2. S376 Synopsis

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Clinical Study Report Synopsis: Study B9E-IT-S376

Title of Study: A Randomized Phase III Trial of Gemcitabine and Docetaxel versus Gemcitabine and Paclitaxel in Patients with Metastatic Breast Cancer: a comparison of different schedules

Number of Investigators: This is a multicenter study which included three coordinating investigators

Study Centers: This study was conducted at 37 study centers in one country.

Publications Based on the Study: None at this time

Length of Study:
Date of first patient enrolled: 22 September 2005
Date of last subject visit: 05 August 2010

Phase of Development: III

Objectives: This study has two primary objectives:

1. To compare Time To Progression (TTP) in patients with metastatic breast cancer (MBC) treated with Docetaxel plus Gemcitabine to patients treated with Paclitaxel plus Gemcitabine
2. To compare TTP in MBC patients treated with a weekly schedule to patients treated with the standard three weekly schedule.

The secondary objectives were to compare

- Overall Toxicity
- Quality of Life (QoL) using the Rotterdam Symptom Scale Checklist
- Incidence of Grade 3/Grade 4 haematological toxicity
- Incidence of Grade 3/Grade 4 non-haematological toxicity
- Overall Survival (OS)
- Overall Response Rate (ORR)

in patients with MBC treated with Docetaxel plus Gemcitabine as compared to patients treated with Paclitaxel plus Gemcitabine, as well as in patients treated with the weekly schedule as compared to patients treated with 3-weekly schedule

Study Design: This is a multicenter, randomized phase III trial to compare the doublet Docetaxel/Gemcitabine versus Paclitaxel/Gemcitabine in terms of efficacy and safety, as well as the use of a weekly schedule compare to the standard 3-weekly schedule, in patients with metastatic breast cancer.

Number of Patients:
Planned: 360
Randomized: 241
Treated (at least 1 dose): 238 [Arm A (Gemcitabine + Docetaxel 3-weekly): 59; Arm B (Gemcitabine + Paclitaxel 3-weekly): 62;Arm C (Gemcitabine + Docetaxel weekly): 58;Arm D (Gemcitabine + Paclitaxel weekly): 59].
Completed: 75 [Arm A (Gemcitabine + 3-weekly Docetaxel): 18; Arm B (Gemcitabine + 3-weekly Paclitaxel): 24; Arm C (Gemcitabine + weekly Docetaxel): 14; Arm D (Gemcitabine + weekly Paclitaxel): 19].

Diagnosis and Main Criteria for Inclusion: Patients are eligible for this study only if they meet all of the following criteria:

1. Have histological diagnosis of breast cancer with evidence of metastatic disease. Lesions should not be amenable of surgery or radiation of curative intent.
2. Age ≥18 years.
3. May have received a prior neoadjuvant or adjuvant taxanes regimen as long as it has been ≥12 months since completion of the regimen.
4. Will have relapsed after [a] receiving one adjuvant/neoadjuvant chemotherapy containing anthracycline, unless [b] clinically contraindicated. Before entry this study patients must have recovered from the toxic effects of prior therapy.
5. Have measurable disease as defined by RECIST; however patients with only bone metastases will be included in the study.

6. Previous hormonal therapy for adjuvant setting or metastatic disease (2 lines) is allowed and should be completed before the enrollment.
7. Prior radiotherapy should be completed 4 weeks before study entry. Lesion that have been radiated in the advanced setting cannot be included as sites of measurable disease.
8. Performance status of 70 or higher on the Karnofsky Scale.
9. Estimated life expectancy of at least 12 weeks.
10. Geographic proximity that allow adequate follow up.
11. Adequate organ function including:
    - Adequate bone marrow reserve: platelets ≥100 x 109 /L, absolute neutrophile count (ANC) ≥1.5 x 109 /L, hemoglobin ≥9.0 g/dL
    - Adequate liver function: bilirubin ≤1 x upper limit of normal (ULN); alanine transaminase (ALT) and aspartate transaminase (AST) ≤2.5 x ULN; alkaline phosphatase ≤5.0 x ULN (unless accompanied by extensive bone metastases). In case ALT and/or AST ≥1.5 x ULN is associated with alkaline phosphatase >2.5 x ULN, the patient is not eligible
12. Must be informed of the investigational nature of this study, sign and give written informad consent in accordance with institutional guidelines.
13. Must use an approved contraceptive method if appropriate (except hormonal substitutive therapy) during and for 3 months after stopping this study.
14. Bisphosphonate therapy is allowed at the discretion of the investigator.

