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Serious Adverse Event

Defined in the protocol as: "any experience that suggested a significant hazard, contraindication, side effect or precaution. With respect to human clinical experience, this included any experience that was fatal, life-threatening, required inpatient hospitalization or prolongation of existing hospitalization resulting in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, or was an overdose."

Endpoints/Statistical Considerations

Endpoints:

Primary Endpoint:

The primary endpoint for this study was time to disease progression (TTP). TTP was defined as: "the time from the date of randomization to the time of disease progression or death or the date the patient was last known to be progression free (censoring)." The analysis was to take into account:

- all deaths,
- all PDs from tumor assessment and follow-up pages,
- censoring time in case neither PD nor death was observed was defined by the date of the last tumor assessment or the last follow-up date. In case this information was not available, the last date in drug log was used.

Secondary Endpoints:

- survival
- overall best response as assessed by the investigator
- overall best response as assessed by the IRC
- time to response as assessed by the investigator
- duration of response as assessed by the investigator,
- quality of life as measured by . and Breast Cancer ,
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For the analysis of survival, the time between the date of randomization and the date of death or the last date the patient was known to be alive (censoring) was to be evaluated.

Reviewer's Comments:

- The Division discussed with the sponsor the ODAC recommendation at the June 7, 1999 meeting, that survival is the primary endpoint of interest in treatment of first line metastatic breast cancer. Therefore, FDA recommended increasing the sample size to detect an improvement in survival. The sponsor stated that they were not going to increase the sample size and that they planned to maintain the predefined primary endpoint as TTP.

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Exploratory analysis:

Additional factors that could influence time to disease progression and death were planned to be tested. This included factors that were to be found significant at the 10% α -level in a univariate analysis, and used for a final multivariate analysis. Potential factors to be included, were previous paclitaxel treatment, center, presence/absence of liver metastases at baseline, predominant site of metastases at baseline and number of previous chemotherapy regimens in the metastatic setting.

Statistical Considerations:

Sample Size:

The protocol was to target a sample size of 454 patients. Power calculations were based on the primary analysis for time to progression. The sample size was determined by assuming that the time to progression in the combination arm (capecitabine + docetaxel) had a benefit of at least 6 weeks over docetaxel monotherapy arm with an 80% power at an overall significance level of 5%. The expected time to progression in the control group was 4.5 months. This calculation assumed no additional dropout rate and a careful follow-up period for each patient of at least 9 months. In addition, some power considerations were done for the secondary analysis of overall response rate. Assuming an overall response rate of docetaxel of 45% and an improvement of combination therapy of 15% (from 45% to 60%), the study had approximately 90% power with 454 evaluable patients in the intent-to-treat analysis.

Analysis Populations:

Three different patient populations were defined in the protocol.

Intent-to-treat population: "All randomized patients who did not receive at least one dose of study medication will be excluded from an intent-to-treat analysis for efficacy."

Standard population: All patients who receive at least six weeks of treatment

Safety Population: "Patients randomized who did not receive at least one dose of study medication and for whom no follow-up safety information was available were to be excluded from the analysis of safety."

Reviewer's Comments:

- Interim analyses were not specified in the protocol.
- The reviewer does not agree with the protocol definition of ITT population. The ITT population should consist of all randomized patients.

Criteria For Exclusion of Patients from Analyses

The following criteria for discontinuation of study were to be used:

- Voluntary discontinuation

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- Serious adverse effect: the investigator was to decide if the patient was to be withdrawn from the study.
- Non-compliance with the protocol.
- Progressive disease

Criteria for exclusion of patients from efficacy analysis:

All patients will be excluded from the standard efficacy analysis who:

- did not receive at least six weeks of treatment (for reasons other than progressive disease or death)
- received less than 50% of the anticipated treatment during the first 6 weeks
- severely violated protocol inclusion or exclusion criteria
- had inadequate information about tumor burden at baseline
- had inadequate tumor assessment information.

D. Study Results

Patient Demographics/Disposition

Patient Demographics

The following results are from the sponsor's analyses and tables:

Enrollment:

Five hundred and eleven patients from 75 investigational sites were enrolled in this study. Two-hundred fifty five patients were randomized in the capecitabine-docetaxel combination arm and 256 in the docetaxel monotherapy arm. Randomization was done by country; stratification was done by previous paclitaxel treatment or not. The sponsor contracted a third party, International Institute for Drug Development to perform the randomization for this study. The following table summarizes all countries and the number of patients enrolled.

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Table 6 Clinical Sites Information

Country	Study Sites (n)	Patients Enrolled (n)
United States	8	47
Canada	11	61
Mexico	4	42
Australia	6	40
Germany	2	7
France	5	42
Great Britain	8	64
Spain	3	16
Italy	6	24
Norway	2	13
Israel	7	38
New Zealand	2	11
Argentina	1	4
Brazil	2	9
Taiwan	3	28
Russia	5	65
Total	77	511

Table 7 Analysis Populations

Patient (n)	Combination arm	Monotherapy arm	All Patients (n)
ITT Population (patients randomized)	255	256	511
Safety Population (patients who received study drug)	251	255	506
Standard Population *	197	218	415

* The standard population included all patients who participated in the study according to the protocol defined criteria for standard treatment.

Four patients in the capecitabine-docetaxel combination therapy group (patients 19945/4511, 19954/5405, 20015/6002, and 20022/2405) and one patient in the docetaxel monotherapy group (patient 19971/7101) did not receive study medication after randomization. One patient was not randomized and treatment was assigned by the sponsor (22248/4302). The safety population included 251 patients in the capecitabine/docetaxel combination therapy group and 255 patients in the docetaxel monotherapy group.

