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Sponsor / Company: Sanofi **Drug Substance:** Docetaxel (XRP6976)	**Study Identifiers:** NCT00174655 **Study Code:** RP56976_V-315 (RP56976_PR_315) (XRP6976D-315)

Title of the study: An Intergroup Phase III Trial to Evaluate the Activity of Docetaxel, Given Either Sequentially or in Combination with Doxorubicin, Followed by CMF, in Comparison to Doxorubicin Alone or in Combination with Cyclophosphamide, Followed by CMF, in the Adjuvant Treatment of Node-positive Breast Cancer Patients

Study center(s): International multicenter study with 9 study groups involving 172 centers in 21 countries:

- Coordinating cooperative group (countries): BR.E.A.S.T. (Belgium, Brazil, Czech republic, Germany, Israel, Italy, Portugal, Slovakia, South Africa)
- Other groups(countries): ABCSG (Austria), ANZ-BCTG (Australia and New Zealand),k DBCZG (Denmark), GEICAM (Spain), ZGOCCHI (Chile), IBCSG (Hungary, Italy, Spain, Slovenia, Sweden, Switzerland and South Africa), ICORG (Ireland), and SBCG (Sweden)

The number of randomized patients/country (no. patients): Australia/New Zealand (605), Austria (174), Belgium (334),Brazil (87), Chile (67), Czech Republic (27), Denmark (156), Germany (56), Hungary (109), Ireland (190), Israel (82), Italy (169), Portugal (22), Slovakia (31), Slovenia (19), South Africa (115), Spain (240), Sweden (202), Switzerland (143), and United Kingdom (59)

Study period:

Date first patient enrolled: **10 June 1998**

Date last patient completed (median 10.06-year follow-up): **06 Sep 2011**

Phase of development: Phase 3

Objectives: Primary objective was to compare Disease-Free Survival (DFS) of an adjuvant treatment with docetaxel given either sequentially (B) or in combination (C) with doxorubicin and followed by cyclophosphamide/methotrexate/5-fluorouracil (CMF) to doxorubicin alone (A1) or in combination (A2) with cyclophosphamide and followed by CMF in operable breast cancer patients with positive axillary lymph nodes (B+C) versus (A1 + A2).

The secondary objectives were:

- To compare DFS of an adjuvant treatment with doxorubicin followed by docetaxel followed by CMF to doxorubicin followed by CMF in operable breast cancer patients with positive axillary lymph nodes (B versus A1).
- To compare DFS of an adjuvant treatment with docetaxel in combination with doxorubicin followed by CMF to doxorubicin in combination with cyclophosphamide followed by CMF in operable breast cancer patients with positive axillary lymph nodes (C versus A2).
- To compare DFS of an adjuvant treatment with doxorubicin followed by docetaxel followed by CMF to doxorubicin in combination with docetaxel followed by CMF in operable breast cancer patients with positive axillary lymph nodes (sequential monochemotherapy versus polychemotherapy) (B versus C).
- To compare Overall Survival (OS) of treatment arms.
- To compare toxicity of treatment arms.
- To evaluate pathologic and molecular markers for predicting efficacy (Note: results are not reported here, they were previously reported as an oral presentation).
- Socioeconomic data were collected in order to be able to perform a socioeconomic analysis by country, when needed.

Methodology: This was a randomized, non-blinded, Phase 3, 4-arm study including 2 control arms of sequential (A1) or combined/concurrent (A2) drug administration and 2 experimental arms of sequential (B) or combined/concurrent (C) docetaxel administration. Randomization was 1:1:2:2 (1:1 control arms: 2:2 experimental arms). Treatment was for 24 weeks for arms A1, A2 and C and 30 weeks for arm B. This report presents final efficacy and safety results for the median follow-up period of 10 years.