Study Drug, Dose, and Mode of Administration:

This is a multicenter, phase III study where patients were randomized in 4 arms. Dose and mode of administration are presented for each arm.

Arm A: Docetaxel 75 mg/m^2 administered intravenously (IV) on day 1with Gemcitabine 1000 mg/m^2 administered IV on day 1 and 8 at each cycle.

Arm B: Gemcitabine 1250 mg/m^2 administered IV on day 1 and 8, in combination with Paclitaxel 175 mg/m^2 administered IV on day 1 of each cycle.

Arm C: Gemcitabine 800 mg/m^2 administered by 30 minutes IV infusion on day 1, 8 and 15 and Docetaxel 30 mg/m^2 administered by 30-60 minutes iv infusion on day 1, 8, 15 at each cycle.

Arm D: Gemcitabine 800 mg/m^2 administered IV on day 1, 8 and 15 and Paclitaxel 80 mg/m^2 on day 1, 8, 15 at each cycle.

Duration of Treatment:

With regard to the treatment arm, and dose and mode of administration of drugs, a cycle is defined as follow:

- For Arm A a cycle is defined as two doses of Gemcitabine on days 1 and 8 and one dose of Docetaxel administered on day 1 every 21 days.
- For Arm B a cyle is defined as two doses of Gemcitabine on days 1 and 8 and 1 dose of Paclitaxel administered on day 1 every 21 day.
- For Arm C a cycle is defined as three doses of Gemcitabine on days 1, 8 and 15 and three doses of docetaxel administered on days 1, 8 and 15 every 28 days.
- For Arm D a cycle is defiened as three doses of Gemcitabine on days 1, 8 and 15 and three doses of Paclitaxel administered on day 1, 8 and 15 every 28 days.

The following number of cycles were given to patients:

- In case of Progressive Disease the patients go off protocol treatment
- In case of Stable Disease a patient undertake a maximum of 6 cycles
- In case of Partial or Complete Response a patient undertake maximum of 10 cycles

Variables:

Efficacy: Primary endpoint of this study was TTP, defined as the time from the day of treatment to first observation of documented disease progression or death due to any cause. TTP was censored at the time of last follow-up for those patients who were still alive without progression. Other efficacy measures were Overall Survival (OS), defined as time from enrollment to time of death as a result of any cause (for participants who were still alive, OS was censored at the last contact), and Overall Response Rate (ORR) rate.

Safety: The safety and AE profile (including grades for laboratory and nonlaboratory AEs) for each treatment arm.

Health Outcomes: Quality of Life (QoL) measures using the Rotterdam Symptom Scale Checklist

Statistical Evaluation Methods:

Samlpe size:

The planned sample size of 360 patients was chosen to allow for the observance of 252 events, which gives 80% power of rejecting the null hypothesis of no difference in TTP rates against an alternative hypothesis of a 30% difference in TTP rates between the treatment groups (schedules or drugs) assuming a two-sided significance level of 5%. These assumptions were based on a constant rate of accrual of 120 patients per year over a 3-year period. However, the slow rate of accrual in the trial prevented the completion of the planned patients enrolment (360 pts) within a reasonable time (March 2009). Consequently, futility analysis was performed to evaluate if the study results observed so far were compatible with the alternative hypothesis, thus reinforcing the need to complete the projected accrual, or indicate that the study should be stopped early.

The interim futility analysis was based on all events (progressions or deaths without documented progression) that occurred before 30 November 2008. The analysis used the standard approach of estimating the conditional power of the study based on the observed results and the projections of the results that would be observed under the following 3 hypothesis should the accrual and follow-up continue until the observation of the 252nd event, as planned: a) the null hypothesis [Hazard Ratio (HR)=1]; b) the original alternative hypothesis (HR=0.7); and c) the hypothesis that the HR observed during the first part of the study is true. It is expected that, with 100-110 events, any observed HR>1 will provide strong support for stopping patients' accrual for futility. Conversely, any observed HR<0.85 will reinforce the need to complete patients' accrual and follow-up and should encourage investigators to achieve this aim. If an HR between 1 and 0.85 is observed, then the decision to continue or stop patients' accrual will be based on an overall study results, including toxicity, response rate, overall survival. Of the 202 patients used in the futility analysis, 113 events (56%) were obtained. This constitute about 45% (113/252) of the planned number of events. The results obtained from evaluation of the data gave an HR (95%CI) of 1.06 (0.73 – 1.54) for the Docetaxel arm versus Paclitaxel treatment arm comparison of TTP and an HR (95%CI) of 1.04 (0.72 – 1.51) for TTP for the weekly versus 3-weekly treatment schedules comparison.