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Patient characteristics:

The demographics and clinical characteristics of the intent-to-treat population are shown in the table below. There were no significant differences between the two treatment groups. The median age in each arm was 52 and 51 years. There was no significant difference in the distribution of performance status between arms. In terms of laboratory tests, hematology parameters were balanced between the two arms. The frequency of abnormal physical findings and vital signs at baseline were similar among the two treatment groups.

Previous breast cancer treatment:

The proportion of patients, who had previous radiation therapy, hormonal therapy, adjuvant chemotherapy or prior doxorubicin, was comparable between the two treatment groups. However, the population in the combination arm had more previous surgical treatments compared to the monotherapy arm (91% versus 84%). This difference is statistically significant ($p=0.024$). About one-third of the patients in both study groups received the study treatment as the first chemotherapy for metastatic disease, and two-thirds as second or third-line chemotherapy for metastatic disease. A minor proportion of the patients in both treatment arms (9.8% in the combination therapy arm and 8.6% in the monotherapy arm) had received pre-study treatment with paclitaxel most as first line therapy for metastatic disease.

Anthracycline Failure:

More than 90% of patients in both treatment arms were resistant to anthracycline based chemotherapy according to protocol definitions (see inclusion criteria). The table below summarizes the types of pre-study anthracycline resistance in the ITT population.

Table 8 Summary of types of Pre-Study Anthracycline Resistance. (modified from sponsor's Table 29, Vol. 12, page 100.

Pre-Study Anthracycline Resistance	Combination arm 255 (%)	Monotherapy arm 256 (%)
No resistance according to protocol.	19 (7.5)	19 (7.4)
Progression on anthracycline therapy	65 (25.5)	73 (28.5)
Disease remained stable after 4 cycles of anthracycline therapy	41 (16)	40 (15.6)
Relapsed within 2 years of completing anthracycline adjuvant therapy	79 (31)	74 (28.9)
Brief response to anthracycline therapy with progression while on therapy or within 12 months after last dose	51 (20)	50 (19.5)

Nineteen patients in each arm did not meet criteria for anthracycline resistance. However, the reasons for non-resistance were similar in both treatment arms. The cumulative doses of anthracyclines were similar in the two treatment groups. Patients without anthracycline

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resistance received a median cumulative dose of 255 mg/m² in the combination arm and 240 mg/m² in the monotherapy arm. The number of patients with a time interval of more than 2 years between anthracycline therapy and randomization was equal in the 2 groups.

Table 9 Summary of patient's characteristics

Characteristics	Combination arm (255)	Monotherapy arm (256)
Age (median)	52	51
Karnofsky Performance Status (median)	90	90
Race (%)		
Caucasian	78	82
Black	3	2
Oriental	7	6
Other	13	10
Previous Therapy		
Surgery	231 (91%)	214 (84%)
Radiation	183 (72%)	176 (69%)
Adjuvant Hormonal	82 (32%)	81 (32%)
Neoadjuvant Chemotherapy	57 (22%)	46 (18%)
Adjuvant Chemotherapy	128 (50%)	131 (51%)
Previous hormonal therapy for metastatic disease	121 (47%)	139 (54%)
Previous chemotherapy for metastatic disease	166 (65%)	189 (74%)
Previous anthracycline regimen	255 (100%)	256 (100%)
Previous 5-FU regimen	196 (77%)	256 (100%)
Previous paclitaxel	25 (10%)	22 (9%)
Number of chemotherapy regimens in the metastatic setting prior to study entry		
0	89 (35%)	80 (31%)
1	123 (48%)	135 (53%)
2	43 (17%)	39 (15%)
3	0	2 (1%)

Tumor Characteristics:

Infiltrating ductal carcinoma was the most common tumor type. For the majority of patients in both treatment arms the primary tumor size was between 2 and 5 cm. Estrogen-receptor status was comparable between both treatment arms. Thirty nine percent to 42% of the patients were estrogen receptor positive, 32%-28% were estrogen receptor negative and 29% to 30% unknown.

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Extent and type of disease

The majority of patients had involvement of two or more metastatic sites. One patient in the combination therapy arm (patient 19955/5501) had no sites of metastatic disease at baseline. This patient had disease confined to the breast. The most common sites of disease were the liver (45% of the patients in the combination arm and 47% in the monotherapy arm), bone (42% of the patients in the combination arm and 46% in the monotherapy arm), lymph nodes (47% of the patients in the combination arm and 49% in the monotherapy arm). The distribution of disease sites was comparable in the two treatment arms.

The CRTs were not designed to capture if the patients had locally advanced disease. The sponsor retrospectively assessed the data and found that seven patients in the combination arm versus 4 patients in the monotherapy arm fit the description of locally advanced disease.

Table 10 Reviewer's Table: Summary of Prognostic Factors.