Sequential arms:

Arm A1 (control): 4 (21-day) cycles A → 3 (28-day) cycles CMF (referred to as group A)

Arm B (test): 3 cycles (21-day) A → 3 (21-day) cycles T → 3 (28-day) cycles CMF (referred to as group A-T)

Combined/concurrent arms:

Arm A2 (control): 4 (21-day) cycles AC → 3 cycles (28-day) CMF (referred to as group AC)

Arm C (test): 4 (21-day) cycles AT → 3 (28-day) cycles CMF (referred to as group AT)

Where
A = doxorubicin (75 mg/m^2) IV
AC = doxorubicin + cyclophosphamide (60/600 mg/m^2) IV
T = docetaxel (100 mg/m^2) IV
AT = doxorubicin + docetaxel (50/75 mg/m^2) IV
CMF = oral cyclophosphamide 100 mg/m^2 from Day 1 to Day 14; methotrexate IV 40 mg/m^2 Day 1 & Day 8; fluorouracil IV 600 mg/m^2 Day 1 & Day 8.

Number of patients:

Planned: 2730 patients (455 patients arm A; 455 patients arm AC; 910 patients arm A-T; 910 patients arm AT)

Randomized: 2887 (481 arm A; 487 arm AC; 960 arm A-T; 959 arm AT)

Treated: 2865 (472 arm A; 485 arm AC; 950 arm A-T; 958 arm AT)

Evaluated at 10.1 years:

Efficacy (intent-to-treat [ITT]): 2887 (481 arm A; 487 arm AC; [968 A + AC]; 960 arm A-T; 959 arm AT; [1919 A-T + AT])

Safety: 2865 (472 arm A; 485 arm AC; [957 A + AC]; 950 arm A-T; 958 arm AT; [1908 A-T + AT])

Diagnosis and criteria for inclusion: Women 18 to 70 years of age with histologically proven, node-positive, operable breast cancer clinical stage T1-3 with clear margins following either mastectomy or breast conservation surgery with axillary lymph node dissection.

Study treatment

Investigational medicinal product: Docetaxel

Formulation: Commercially available

Route(s) of administration: IV

Dose regimen:
100 mg/m^2, 1 hour infusion Day 1 q21 days for 3 cycles (following doxorubicin)(Arm A-T)
75 mg/m^2, 1 hour infusion (1 hour after doxorubicin), Day 1 q21 days for 4 cycles (Arm AT)

Noninvestigational medicinal product(s): Doxorubicin, cyclophosphamide, methotrexate, 5-fluorouracil

Formulations: Commercially available products

Dose regimens:
Doxorubicin:

75 mg/m^2 IV Day 1 q21 days for 4 cycles (Arm A)
75 mg/m2 IV Day 1q21days for 3 cycles (Arm A-T)
60 mg/m^2 IV Day 1 q21 days for 4 cycles (Arm AC)
50 mg/m^2 IV Day 1 q21 days for 4 cycles (Arm AT)

Cyclophosphamide:

600 mg/m^2 IV Day 1 q21 days for 4 cycles (Arm AC)

CMF (following chemotherapy in all arms) for 3 cycles:

cyclophosphamide 100 mg/m^2 PO (oral) Days 1-14
methotrexate 40 mg/m^2 IV Days 1 and 8
5-FU 600 mg/m^2 IV Days 1 and 8 q28 days

Duration of treatment: Arms A, AC, and AT: 24 weeks; Arm A-T: 30 weeks

Duration of observation: 10 years from date of randomization

Criteria for evaluation:

Efficacy: Disease-free survival (DFS) and overall survival (OS) at 10 years follow-up

Safety:

- Adverse events assessed according to the National Cancer Institute (NCI) common toxicity criteria (CTC), version 1
- Toxicity severities that could not be graded using NCI CTC were graded by COSTART as mild (asymptomatic), moderate (symptomatic but not interfering significantly with function), severe (causing significant interference with function), or life-threatening
- Late side effects, included toxic deaths, cardiac toxicities, hematological toxicities, second primary malignancies, fluid retention.