Based on these results, it was estimated that if the original alternative hypothesis (HR= 0.7) were true and the study was brought to its natural conclusion, the chance (that is, conditional power) of observing a significant difference in favour of Docetaxel arm is 16% and only 6% between the treatment schedules. On the basis of the results from the futility analyses, a committee constituted by the three principal investigators and the project statistician in charge of this evaluation, noted that the two alternative hypotheses for the primary endpoint were less likely than when the study was initiated and, consequently, decided that it was not appropriate to continue the patients accrual for the study.

Efficacy: This study has two primary objectives:

1. To compare Time To Progression (TTP) in patients with metastatic breast cancer (MBC) treated with Docetaxel plus Gemcitabine to patients treated with Paclitaxel plus Gemcitabine
2. To compare TTP in MBC patients treated with a weekly schedule to patients treated with the standard three weekly schedule

To this aim, a multivariate Cox proportional hazard model was fitted to the data, with TTP as the dependent

variable and the following covariates:presence or absence of visceral metastases (defined as metastases to the major organs except bone, skin, soft tissue and lymph nodes), menopausal status, prior adjuvant/noeadjuvant taxane therapy, prior hormonal therapy, type of taxane (Docetaxel or Paclitaxel), schedule assigned at randomization (weekly vs 3-weekly) and interactions between the last two covariates. According to the intention to treat principle, all randomized patients were included in this analysis according to the treatment arm assigned at randomization. For descriptive purposes, Kaplan-Meier survival plots and median survival estimates were presented as well for each of the time-to-event endpoints.
Other efficacy measures were Overall Survival (OS) (this analysis resemble that described for TTP) and Overall Response Rate (ORR) (this analysis rensemble that described for TTR as well but fitting a multivariate logistic regression model rather than the Cox's model). These analyses were conducted on all randomized patients.

Safety: Safety analyses included summaries of the blood/platelet transfusion required, summary of adverse events rates and laboratory changes, summary of the number of the CTC(common toxicity criteria, version 3.0) toxicities grade for laboratory and non-laboratory parameters. Safety analyses were conducted on the data from all randomized patients treated with at least one dose of Docetaxel, Paclitaxel or Gemcitabine

Health Outcomes: Quality of Life was measured using the Rotterdam Syndrome Checklist (RSCL). The RSCL was assessed for each patients no more than one week before entering the study, every 3 weeks for arms A and B, every 4 weeks for arms C and D and at 30 days post-therapy visit. All randomized patients were included in these analyses. For each treatment arm, descriptive statistics (number of response and percentages) were tabulated for the QoL measures.

Summary:

Study population
The study population included 241 adult female patients with histological diagnosis of breast cancer with evidence of metastatic disease.

Demographic characteristics
Of the 241 patients enrolled, 238 (98.8%) patients were Caucasian while 3 (1.2%) were of other ethnicities (1 African, 1 Creole and 1 Asian). Mean±SD age was 55.85±9.76 years (median: 57.00years, range: 31 to 77years). Selected covariates that were included in the Cox and logistic modeling are presented stratified by treatment arms in Table S376.2.1.