	Combination arm (255)	Monotherapy arm (256)
Karnofsky Performance Status median range	90 (70 – 100)	90 (70 – 100)
Interval from breast cancer diagnosis to recurrence (days) median range	683 (63 – 7399)	732 (85 – 7780)
Predominant Site of relapse Visceral Bone/soft tissue	189 (74%) 66 (26%)	183 (72%) 73 (28%)
Number of Sites 0-1 2 or more	35 (14%) 220 (86%)	27 (11%) 229 (89%)
Hormone Receptor Status Positive Negative Unknown	100 (39) 81 (32) 74 (29)	108 (42) 71 (28) 77 (30)

Reviewer's Comment:

The baseline demographic characteristics were balanced between the two arms. The tumor characteristics were also balanced among treatment groups. Her2/neu status was not reported in this study. Previous breast cancer treatments were balanced except for prior breast surgeries,

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which was higher in the combination arm, though the clinical significance of this imbalance is not known. There was a slight increase in the number of patients with more than 2 metastatic sites in the monotherapy arm (89% versus 86%); however, the difference is not significant. Both arms were well balanced for prognostic factors that are accepted predictors of survival (see table above).

Patient Disposition

Removal from study:

Patients were removed from study for the reasons summarized in the following table:

Table 11 Reason for withdrawal (From sponsor's Vol. 12 page 65)

Primary Reason	Combination Arm		Monotherapy Arm	
	255 N	(100) (%)	256 N	(100) (%)
Safety-Related				
Abnormal labs	6	(2)	4	(2)
Adverse Event	66	(26)	50	(19)
Death of Patient	6	(2)	6	(2)
Efficacy-Related				
Progressive Disease	110	(43)	153	(60)
Administrative				
Withdrawn Consent	21	(8)	12	(5)
Protocol Violation	2	(1)	3	(1)
Investigator's Discretion	0		1	(.4)
Lost to Follow-Up	1	(.4)	0	
Other	26	(10)	22	(9)
Total	238	(93)	250	(98)

Ninety-three percent of the patients in the combination therapy arm versus 98% in the monotherapy arm were withdrawn from the study during the treatment period (i.e., 48 weeks after study start). A higher percentage of patients in the monotherapy group (153 of 256 patients, 59.8%) withdrew due to PD/insufficient therapeutic response than patients in the combination therapy group (110 of 255 patients, 43.1%). A higher percentage of patients in the combination arm (26%) versus 19% in the monotherapy arm were withdrawn for adverse events. The most frequent adverse events leading to premature withdrawal were hand and foot syndrome (6%), stomatitis (5% in the combination arm versus < 1% in the monotherapy arm), diarrhea (3% in the combination arm versus < 1% in the monotherapy arm and neutropenic fever (similar in both treatment arms 1-2%). Six patients in the combination therapy arm and four patients in the monotherapy arm were withdrawn from the study due to laboratory abnormalities. In the combination therapy group premature withdrawals were due to: neutropenia (1 patient), thrombocytopenia (1 patient), increase of ASAT and ALAT (1 patient) and increased bilirubin (3

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patients). In the monotherapy treatment group increased ASAT and ALAT (2 patients), increased bilirubin (1 patient) and multiple causes (decreased hemoglobin and hematocrit, increased calcium and Creatinine: 1 patient). Treatment discontinuations due to patients death are discussed in section VII-C and Table 27. Reasons for withdrawing consent were similar in both treatment groups. From this group, only one patient (19945/4511) withdrew consent before receiving treatment. Also, a higher percentage of patients in the combination arm refused treatment (8% versus 5%). Treatment was discontinued due to protocol violation(s) in two patients in the combination arm and three patients in the monotherapy arm. One of the patients in the combination group (19955/5501), violated the protocol by taking other investigational drugs and the other (20015/6002) had elevated liver function tests (LFTs). Three patients in the monotherapy arm (19949/4910, 19971/7101 and 22248/4303) were considered violators, since they had only bone lesions, hepatic failure and no evaluable lesions at baseline, respectively.

Treatment Delivered

Forty five patients in the combination arm discontinued docetaxel and continued on capecitabine treatment alone. The median study day for discontinuation of docetaxel in these patients was day 98. The median number of capecitabine monotherapy cycles received after discontinuation of docetaxel was 3 with a median cumulative dose of 138100 mg.

Dose Reductions

The incidence of dose reductions was higher in the combination arm (65% versus 36%) compared to the monotherapy group. See table below:

Table 12 Dose reductions (From sponsor's Table 100 Vol. 12 page 222)

	Combination Arm N=251			Monotherapy Arm N=255
	Capecitabine only	Docetaxel only	Both drugs	Docetaxel
Dose reduction Patients (%)	11 (4.4%)	25 (10%)	127 (50.6%)	92 (36.1%)

The percentage of patients requiring dose reductions and/or treatment interruptions due to adverse events (including those assessed as unrelated to treatment) was higher in the combination therapy arm (83.7%) than in the docetaxel monotherapy arm (36.9%). The most common adverse events leading to dose modifications were hand-foot syndrome, diarrhea, and stomatitis in the combination therapy arm, and neutropenic fever, neutropenia, and diarrhea in the monotherapy arm. See table below.

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Table 13 Most frequent adverse events leading to dose modifications. (Modified from sponsor's Table 111 Vol. 12 page 239)

Adverse Event	Combination Arm		Monotherapy Arm	
	251	(100)	255	(100)
Hand Foot Syndrome	108	(43)	1	(<1)
Diarrhea	74	(29)	11	(4)
Stomatitis	69	(27)	6	(2)
Nausea/vomiting	21	(8)	2	(1)
Neutropenic Fever	30	(12)	30	(12)
Neutropenia	19	(8)	13	(5)

After discontinuation of docetaxel treatment, the dose of capecitabine was increased in 15 patients who had undergone capecitabine dose reduction to either 75% or 50% of starting dose during the combination therapy.