Statistical methods:

Efficacy analyses in the ITT population were intended as confirmatory analyses for 5- and 8-year results.

Categorical data were summarized in contingency tables presenting frequencies and appropriate percentages. Continuous data were summarized using frequency (n), median (if n ≥ 3), minimal and maximal values, and the mean and the standard error (or deviation), when relevant. Descriptive analyses were summarized by treatment group and overall. For categorical data, the chi-square test was used to compare proportions. To test association adjusting for stratification variables, the Cochran-Mantel-Haenszel test was used. The 95% confidence interval (CI) for proportions was calculated. Comparisons of ordinal variables between the treatment groups were performed using the nonparametric Wilcoxon test.

Unless otherwise specified, statistical tests were two-sided at a significance level of 5%. Efficacy and safety analyses were performed, respectively, on the intent-to-treat (ITT) and the Safety populations. The primary efficacy endpoint (DFS) was evaluated using logrank test. The Closed Testing Procedure principle was used: ([A-T +AT] versus [A +AC]) was tested first at the one-sided 2.5% level; if significant, then (A-T versus A), (AT versus AC), and (A-T versus AT) were tested.

Summary:

Among the 2887 randomized patients in the ITT population, 968 patients were in the combined control group (A + AC) and 1919 patients were in the combined docetaxel group (A-T + AT) control groups. A total of 2865 patients were treated with study medication and included in the Safety population as follows: 472 patients in the A group, 485 patients in the AC group, 950 patients in the A-T group, and 958 patients in the AT group.

Demographics and baseline disease characteristics (ITT Population)

	A n=481	**AC N=487**	**A-T N=960**	**AT N=959**
Age (Stratification factor) (%)				
< 50 years	53%	55%	53%	53%
≥ 50 years	47%	45%	47%	47%
No. positive nodes (%)				
1-3 (Stratification factor)	54%	55%	54%	54%
4 or more	46%	45%	46%	46%
Hormone Receptors (%)				
ER and/or PR	75%	75%	75%	77%
ER and PR negative	25%	25%	24%	23%
Menopausal status (%)				
Premenopausal	53%	54%	53%	55%
Postmenopausal	41%	40%	42%	40%
Other	5%	6%	6%	5%
Tumor size (%)				
pT1-2	93%	92%	93%	91%
pT3	6%	7%	7%	8%
Most recent breast surgery (%)				
Breast conserving	42%	40%	42%	38%
Mastectomy	53%	55%	54%	56%
Other	5%	5%	4%	6%

Efficacy results:

Hazard ratios (HR) for Disease Free Survival and Overall Survival indicated that at a median of 10.1 years follow-up it was possible to still observe some benefit of docetaxel treatment regardless of sequence of administration compared with control doxorubicin + CMF treatment in patients with node-positive breast cancer (p=.163). Hazard ratios also indicated some benefit for sequential docetaxel compared with sequential control treatment, concurrent docetaxel compared with concurrent control treatment, and sequential docetaxel treatment compared with concurrent docetaxel treatment.

DFS Hazard Ratios (HR) (ITT population)					
Comparison	**No. patients per group**	**Total No. patients**	**Treatment comparison**	**HR (95% CI)[a]**	**P value [b]**
Primary comparison					
Docetaxel vs control	1919 vs 968	2887	(A-T + AT) vs (A + AC)	0.91 [c] (0.81 to 1.04)	.163
Secondary comparisons[d]					
Sequential docetaxel vs sequential control	960 vs 481	1441	A-T vs A	0.86 [e](0.72 to 1.03)	.109
Concurrent docetaxel vs concurrent control	959 vs 487	1446	AT vs AC	0.96 (0.81 to 1.15)	.686
Sequential docetaxel vs concurrent docetaxel	960 vs 959	1919	A-T vs AT	0.88 (0.76 to 1.02)	Not planned [f]

a The primary comparison was stratified for number of positive lymph nodes, age at random assignment to treatment, and schedule of drug administration.

