4)	434 (90.2)	0.0087
Neutropenia at recycling	50 (10.4)	59 (12.4)	0.4158
Febrile neutropenia	30 (6.2)	56 (11.6)	0.0032
Anemia	10 (2.1)	12 (2.5)	0.6739
Thrombocytopenia	11 (2.3)	11 (2.3)	0.9999
Leucopenia	244 (50.6)	315 (65.5)	<0.0001

Grade 3-4 nonhematologic adverse events are reported in the table below.

Non hematological toxicity: grade 3-4 events according to treatment arm

	Arm A E → CMF n. (%)	Arm B E → T →CMF n. (%)	*P**
Allergy	0 (0.0)	8 (1.6)	0.0037
Arthralgia	1 (0.2)	6 (1.2)	0.0689
Asthenia	12 (2.5)	31 (6.4)	0.0029
Cardiac arrhythmias	0 (0.0)	0 (0.0)	0.9999
Cardiac function	0 (0.0)	1 (0.2)	0.499
Cardiac ischemia	1 (0.2)	0 (0.0)	0.9999
Cardiac pericardial	0 (0.0)	0 (0.0)	0.9999
Diarrhea	5 (1.0)	22 (4.5)	<0.0001
Local toxicity	2 (0.4)	3 (0.6)	0.6862
Myalgia	0 (0.0)	7 (1.5)	0.0075
Nail disorders	0 (0.0)	8 (1.7)	0.0037
Nausea	23 (4.7)	34 (7.0)	0.1353
Neuromotor	0 (0.0)	5 (1.0)	0.0306
Neurosensory	0 (0.0)	5 (1.0)	0.0306
Pain	0 (0.0)	4 (0.8)	0.0616
Peripheral edema	0 (0.0)	3 (0.6)	0.1238
Pulmonary	2 (0.4)	2 (0.4)	0.9999
Skin	0 (0.0)	15 (3.1)	<0.0001
Stomatitis	30 (6.2)	46 (9.5)	0.0565
Vomiting	25 (5.2)	35 (7.2)	0.1851
Weight gain	1 (0.2)	1 (0.2)	0.9999

One toxic death was recorded in the experimental arm, which was probably due to typhilitis.
*Fisher's exact test

As previously stated, arm C was closed early because toxicity rules allowed by the protocol were exceeded. The following two tables show the non hematologic and hematologic toxicity data for arm C.

Worst grade non hematological toxicity in arm C (n=25)*

	0	1	2	3	4
Allergy	25 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Alopecia	0 (0)	2 (8)	23 (92)		
Amenorrhea ≥ 3 months ^	12 (92.3)	1 (7.7)			
Irregular menses ^	12 (92.3)	1 (7.7)			
Arthralgia	11 (44)	12 (48)	1 (4)	1 (4)	0 (0)
Asthenia	7 (28)	13 (52)	5 (20)	0 (0)	0 (0)
Cardiac arrhythmias	24 (96)	1 (4)	0 (0)	0 (0)	0 (0)
Cardiac Function	25 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Cardiac Ischemia	25 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Cardiac Pericardial	25 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhea	17 (68)	5 (20)	2 (8)	1 (4)	0 (0)
Local toxicity	25 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Myalgia	16 (64)	7 (28)	2 (8)	0 (0)	0 (0)
Nail disorders	14 (56)	8 (32)	2 (8)	1 (4)	0 (0)
Nausea	3 (12)	14 (56)	7 (28)	1 (4)	0 (0)
Neuromotor	24 (96)	1 (4)	0 (0)	0 (0)	0 (0)
Neurosensory	17 (68)	5 (20)	3 (12)	0 (0)	0 (0)
Pain	19 (76)	4 (16)	2 (8)	0 (0)	0 (0)
Peripheral edema	19 (76)	2 (8)	3 (12)	1 (4)	0 (0)
Pulmonary	23 (92)	1 (4)	1 (4)	0 (0)	0 (0)
Skin	12 (48)	2 (8)	3 (12)	6 (24)	2 (8)
Stomatitis	7 (28)	8 (32)	6 (24)	4 (16)	0 (0)
Vomiting	9 (36)	7 (28)	8 (32)	1 (4)	0 (0)
Weight gain	23 (92)	1 (4)	0 (0)	1 (4)	0 (0)

*One patient did not start treatment; ^premenopausal only

Worst degree of hematological toxicity in arm C (n=25)

	0	1	2	3	4
Neutropenia	0 (0)	0 (0)	6 (24)	6 (24)	13 (52)
Anemia	0 (0)	1 (4)	19 (76)	4 (16)	1 (4)
Thrombocytopenia	6 (24)	15 (60)	3 (12)	1 (4)	0 (0)
Leucopenia	0 (0)	2 (8)	6 (24)	7 (28)	10 (40)
Febrile neutropenia	17 (68)	-	-	-	8 (32)

Date of report:	22-JUL-2009