Dose-intensity

The median received dose of capecitabine during the course of the study was 77% of the planned dose. For docetaxel, the median received doses were 87% of the planned dose for patients in the combination therapy arm and 100% of the planned dose for patients in the monotherapy arm. The number of patients who had a docetaxel or capecitabine first level dose reduction in the combination arm doubles the number of patients who were dose reduced in the monotherapy arm. The second level dose reductions in the combination arm triple the number of patients who had a second level dose reduction in the monotherapy arm. See table below (from sponsor's Table 101 Vol. 12 page 223).

Table 14 Dose intensity (from sponsor's Table 101 Vol. 12 page 223).

	Combination Arm N=251			Monotherapy Arm N=255
	Capecitabine	Docetaxel	Either drug	Docetaxel
Dose reduction: first level Patients (%)	127 (50.6%)	148 (59%)	156 (62.2%)	87 (34.1%)
Time to reduction (days) Median Range	45	44	44	23
Dose reduction: second level Patients (%)	46 (18.3%)	10 (4.0%)	52 (20.7%)	18 (7.1%)
Time to reduction (days)				

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Median	85	69	84	64.5
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Subsequent therapy

Most of the patients in both treatment arms had subsequent anticancer therapy including chemotherapy, radiation therapy, hormonal therapy and surgery. There was no significant difference between the two groups in the number of patients who received any of these modalities. However there was an imbalance in the use of subsequent capecitabine and docetaxel. The post-study treatment with docetaxel was higher in the combination group (19.2%) than in the monotherapy group (6.6%), and the use of capecitabine was higher in the monotherapy group (14.5%) as compared to the combination group (2.7%). See table below.

Table 15 Post-study treatments (Modified from sponsor's Table 74 Vol.12 page 176)

Post-Study Treatments	Combination arm		Monotherapy arm	
	255	(%)	256	(%)
Surgery	14	(5.5)	11	(4.3)
Radiotherapy	71	(27.8)	70	(27.3)
Endocrine Therapy	69	(27.1)	66	(25.9)
Trastuzumab Treatment	20	(7.8)	20	(7.8)
Chemotherapy	161	(63.1)	156	(60.9)
Docetaxel	49	19.2)	17	(6.6)
Capecitabine	7	(2.7)	37	(14.5)
Paclitaxel	23	(9)	18	(7)
Anthracyclines	21	(8.2)	22	(8.6)
5-FU	45	(17.6)	52	(20.3)
Vinorelbine	66	(25.9)	60	(23.4)

Forty-nine patients in the combination group started post-study treatment before progressive disease compared to the monotherapy group (14 patients). The number of patients starting post-study endocrine therapy before recorded progressive disease were similar in the two treatment groups (8.2% in the combination therapy group and 6.6% in the monotherapy group).

Reviewer Comment:

- Subsequent therapy after tumor progression might obscure any survival effect of the study drugs. The number of patients who had subsequent docetaxel and capecitabine is significantly different and it may confound the survival effect in both treatment groups.
- In addition, the protocol stated that patients treated in the combination group could not continue docetaxel monotherapy within the protocol if capecitabine had to be discontinued.

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- A higher percentage of patients in the combination arm received post-study treatment before they had progressive disease. This imbalance could impact the validity of the primary endpoint of time to progression.

E. Efficacy Conclusions[Note6]

For reporting the efficacy parameters, the intent-to-treat and the standard population were used.

The analysis was to be done primarily by taking all information into account, thus including follow-up information recorded after end of treatment ('primary' approach). A second 'on treatment' analysis was to exclude the follow-up information.

Time to Progression:

At the analysis time point, 230 of the 255 combination therapy patients had progressive disease (90%) and 247 of the 256-monotherapy patients had progressed (96%). The time to progression was 186 days for the combination therapy patients and 128 days for the monotherapy patients. This difference is equivalent to a 25% reduction in the risk of tumor progression for combination therapy patients (hazard ratio 0.65, $p=0.0001$). Although the protocol prohibited additional therapy prior to clinical evidence of progression, 49 patients in the combination arm and 14 patients in the monotherapy arm, started post-study treatment before PD.

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Time to Progression Curves for Study SO14999

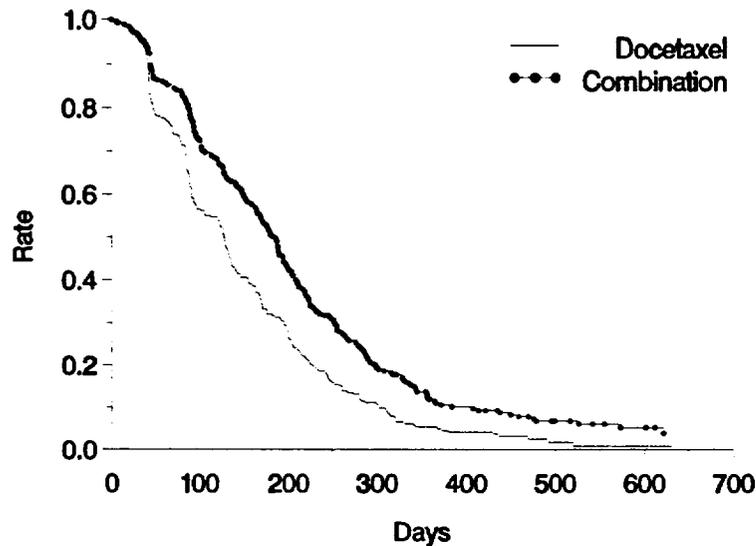


Figure 1 Kaplan-Meier TTP Curves for study SO14999

Reviewer's Comments:

- Given the imbalance in post-therapy treatment before documentation of PD, the reviewer used two methods to measure time to progression. The first one used the conventional date of first study drug administration until documentation of progressive disease. The second censored patients at the time of any therapy following removal from the study but prior to clinical evidence of recurrence or progression. Although this method is not conventionally used, it will decrease the likelihood that a benefit that resulted from the new therapy is mistakenly attributed to the study therapy.
- The following table summarizes the TTP results using both methods.