b Stratified two-sided log rank test.

c For the primary comparison: in the hormone receptor – positive subgroup, HR = 0.92 (95% CI = 0.79 to 1.07); in the hormone receptor-negative subgroup, HR = 0.93 (95% CI = 0.74 to 1.17).

d As per closed testing procedure, secondary comparisons p values are to be considered only if primary comparison is statistically significant.

e For the secondary sequential comparison: the hormone receptor – positive subgroup, HR = 0.86 (95% CI = 0.70 to 1.07); in the hormone receptor-negative subgroup, HR = 0.87 (95% CI = 0.62 to 1.22). In the subgroup with one to three positive lymph nodes, HR = 1.02 (95% CI = 0.76 to 1.38); in the subgroup with four or more positive lymph nodes, HR = 0.78 (95% CI = 0.62 to 0.98).

f This comparison evaluated whether both treatment groups were equivalent, by use of the two-sided 95% confidence intervals only.

OS HR (ITT population)					
Comparison	**No. of patients per group**	**Total No. of patients**	**Treatment comparison**	**HR (95% CI) [a]**	***P* value [b]**
Docetaxel vs control	1919 vs 968	2887	(A-T + AT) vs (A + AC)	0.88 (0.75 to 1.03)	.107
Sequential docetaxel vs sequential control	960 vs 481	1441	A-T vs A	0.85 (0.68 to 1.06)	.152
Concurrent docetaxel vs concurrent control	959 vs 487	1446	AT vs AC	0.91 (0.74 to 1.13)	.385
Sequential docetaxel vs concurrent docetaxel	960 vs 959	1919	A-T vs AT	0.84 (0.70 to 1.01)	Not planned

a The primary comparison was stratified for number of positive lymph nodes, age at random assignment to treatment, and schedule of drug administration.

b Stratified two-sided log rank test.

Safety results:
At least 1 Adverse Event (AE) was reported during treatment or follow-up among all 2865 patients in the safety population. Over the entire study period, the overall incidence of Serious Adverse Events (SAEs) was greater in the docetaxel groups (A-T, AT) than in the control groups (A, AC) without important differences between the sequential and concurrent docetaxel groups or between the sequential and concurrent control groups. The following tabulations do not include hematologic toxicities.

Adverse events during treatment or follow-up (Safety population)
N (%)

Number of patients	A N=472	AC N=485	A-T N=950	AT N=958
No. of patients with at least 1				
AE	472 (100%)	485 (100%)	950 (100%)	958 (100%)
G3/4 or severe AE	125 (26.5%)	133 (27.4%)	363 (38.2%)	311 (32.5%)
AE related	471 (99.8%)	485 (100%)	950 (100%)	958 (100%)
G3/4 or severe AE related	96 (20.3%)	112 (23.1%)	304 (32.0%)	236 (24.6%)
SAE	104 (22.0%)	82 (16.9%)	290 (30.5%)	307 (32.0%)
G3/4 or severe SAE	50 (10.6%)	37 (7.6%)	126 (13.3%)	121 (12.6%)
SAE related	81 (17.2%)	62 (12.8%)	224 (23.6%)	261 (27.2%)
G3/4 or severe SAE related	34 (7.2%)	25 (5.2%)	81 (8.5%)	83 (8.7%)

Adverse events during treatment

The overall frequency of AEs during treatment was greater among patients in the A-T and AT groups compared with the A and AC groups. No important differences were seen between the A-T and AT groups or between the A and AC groups.