Table S376.2.1: Demographic characteristic of this study population

		Arm A n=60		Arm B n=64		Arm C n=58		Arm D n=59		Total n=241	
Age(years)											
Mean±SD		56.58±10.21		56.31±9.84		55.78±8.99		54.66±10.04		55.85±9.76	
Median (Range)		58.5 (37, 76)		57.5 (31, 74)		56 (38, 77)		55 (33, 76)		57.0 (31, 77)	
		N	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Origin	Caucasian	58	96.6	63	98.4	58	100	59	100	238	98.8
	African	1	1.7	0	0.0	0	0.0	0	0.0	1	0.4
	Asian	1	1.7	0	0.0	0	0.0	0	0.0	1	0.4
	Other*	0	0.0	1	1.6	0	0.0	0	0.0	1	0.4
Menopausal status	pre	19	31.7	17	26.6	16	27.6	21	35.6	73	30.3
	post	41	68.3	47	73.4	42	72.4	38	64.4	168	69.7
Previous hormonal therapy†	Yes	44	73.7	48	75.0	40	69.0	46	78.0	178	73.9
	No	16	26.7	16	25.0	17	29.3	13	22.0	62	25.7
Visceral metastases	Absence	19	31.7	19	29.7	16	27.6	23	39.0	77	32.0
	Presence	41	68.3	45	70.3	42	72.4	36	61.0	164	68.0
Previous adjuvant/neoadjuvant taxane therapy†	Yes	21	35.0	24	37.5	12	20.7	19	32.2	76	31.5
	No	39	65.0	40	62.5	45	77.6	40	67.8	164	68.0

*Other: 1 Creole; †1patient in Arm C has no record for previous hormonal therapy and adjuvant/neoadjuvant therapy.

Patient Disposition

The 241 patients enrolled in this study were randomized as follow:

Arm A	Docetaxel and Gemcitabine with 3 weekly schedule	60 (24.9%)
Arm B	Paclitaxel and Gemcitabine with 3 weekly schedule	64(26.6%)
Arm C	Docetaxel and Gemcitabine with weekly schedule	58 (24.1%)
Arm D	Paclitaxel and Gemcitabine with weekly schedule	59 (24.5%)

Overall, 75 patients (31.1%) [Arm A: 18 patients (30.0%); Arm B: 24 patients (37.5%); Arm C: 14 patients (24.1%): Arm D: 19 patients (32.2%)] completed the study protocol whereas 166 (68.9%) prematurely discontinued the study. The causes of early discontinuation are summarized in Table S376.2.2.

Table S376.2.2: Causes of early discontinuation from this study

	Overall N pts (%)	Arm A N pts (%)	Arm B N pts (%)	Arm C N pts (%)	Arm D N pts (%)
Lack of Efficacy	84 (34.9)	18 (30.0)	18 (28.1)	25 (43.1)	23 (39.0)
Physician Decision	28 (11.6)	7 (11.7)	8 (12.5)	7 (12.1)	6 (10.2)
Adverse Events	22 (9.1)	4 (6.67)	4 (6.25)	6 (10.35)	8 (13.56)
Subject Decision	17 (7.1)	6 (10.0)	4 (6.3)	5 (8.6)	2 (3.4)
Death	8 (3.3)	4 (6.7)	4 (6.3)	0 (0.0)	0 (0.0)
Satisfactory Response	3 (1.2)	2 (3.3)	0 (0.0)	0 (0.0)	1 (1.7)
Entry Criteria Exclusion	2 (0.8)	0 (0.0)	1 (1.6)	1 (1.7)	0 (0.0)
Protocol Violation	1 (0.4)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to Follow-up	1 80.4)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)

Efficacy

Time To Progression (TTP):

For the treatment schedule, 101 (86.3%) and 107 (86.3%) patients showed progression in the weekly and 3-weekly treatment schedule respectively. The difference between the median TTP of the two treatment groups was not statistically significant: median TTP was 8.33 months (95%CI:6.19-10.16) for the weekly schedule group while it was 7.51 months (95%CI: 5.93-8.33) for the 3-weekly schedule group (Hazard Ratio (HR) of 1.15; (95% CI: 0.87 to 1.51); p-value= 0.319). From the Cox regression analysis, similar results were obtained (HR: 1.14; (95% CI: 0.87 to 1.50); p-value= 0.345) when adjusted for treatment drug and visceral metastases (the only covariate that significantly influence TTP [P-value = 0.023]).

For the TTP comparison between the two treatment drugs assignment, the number of patients who showed progression was 101 (85.6%) and 107 (87.0%) for Docetaxel and Paclitaxel treatment groups respectively. Again, there was no statistically significance difference in the median TTP between the two treatment drugs group: the median TTP was 7.74 months (95%CI:5.57-9.80) and 7.80 months (95%CI: 6.20-8.72) respectively for the Docetaxel group and Paclitaxel group (HR of 1.16 (95%CI: 0.88 to 1.52); p-value=0.302). Again, from the Cox regression model, similar results were obtained (HR: 1.23 (95%CI: 0.93 to 1.62); p-value=0.150) when adjusted for treatment schedule and visceral metastases as covariates.