Table 16 FDA's analysis for TTP.

ITT Population N=511	Median (95% CI) days	Hazard Ratio	95% CI for Hazard Ratio	Log-rank P-value
Combination	186 (165-198)	0.65	0.54-0.77	0.0001
Monotherapy	128 (105-136)			

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Censoring at the start of new therapy and prior to progressive disease				
Combination	183 (165-201)	0.658	0.54-0.79	0.0001
Monotherapy	128 (105-137)			

- Regardless of the method used, treatment with capecitabine + docetaxel resulted in a significantly longer time to progression.
- The median time to progression observed in the control arm (docetaxel) is comparable to those cited in the literature.
- This finding represents significant clinical benefit.
- Six patients in the combination arm (2204, 2604, 5404, 6103, 7603 and 1803) and eight patients in the monotherapy treatment arm (4904, 5403, 6102, 6502, 6904, 8802, 8803, and 9401) died before disease progression was formally documented but the cause of death was apparently due to disease progression.

Table 17 FDA's analysis for TTP excluding patients who died before disease progression was documented but apparently died from PD.

ITT Population N=497	Median (95% CI) days	Hazard Ratio	95% CI for Hazard Ratio	Log-rank P-value
Combination	187 (165-196)	0.645	0.54-0.77	0.0001
Monotherapy	128 (105-136)			

- Exclusion of these patients did not altered TTP. Patients who died of disease without a previous date of progression did not overestimated time to progression in these patients.

Survival:

At the time of data base closure (May 11, 2000), 149 (58%) of combination therapy versus 166 (65%) of the monotherapy patients died. The median duration of survival was 418 months for the combination arm versus 338 months for the monotherapy arm. The stratified log-rank p-value was 0.012 and the Hazard risk ratio (monotherapy:combination) was 0.75. The survival analysis results including the 4-month survival update are summarized in the following table.

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Table 18 FDA's survival analysis (ITT population)

ITT Population N=511	NDA Submission Data		NDA 4-month update	
	Combination 149/255	Monotherapy 166/256	Combination 183/255	Monotherapy 201/256
Median (95% CI) days	418 (374-492)	338 (298-379)	442 (375-497)	352 (298-387)
Hazard Ratio	0.75		0.78	
2-sided 95% CI for Hazard Ratio	0.60-0.94		0.63-0.95	
Log-rank p-value	0.012		0.013	

The figures below shows the Kaplan-Meier estimates of the survival distribution for the two treatment arms in the ITT population. The one year survival rates were 57.25% (95% CI 51.18%, 63.32%) for the combination therapy arm and 47.27% (95% CI 41.15%, 53.39%) for the monotherapy arm.

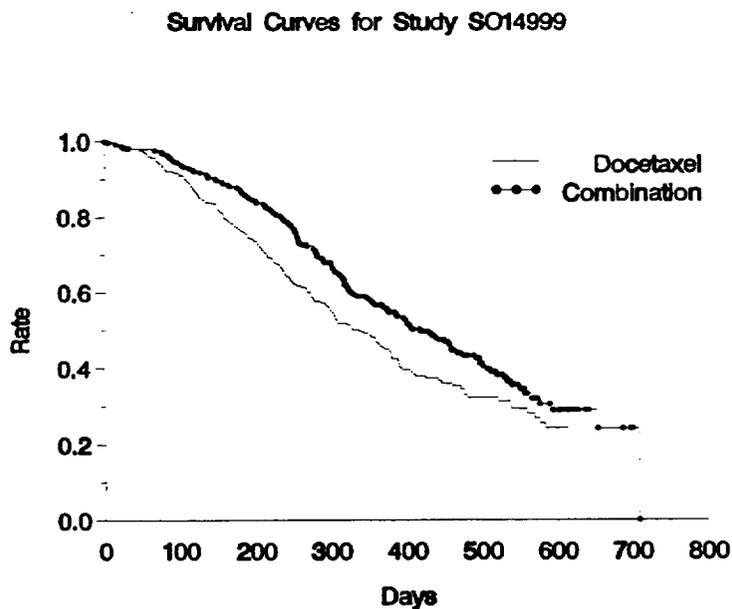


Figure 2 Kaplan-Meier Survival Curves for Study SO14999

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Updated Survival Curves for Study SO14999

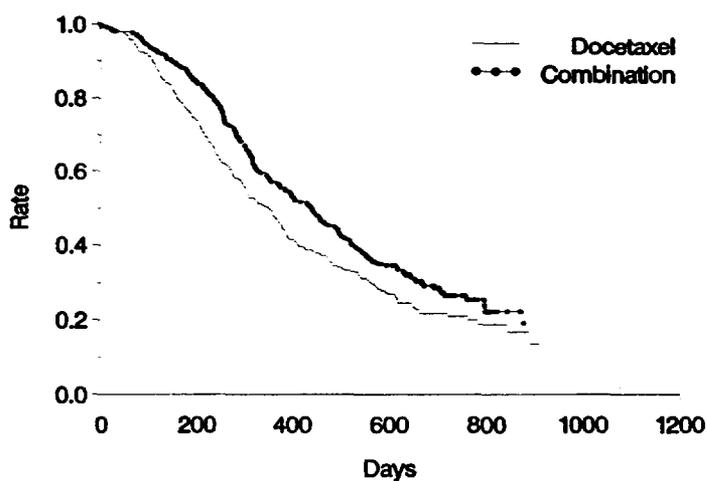


Figure 3 Survival Curves for Study SO14999 (4-month update)