The most common (at least 30% of patients/treatment group) AEs of all grades regardless of relationship to study medication during treatment in the each treatment group were as follows:

- A-T group: alopecia (99.5%), leucopenia (92.4%), neutropenia (90.9%), anemia (88.8%), nausea (87.5%), stomatitis (71.1%), vomiting (50.2%), infection (49.8%), neuro-sensory (46.3%), diarrhea (43.2%), skin (40.1%), and neuro-constipation (30.6%).
- AT group: alopecia (98.5%), leucopenia (92.8%), neutropenia (91.4%), anemia (87.9%), nausea (84.6%), stomatitis (67.4%), vomiting (46.0%), infection (41.9%), diarrhea (39.7%), and fever in absence of infection (31.4%).
- A group: alopecia (98.7%), neutropenia (88.9%), leucopenia (88.3%), nausea (87.5%), anemia (85.8%), stomatitis (65.7%), vomiting (52.3%), infection (44.7%), and diarrhea (31.8%).
- AC group: alopecia (99.0%), leucopenia (92.0%), neutropenia (89.7%), nausea (89.3%), anemia (85.8%), vomiting (57.5%), stomatitis (54.6%), and infection (45.4%).

Adverse events during treatment (Safety population) N (%)				
Number of patients	**A N=472**	**AC N=485**	**A-T N=950**	**AT N=958**
No. of patients with at least 1				
AE	471 (99.8%)	485 (100%)	950 (100%)	958 (100%)
G3/4 or severe AE	108 (22.9%)	120 (24.7%)	335 (35.3%)	275 (28.7%)
TEAE	471 (99.8%)	485 (100%)	950 (100%)	958 (100%)
AE related	471 (99.8%)	485 (100%)	950 (100%)	958 (100%)
G3/4 or severe AE related	94 (19.9%)	107 (22.1%)	298 (31.4%)	231 (24.1%)
SAE	99 (21.0%)	75 (15.5%)	275 (28.9%)	292 (30.5%)
G3/4 or severe SAE	44 (9.3%)	29 (6.0%)	114 (12.0%)	109 (11.4%)
Serious TEAE	99 (21.0%)	75 (15.5%)	273 (28.7%)	292 (30.5%)
G3/4 or severe serious TEAE	44 (9.3%)	29 (6.0%)	113 (11.9%)	109 (11.4%)
SAE related	81 (17.2%)	59 (12.2%)	217 (22.8%)	259 (27.0%)
G3/4 or severe SAE related	32 (6.8%)	22 (4.5%)	77 (8.1%)	82 (8.6%)

Adverse events during follow-up

During the 10-year follow-up period, no important differences (<10% differences) were seen between each of the docetaxel groups and their respective control groups for the overall frequency of AEs and SAEs.

Overview of adverse events reported during follow-up (Safety population)				
Number of patients	**A N=472**	**AC N=485**	**A-T N=950**	**AT N=958**
No. of patients with at least 1				
AE	305 (64.6%)	324 (66.8%)	670 (70.5%)	672 (70.1%)
G3/4 or severe AE	26 (5.5%)	23 (4.7%)	50 (5.3%)	51 (5.3%)
AE related	106 (22.5%)	117 (24.1%)	279 (29.4%)	261 (27.2%)
G3/4 or severe AE related	4 (0.8%)	10 (2.1%)	8 (0.8%)	10 (1.0%)
SAE	14 (3.0%)	10 (2.1%)	22 (2.3%)	23 (2.4%)
G3/4 or severe SAE	10 (2.1%)	10 (2.1%)	14 (1.5%)	17 (1.8%)
SAE related	3 (0.6%)	5 (1.0%)	6 (0.6%)	6 (0.6%)
G3/4 or severe SAE related	3 (0.6%)	5 (1.0%)	5 (0.5%)	6 (0.6%)