Overall Survival (OS)

For the comparison of OS between the two treatment schedule, the median OS was 21.11 months (95%CI:17.28-26.75) and 20.95 months (95%CI: 18.92-33.21) for the weekly schedule and the 3-weekly schedule respectively. The difference in OS between the two schedule was not statistically significant (HR of 0.98 (95%CI: 0.69, 1.37); p-value = 0.886).

For the two treatment assignments, the median OS was 19.11 months (95%CI:16.59-24.0) and 23.80 months (95%CI: 19.38-31.97) for the Docetaxel and Paclitaxel treatment group respectively. Again, the difference in OS between the two treatment assignments was not statistically significant (HR of 1.01 (95%CI: 0.71. 1.42); p-value = 0.980). None of the covariates assessed using the Cox regression indicate a significant influence on OS.

Overall Response Rate (ORR):

The ORR rate results are presented by treatment drug assignment and treatment schedule. For the treatment drug assignments the distribution of the responses for the Docetaxel group are as follows: 6 patients (5.1%) had complete response (CR), 45 (38.1%) had partial response (PR), 38 (32.2%) had stable disease (SD), 21 (17.8%) had progressive disease (PD), 1 (0.9%) patient's best response was unknown and for 7 patients (5.9%) the responses were not assessed. For the Paclitaxel group, the distribution of the responses obtained are: 9 patients (7.3%) had CR, 40 (32.5%) had PR, 40 (32.5%) had SD, 20 (16.3%) had PD, 2 (1.6%) patients' responses were unknown and 12 patients (9.8%) were without response evaluation. The ORR(CR plus PR) was 43.2% for Docetaxel treatment group and 39.8% for the Paclitaxel treatment group and the difference between the was not statistically significant (odds ratio of 0.82 (95%CI: 0.48. 1.39) and p-value = 0.457 from the fitted logistic regression model).

For the treatment schedule, the distribution of the responses for the weekly schedule are: 8 patients (6.84%) had CR, 51 (43.6%) had PR, 28 (23.9%) had SD, 25 (21.4%) PD, 1 (0.9%) patient's best response was unkown and for 4 patients (3.4%) the responses were not assessed. For the 3-weekly treatment schedule, the distribution of the responses are 7 patients (5.7%) had CR, 34 (27.4%) had PR, 50 (40.3%) had SD, 16 (12.9%) had PD, 2 patients (1.6%) had unknown best response and for 15 (12.1%) patients the responses were not assessed. The ORR was higher in the weekly treatment schedule compared to the 3-weekly treatment schedule (50.43% versus 33.1%; odds ratio of 0.44 (95%CI: 0.26. 0.75) and p-value = 0.003 from the logistic regression model adjusted for covaraites). Similar results were obtained from the logistic regression analyses unadjusted for any covariates (odds ratio: 0.49 (95%CI : 0.29. 0.82) and p-value = 0.007).

Safety

A total of three patients were randomized but not treated (1 in the Docetaxel 3-weekly group and 2 in the Paclitaxel 3-weekly group). Thus, the safety population consist of a total of 238 patients.

Adverse Events (AEs): Overall, Treatement Emergent Adverse Events (TEAEs) were reported in 224 patients (94.1%) while 37 patients (15.5%) experienced at least one treatment emergent serious adverse event (TESAE). Six patients (2.5%) died. Chemotherapy-related TEAEs and TESAEs were reported in 218 (91.6%) and 17 (7.1) patients respectively. Grade III-IV (G3-G4) toxicities were reported in 168 (70.6) subjects. Twenty-two (9.2%) patients discontinued the study due to TEAE while 14 patients (5.9%) were without TEAE. These results stratified by treatment drugs and schedule are presented in Table S376.2.3:

Table S376.2.3: Summary of treatment emergent adverse events

	Docetaxel 3-weekly (N=59) n(%)	**Paclitaxel 3-weekly (N=62) n (%)**	**Docetaxel weekly (N=58) n (%)**	**Paclitaxel weekly (N=59) n (%)**
Deaths	3 (5.1)	1 (1.6)	1 (1.7)	1 (1.7)
Subject with at least one TESAE	9 (15.3)	10 (16.0)	7 (12.1)	11 (18.6)
Subject with at least one TEAE	57 (96.6)	58 (93.5)	53 (91.4)	56 (94.9)
Subject discontinued the study due to TEAE	4 (6.8)	4 (6.5)	6 (10.3)	8 (13.6)
Subjects with at least one Chemotherapy-related TEAE	56 (94.9)	57 (91.9)	50 (86.2)	55 (93.2)
Subjects with at least one Chemotherapy-related TESAE	5 (8.5)	4 (6.5)	3 (5.2)	5 (8.5)
Subjects with Grade III-IV toxicities	48 (81.4)	43 (69.4)	33 (56.9)	44 (74.6)
Subjects without TEAE	2 (3.4)	4 (6.5)	5 (8.6)	3 (5.1)

The most involved System Organ Class (SOCs) were blood and lymphatic systems disorders, respiratory, thoracic and mediastinal disorders and gastrointestinal disorders.

Incidence of G3 and G4 toxicities: The most frequent hematological G3 and G4 toxicities experienced by patients in this study were Leukopenia, Neutropenia, increase of Alanine Aminotransferase and deacreased WBC count. Non-hematological G3-G4 toxicities were Diarrohoea, Alopecia, Hepatotoxicities, Astenia and fatigue. These results stratified by treatment arm are presented in Table S376.2.4.

Table S376.2.4: Summary of incidence of grade 3/4 toxicities

Toxicity		Docetaxel 3-weekly		Paclitaxel 3-weekly		Docetaxel weekly		Paclitaxel weekly	
MedDra SOC	**Preferred term**	**G 3 n (%)**	**G 4 n (%)**	**Grade 3 n (%)**	**G 4 n (%)**	**G3 n (%)**	**G4 n (%)**	**G 3 n (%)**	**G4 n (%)**
Hematological									
Blod and Lymphatic system disorder	Leukopenia[1]	11 (18.3)	1 (1.7)	5 (7.8)	2 (3.1)	5 (8.6)	0 (0.0)	5 (8.5)	0 (0.0)
	Neutropenia[2]	23 (38.3)	21 (35.0)	20 (31.3)	6 (9.4)	13 (22.4)	4 (6.9)	20 (33.9)	9 (15.3)
Investigations	ALT increased[3]	1 (1.7)	0 (0.0)	5 (7.8)	0 (0.0)	8 (13.8)	0 (0.0)	6 (10.2)	0 (0.0)
	Neutrophil count decreased[2]	1 (1.7)	1 (1.7)	2 (3.1)	1 (1.6)	2 (3.4)	0 (0.0)	3 (5.1)	2 (3.4)
	WBC count [1] decreased	4 (6.7)	0 (0.0)	2 (3.1)	1 (1.6)	1 (1.7)	0 (0.0)	2 (3.4)	1 (1.7)
Non-hematological									
gastrointestinal disorder	Diarrhoea	0 (0.0)	2 (3.3)	0 (0.0)	0 (0.0)	4 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)
Muscoloskeletal and connettive tissue disorder	Mialgya	0 (0.0)	0 (0.0)	4 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	Alopecia	4 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.7)	0 (0.0)
Hepatobiliary disorders	Hepatotoxicities[3]	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.1)	0 (0.0)
General disorder and administration site conditions	Asthenia	4 (6.7)	0 (0.0)	3 (4.7)	0 (0.0)	5 (8.6)	0 (0.0)	6 (10.2)	1 (1.7)
	Fatigue	3 (5.0)	0 (0.0)	3 (4.7)	0 (0.0)	3 (5.32)	0 (0.0)	4 (6.8)	0 (0.0)

[1] These items were reported with different names from study investigators but refers to the same toxicity. [2] As per note number 1; [3] ALT are included into hepatotoxicities but separately reported by different study investigators

Health Outcomes

Quality of Life: The summary results of Quality of Life (QoL) measures, obtained using the Rotterdam Symptom Checklist (RSCL) at the beginning of study treatment (visit 1) and at 30-day post-therapy visit (visit 101), is provided in Table S376.2.5. For each treatment arm, there is a substantial reduction in the number of patients who completed the QoL questionnaire at the post-therapy visit when compared to those obtained at the beginning of the treatment.