Reviewer's Comments:

- This survival data is mature (about 72% dead in the combination arm and 78% in the monotherapy arm) for analysis.
- The survival was significantly better for patients in the combination arm than for patients in the monotherapy arm despite crossover in 15% to 20% of the patients. The median survival observed in the monotherapy arm is comparable to that reported in the literature for docetaxel at the same doses.
- The dates of death listed in the database "DIED" were included in the FDA review. These dates were then used in a JMP query to calculate survival times. Patients that did not die were censored at date of last contact. This dataset was incomplete. Therefore, FDA requested the sponsor to clarify where the censoring dates came from. The sponsor submitted the requested datasets. Censoring time was the maximum time of 3 variables: date

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of last dose (TTTEXT), date the patient was last known alive (TTFuPALV) and date of last tumor assessment (TTLAST). The survival time was calculated for each 511 patients enrolled and the data used to create a Kaplan-Meier curve. These results were identical to those calculated by the sponsor.

- The majority of deaths in both treatment arms were due to progressive disease. See safety section for a summary of mortality.

Exploratory Analysis:

Previous Treatment with Paclitaxel

Patients recruited in the study were allowed to have previously received treatment with paclitaxel, which was used as a stratification variable at the time of randomization. Less than 10% (47/511) of the patients in the ITT population had previously received paclitaxel. Therefore, an accurate assessment of the treatment effect in this subgroup is difficult. The table below shows a summary of the sponsor's analysis of survival times and confidence intervals for patients with and without previous treatment with paclitaxel.

Table 19 Summary of Survival Results for Patients with and without prior Paclitaxel (From sponsor's 4-month survival update submission)

ITT Population	Combination arm (255)	Monotherapy arm (256)	Log-rank p-value
NDA submission			
Time to Death Previous Paclitaxel			
Number of Events	17 of 25	9 of 22	0.3323
Median (days)	351	577	
95% CI	[256, 551]	[328, NE]	
Time to Death without Previous Paclitaxel			
Number of Events	132 of 230	157 of 234	0.0028
Median (days)	438	158 321	
95% CI	[376, 497]	159 [287, 378]	
4-Month Safety Update			
Time to Death Previous Paclitaxel			
Number of Events	22 of 25	12 of 22	0.0550
Median (days)	351	577	
95% CI	[256, 496]	[328, NE]	
Time to Death without Previous Paclitaxel			
Number of Events	161 of 230	189 of 234	0.0012
Median (days)	450	327	
95% CI	[395, 512]	[292, 378]	

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Reviewer's Comments:

- Survival was statistically superior for patients with previous paclitaxel exposure who were treated in the monotherapy arm. To understand the difference in survival for this subgroup, the reviewer looked at factors that could impact survival in metastatic breast cancer. The following factors were explored: dose intensity, post study therapy, prognostic factors and toxicity. Subsequent therapy was similar in both treatment groups. The only difference between the previous paclitaxel subgroup and the ITT population was the docetaxel cumulative dose, which was higher in the monotherapy arm of the subgroup. See table.
- Most of the previous paclitaxel therapy was administered as first line metastatic setting. The paclitaxel cumulative dose was similar in both groups. Only 28-30% of the patients in both treatment arms probably were refractory to paclitaxel. See table below.
- The meaning of the negative survival in this subset of patients treated in the combination arm is unknown. Overall, less than 10% of the ITT population had previously been treated with paclitaxel. Moreover, response rate and time to progression in the combination arm was superior regardless of previous treatment with paclitaxel (See table 19).

Table 20 Summary of Previous Paclitaxel Therapy.

Pre-Study Paclitaxel	Combination arm (255)	Monotherapy arm (256)
Pre-study Treatment Setting		
Neoadjuvant	1 (0.4)	1 (0.4)
Adjuvant	4 (1.6)	3 (1.2)
Adj + Metastatic	0	1 (0.4)
Metastatic	20 (7.8)	17 (6.6)
Total	25 (9.8)	22 (8.6)
Line of Metastatic Setting		
1 st	16 (6.3)	11 (4.3)
2 nd	4 (1.6)	5 (1.9)
3 rd	0	2 (0.8)
Total	20 (7.8)	18 (7)
Interval Paclitaxel to randomization (median days)	150	121
Paclitaxel Cumulative Dose Median (mg/m²)	900	910
Best Response to Paclitaxel		
CR	4 (20)	1 (5.6)
PR	5 (25)	7 (38.9)
SD	3 (15)	4 (22.2)
PD	6 (30)	5 (27.8)

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Unknown	2 (10)	1 (5.6)
Total	20 (100)	18 (100)

Table 21 Previous paclitaxel subgroup treatment characteristics.