During follow-up, the only NCI (National Cancer Institute) gradable and non-NCI gradable AEs that occurred in at least 5% of patients in any treatment group during follow-up were skin (9.1% A-T, 7.4% AT, 9.3% A, 9.7% AC), amenorrhea (48.0% A-T, 46.0% AT, 38.3% A, 43.7% AC), vasodilatation (13.8% A-T, 12.7% AT, 12.9% A, 14.0% AC), menstrual disorder (7.2% A-T, 8.4% AT, 11.0% A, 11.1% AC), and pain (5.4% A-T, 6.1% AT, 5.3% A, 6.4% AC). The Grade 4 AEs that occurred in 2 patients in a treatment group was cerebrovascular accident (0.2% A-T); single patients experienced cardiac function (0.2% A), cardiac ischemia (0.1% A-T, 0.2% A), neuro-cortical (0.2% A), neuro-mood (0.1% A-T), and skin (0.1% A-T; 0.2% A). Life-threatening AEs occurred in single patients in 1 or more treatment groups and included cerebrovascular accident (0.2% A-T), pain (0.1% AT), arrhythmia (0.1% A-T), embolus (0.1% A-T), myocardial infarct (0.1% AT), pulmonary embolism (0.2% A, 0.2% AC, 0.1% A-T, 0.1% AT), thrombosis (0.1% AT), hepatitis (0.1% A-T), acute myeloblastic leukemia (0.1% AT, 0.2% AC), convulsion (0.2% A), pulmonary thrombosis (0.2% AC), and retinal disorder (0.1% AT).

Related NCI gradable AEs during follow-up reported in more than 1 patient in any treatment group were:

- A-T group: alopecia (1.8%), neuro-sensory (1.7%), neuro-motor (0.4%), neuro-headache, neuro-mood (each 0.3%), pulmonary, and weight gain (each 0.2%).
- AT group: alopecia (1.8%), neuro-sensory (0.8%), weight gain (0.8%), infection (0.4%), neuro-motor, and pulmonary (each 0.2%)
- A group: alopecia (1.5%), neuro-sensory (0.6%), weight gain, and cardiac function (each 0.4%)
- AC group: alopecia (1.4%), neuro-sensory (1.2%), and skin (0.4%).

Non-NCI gradable related AEs reported during follow-up by at least 1.0% of patients in a treatment group were:

- A-T group: amenorrhea (18.6%), menstrual disorder (5.7%), arthralgia (1.5%), vasodilatation, and asthenia (each 1.3%).
- AT group: amenorrhea (17.1%), menstrual disorder (5.8%).
- A group: amenorrhea (13.3%), menstrual disorder (8.1%).
- AC group: amenorrhea (13.2%), menstrual disorder (7.6%), arthralgia (1.6%).

The majority of related NCI gradable AEs during follow-up were Grade 1 or 2. The only Grade 4 related NCI gradable AE during follow-up was cardiac function in the A group (0.2%). The majority of related non-NCI gradable AEs during follow-up were mild or moderate in severity. The only severe related AE during follow-up that was reported in more than 1 patient in the study was vasodilatation (0.1% A-T, 0.1% AT). The only life-threatening related AE reported during follow-up was arrhythmia in the A-T arm (0.1%).

Deaths:

As of 10 years from the date of first administration of study drug, 694 study patients (24.2%) have died, including 3 patients (1 A, 1 A-T, and 1 AT]) who died during the treatment period and 691 patients (110 [23.3%] A, 134 [27.6%] AC, 207 [21.8%] A-T, and 240 [25.1%] AT) who died during the follow-up period. The majority of deaths were not related, resulting mostly from breast cancer (86.9%). Of the 7 deaths considered by the investigator to be related to study treatment, 3 deaths were due to sepsis or infection (1 A, 1 AC, 1 AT), 2 deaths due to nonseptic causes (1 A, 1 AT), and 2 deaths (2 A-T) due to toxicity after breast cancer relapse. In addition, 3 deaths resulted from SAEs during follow-up that were considered related to study treatment, including infection meningitis (1 AT), AML (1 AT), and sepsis (1 A-T).