Table S376.2.5: Summary of the quality of life measures obtained using the Rotterdam Symptom Checklists

	Docetaxel 3-weekly n (%)		**Paclitaxel 3-weekly n (%)**		**Docetaxel weekly n (%)**		**Paclitaxel weekly n (%)**	
	Visit_1*	**Post-study**	**Visit_1***	**Post-study**	**Visit_1***	**Post-study**	**Visit_1***	**Post-study**
Excellent	3 (5.0)	0 (0.0)	1 (1.6)	0 (0.0)	2 (3.5)	0 (0.0)	4 (6.8)	0 (0.0)
Good	13 (21.7)	7 (11.7)	13 (20.3)	7 (10.9)	9 (15.5)	2 (3.5)	5 (8.5)	4 (6.7)
Moderately good	6 (10.0)	2 (3.3)	8 (12.5)	6 (9.4)	9 (15.5)	3 (5.2)	9 (15.3)	2 (3.4)
Neither good nor bad	6 (10.0)	3 (5.0)	7 (10.9)	6 (9.4)	6 (10.3)	0 (0.0)	7 (11.9)	3 (5.1)
Rather poor	2 (3.3)	0 (0.0)	3 (4.7)	1 81.6)	3 (5.2)	1 (1.7)	6 (10.2)	1 (1.7)
Poor	0 (0.0)	2 (3.3)	3 (4.7)	0 (0.0)	7 (12.1)	1 (1.7)	2 (3.4)	2 (3.4)
Extremely poor	0 (0.00)	1 (1.67)	3 (4.69)	0 (0.00)	0 (0.00)	2 (3.45)	1 (1.69)	0 (0.00)
Total responders	30 (50%)	15 (25.0)	38 (59.4)	20 (31.3)	36 (62.1)	9 (15.5)	34 (57.6)	12 (20.3)

*Visit 1: beginning of the 3 or 4 cycles; Post-study: 30-day post-therapy visit.

Conclusions:

- The results obtained from these analyses should be interpreted with caution because of early termination of the study.
- Due to the slow rate of accrual in this study a futility analysis was performed to evaluate whether enrollment could be completed in a reasonable time. After evaluation of futility analysis, it was concluded that there were neither scientific nor ethical justifiable reasons to continue enrolling patients for additional 2-3 years, and as a result, the study was terminated before the planned sample size population was reached. Subjects who have not completed the study protocol at that time were treated in accordance with the study protocol.
- Toxicity data are acceptable with regard to the study drugs and schedule administration.
- The most frequent grade 3/4 toxicity was Neutropenia (51.7% and 44.7% for Doclitaxel and Paclitaxel group respectively and 39.3% and 56.5% for weekly and 3-weekly schedule respectively). This is known to be mostly related to taxanes.
- There was no statistically significant difference in TTP between the treatment drugs and the treatment schedule based on the analysed data. The median TTP was 7.74 (95% CI: 5.57-9.80) and 7.80 (95% CI: 6.20-8.72) months for patients treated with Docetaxel plus Gemcitabine and Paclitaxel plus Gemcitabine respectively. Median TTP for patients treated with the weekly schedule and the 3 weekly schedule was 8.33 (95% CI:6.19-10.16) and 7.51 (95% CI: 5.93-8.33) months respectively.

- The difference in OS between the treatment schedules was not significant (median OS was 21.11 months [95%CI:17.28-26.75] and 20.95 months [95%CI: 18.92-33.21] for the weekly schedule and the 3-weekly schedule respectively) Also, the difference in OS between treatment drugs was not significant (median OS was 19.11 months [95%CI:16.59-24.0] and 23.80 months [95%CI: 19.38-31.97)]for the Docetaxel and Paclitaxel treatment group respectively).
- ORR was higher in the weekly arm compared to the 3-weekly arm (odds ratio: 0.442 (95%CI: 0.26-0.75) and p-value=0.0028) but there was no significant difference in ORR between the treatment drugs based on the data analysed. Note that the study was not designed to detect statistical difference in the secondary endpoints.
- There was no significance difference in the QoL measures between the treatment drugs and between the treatment schedules based on the data obtained and analysed.