	No Previous Paclitaxel Population		Pre-Study Paclitaxel Population	
	Combination arm (230)	Monotherapy arm (234)	Combination arm (25)	Monotherapy arm (22)
Docetaxel Cumulative Dose (median)	527	730	442.5	800
Post-study treatments				
Chemotherapy	56	49	5	6
Hormonal	28	21	1	0
Radiotherapy	71	70	8	5
Surgery	14	11	3	0

Table 22 Reviewer's Table: Time to Progression Results for Patients with and without prior Paclitaxel.

TTP	No Previous Paclitaxel Population		Pre-Study Paclitaxel Population	
	Combination arm (230)	Monotherapy arm (234)	Combination arm (25)	Monotherapy arm (22)
Median (95% CI) Days	186 (165-198)	127 (105-136)	180 (80-222)	128 (88-245)
Hazard Ratio	0.63		0.91	
2-sided 95% CI for Hazard Ratio	0.52-0.76		0.50-1.65	
Log-Rank P-value	0.0001		0.76	

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Response Rate:

Objective response rate was a protocol-defined secondary efficacy endpoint. The sponsor stated that assessments made after end of treatment (more than 28 days after the last dose of trial medication) were excluded from the assessment of the overall response. The overall response assessment (CR, PR, SD or PD) by the investigator was used in the analysis; no recalculation of response assessments on the basis of total lesion sizes was performed by the sponsor. Four patients (19949/4910, 19983/8306, 19996/9607 and 22248/4303) did not have tumor assessments at baseline. The number of patients with no post-baseline tumor response information was higher in the combination arm (33, 12.9%) than in the monotherapy arm (22, 8.6%).

Assessment of Response:

Investigator, IRC and reconciled response results are presented in the table below. According to the investigator's assessment of response, 42% of patients in the combination treatment group had a complete or partial response to treatment compared to 30% of the patients in the monotherapy treatment group. The sponsor claims that response rate assessed by the IRC was 32% in the combination arm compared to 23% in the monotherapy arm. IRC blindly assessed tumors by radiographic means and photographic documentations. The IRC reviewers did not have access to physical examination data. Therefore, 21 patients (4%) with indicator lesions measured only by physical exam were not available to the IRC. There were 147 (29%) patients in which the IRC and the investigator assessments were different.

Table 23 Reviewer's Table: Overall Response Rate

Overall Response Rate							
N (%)							
Investigator Assessment		IRC Assessment		Reconciled		FDA Assessment	
Combination 255 (%)	Monotherapy 256 (%)						
106 (41.6)	76 (29.7)	82 (32.2)	59 (23.1)	84 (32.9)	55 (21.5)	83 (32)	56 (22)
P= 0.0058		P= 0.0246		P= 0.0043		P=0.009	
Complete Response							
N (%)							
12 (4.7)	9 (3.5)	7 (2.7)	3 (1.2)	8 (3.1)	2 (0.8)	8 (3.1)	4 (1.6)

FDA Review of Response:

CRFs from the 147 patients in which the IRC and the investigator assessments were different were checked. Responses were assessed using the tumor measurements and confirmed with electronic databases provided by the sponsor. The following guidelines were used:

- Assessments of tumor response from all baseline disease were done per WHO criteria.
- The confirmation of response was verified electronically to ensure that it was at least 4 weeks later than the first response.

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- When the only available confirmation for partial response was less than 4 weeks after the first measurement or the confirmation was missing, the best overall response was classified as SD.
- Only patients with complete response or a confirmation of partial response were regarded as responders.
- Patients with no tumor assessment after start of treatment were considered as non-responders.
- In cases where disease assessment was performed by physical examination measurements only, the response was the best response reported by the investigator.

FDA disagreed with the assessment of one patient in the combination arm.

- Patient # 19995/9504 had two skin nodules that were followed by physical examination and photographs and were assessed as PR by the investigator and the sponsor's reconciled comments. FDA's assessment is a non-confirmed PR since photographs were not taken to confirm the response and the following visit was found to have progressive disease by a bone scan showing a new left rib lesion (see CRF notes days 85 and 127 dated 12/04/99).

FDA disagreed with the assessment of 1 patients in the monotherapy arm.

- Patient # 19960/2628 had several lung lesions at baseline that were followed by CT scan. The investigator assessment is a PR. The IRC notes confirm the investigator assessment. The sponsor's reconciled assessment is consistent with stable disease. The FDA reviewer considers this patient as a responder because the CRF tumor measurements and notes (from Days 85 and 127) are consistent with a PR.

The sponsor was sent a facsimile (July 31, 2001) of the patients that had discordant results between the FDA and the sponsor evaluation. The sponsor agreed that patient # 19995/9504 had an unconfirmed partial response. The sponsor does not consider patient # 19960/2628 a responder. FDA still considers this patient had a partial response. We took the following into consideration: IRC deemed only one of the three lesions measurable; however, not for the entire course. Lesions #1 and #3 were measurable for some time for the IRC and the investigator. Lesion #1 was non-measurable for the IRC on June 2, 1999 (visit 1), so we agree this lesion can not be factored into assessment of response. Lesions #2 and #3 were measurable for both visit 1 and visit 2, lesion #3 becomes non-measurable on visit 3. The sum of the products for these two lesions are a partial response for two visits, which is consistent with the investigator.

FDA Reviewer's Response Rate Conclusions:

Based on this review an one additional responder was added to the monotherapy arm for a total of 56. Combination therapy was statistically superior to monotherapy in terms of response rate based upon the investigator, IRC and the sponsor's assessments for reconciliation of the tumor response data. This was consistent with the FDA assessments.