Other SAEs(Serious Adverse Events):

The majority of NCI gradable and non-NCI gradable SAEs during follow-up occurred in only 1 patient per treatment group; NCI gradable cardiac function was reported in 2 (0.4%) patients in group A and non-NCI gradable pulmonary embolism was reported in 2 (0.2%) patients in the AT group and cerebrovascular accident was reported in 2 (0.2%) patients in the A-T group. The NCI-gradable SAEs during follow-up considered related to study treatment were 2 cardiac function (0.4% A), 2 pulmonary (0.2% A, 0.1% AT), 1 diarrhea (0.1% AT), and 1 vomiting (0.1% AT). The non-NCI gradable SAEs during follow-up related to study treatment and reported in more than 1 patient were acute myeloblastic leukemia (0.2% AC and 0.1% AT) and atrial fibrillation (0.2% A and 0.2% AC).

Late toxicities

Cardiotoxicity: During treatment, CHF (Congestive Heart Failure) was reported in 11 patients: 4 (0.4%) A-T, 1 (0.1%) AT, 4 (0.8%) A, and 2 (0.4%) AC. No docetaxel-related trend in the occurrence of CHF was evident.

Late cardiac toxicities were reported in 9 patients in the A group (5 abnormal cardiac function, 2 CHF, 1 angina pectoris, 1 chest pain), 4 patients in the AC group (2 cardiac function abnormal, 1 CHF, 1 cardiomyopathy), 2 A-T (1 cardiomyopathy, 1 cardiac arrhythmia), 4 patients in the AT group (1 acute fatal MI, 1 cardiac function abnormal, 2 cardiac/myocardial ischemia)

Hematologic toxicities: During treatment, Grade 3 or 4 leucopenia and neutropenia were seen slightly more frequently among docetaxel treated patients compared with control patients; during follow-up, there were no apparent differences among the treatment groups for hematologic toxicities.

Grade 3 or 4 Hematologic toxicities, febrile neutropenia and infection during follow-up (Safety population)

Number of patients	Arm A N=472	Arm AC N=485	Arm A-T N=950	Arm AT N=958
White Blood Cells Grade 3+4	2(0.4%)	2(0.4%)	11(1.2%)	3(0.3%)
Neutrophils Grade 3+4	4(0.9%)	6(1.3%)	4(1.6%)	4(1.0%)
Hemoglobin Grade 3+4	5(1.1%)	5(1.0%)	5(0.3%)	5(0.6%)
Platelets Grade 3+4	6(1.3%)	6(1.2%)	6(0.6%)	6(0.8%)
Febrile Neutropenia	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Infection Grade 3 or 4	0(0.0%)	1(0.2%)	2(0.2%)	2(0.2%)

Fluid retention during treatment: Fluid retention was seen approximately twice as frequently in patients treated with docetaxel (36.7% - 41.5%) compared with the control patients (19.0% - 20.1%). The majority of these events were considered probably or possibly related to study treatment. The most common symptoms of fluid retention considered probably or possibly related to treatment were edema and weight gain.

Biochemical abnormalities during treatment: There were no important differences among the treatment groups for the occurrence of Grade 3 or 4 biochemical toxicities during treatment.

Number of patients	Arm A N=472	Arm AC N=485	Arm A-T N=950	Arm AT N=958
ALAT (SGPT) Grade 3+4	22(4.7%)	11(2.3%)	24(2.5%)	31(3.3%)
ASAT (SGOT) Grade 3+4	3(0.7%)	2(0.4%)	5(0.5%)	6(0.6%)
Alkaline phosphatase Grade 3+4	0(0.0%)	0 (0.0%)	2 (0.2%)	3(0.3%)
Creatinine Grade 3+4	1(0.2%)	1(0.2%)	3(0.3%)	4(0.4%)
Bilirubin Grade 3+4	13(2.8%)	20(4.1%)	42(4.4%)	28(2.9%)

Second primary malignancy: 3 patients were diagnosed with a second primary malignancy and 2 patients had endometrial polyps, including 4 patients in the AT group (1 CML, 1 AML, 2 uterine neoplasm [1 in treatment, 1 in follow-up]), and 1 patient in the AC group (AML).

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