VII. Integrated Review of Safety

For reporting the safety parameters, the safety population was used.

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A. Brief Statement of Conclusions

The toxicity of the xeloda/docetaxel combination regimen was greater. The adverse events were consistent with those described in the label for xeloda and docetaxel. Gastrointestinal adverse events such as stomatitis, diarrhea and mucositis were all more common in the combination therapy arm. Hand and foot syndrome was presented in 63% of the patients receiving combination of xeloda/docetaxel. Treatment related neutropenia leading to medical intervention occurred with similar frequency in both treatment arms. The incidence of neutropenic fever was higher in the monotherapy treatment group. Treatment related mortality was higher in the xeloda/docetaxel arm (4 patients: enterocolitis, sepsis, hepatic coma and pulmonary edema) compared to the docetaxel monotherapy arm (1 patient: sepsis). There was a higher incidence of hyperbilirubinemia grade ≥ 3 in the combination therapy arm (11%) compared to the monotherapy arm (5%).

B. Description of Patient Exposure

Please refer to section VIII. The percentage of patients requiring dose reductions and or treatment interruptions was higher in the combination therapy treatment arm (84%) compared to the monotherapy treatment arm (37%). The most common adverse event leading to dose modification were hand and foot syndrome, diarrhea and stomatitis in the combination treatment arm and neutropenic fever and diarrhea in the monotherapy treatment group.

C. Methods and Specific Findings of Safety Review

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Clinical Toxicities

In both treatment groups, most patients had at least one adverse event reported during the study (99% in the combination arm and 97% in the monotherapy arm). The number of Grade 3 adverse events was higher in the combination arm (76%) than the monotherapy arm (58%). The overall incidence of Grade 4 adverse events were 29% in the combination arm and 32% in the monotherapy arm. This difference was mainly due to a lower incidence of neutropenic fever in the combination arm. See table below.

Table 24 Reviewer's Table: Overview of the incidence of related and unrelated adverse events.

	Combination Arm 251 (100%)			Monotherapy Arm 255 (100%)		
	Total %	Grade 3 %	Grade 4 %	Total %	Grade 3 %	Grade 4 %
Number of patients with at least one adverse event	99	76.5	29.1	97	57.6	31.8

Clinical toxicities are summarized in the table below. Gastrointestinal toxicity and hand-foot-syndrome were the most common adverse events. Stomatitis (67% vs. 42%), diarrhea (67% vs. 48%), vomiting (35% vs. 24%) and hand-foot-syndrome (63% vs. 7%) were more common in the combination arm compared to the monotherapy arm. Hematologic toxicities were similar in both treatment groups: neutropenia (16% vs. 18%), anemia (14% vs. 12%) and grade 4 thrombocytopenia (0.4% in both arms). The incidence of Grade 3 or 4 neutropenic fever was slightly higher in the monotherapy arm (21% vs. 16%). However, the percentage of patients with sepsis was the same in the two treatment groups (3%). Unusual clinical toxicities included: capillary leak syndrome (1 patient in the monotherapy arm), hepatic coma (1 patient in the combination arm), drug hypersensitivity (1 patient in the monotherapy arm).

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Table 25 Most Frequent Adverse Events (modified from sponsor's tables 91 and 93 Vol. 12 page 205)

Adverse Event	Combination Arm 251 (100%)		Monotherapy Arm 255 (100%)		P values
STOMATITIS					
All Grades	167	(67)	108	(42)	< 0.001
Grade ≥ 3	44	(18)	12	(5)	< 0.001
DIARRHEA					
All Grades	167	(67)	122	(48)	< 0.001
Grade ≥ 3	35	(14)	15	(6)	0.023
VOMITING					
All Grades	87	(35)	61	(24)	0.008
Grade ≥ 3	11	(4)	2	(1)	0.01
HAND-AND-FOOT SYNDROME					
All Grades	159	(63)	19	(7)	< 0.001
Grade ≥ 3	61	(24)	3	(1)	< 0.001
NEUTROPENIC FEVER					
All Grades	40	(16)	53	(21)	0.16
Grade ≥ 3	40	(16)	53	(21)	0.16
NEUTROPENIA					
All Grades	44	(18)	42	(16)	0.74
Grade ≥ 3	39	(16)	36	(14)	0.65
ANAEMIA					
All Grades	35	(14)	30	(12)	0.46
Grade ≥ 3	9	(4)	10	(4)	0.80
ALOPECIA					
All Grades	103	(41)	106	(42)	0.89
Grade ≥ 3	15	(6)	17	(7)	0.74
ASTHENIA					
All Grades	65	(26)	64	(25)	0.83
Grade ≥ 3	9	(4)	14	(5)	0.31
DERMATITIS					
All Grades	21	(8)	27	(11)	0.40
Grade ≥ 3	0		0		
ARTHRALGIA					
All Grades	38	(15)	61	(24)	0.013
Grade ≥ 3	3	(1)	6	(2)	0.333
MYALGIA					
All Grades	36	(14)	64	(25)	0.002
Grade ≥ 3	4	(2)	5	(2)	0.71
DEHYDRATION					
All Grades	24	(10)	17	(7)	0.24
Grade ≥ 3	5	(2)	2	(1)	0.26

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Clinical Laboratory Evaluations:

Neutropenia was the most common laboratory abnormality (68% in the combination arm and 76% in the monotherapy arm). The most common Grade 3 and 4 blood chemistry abnormalities are detailed on sponsor's table 128 Vol. 12 page 270. Hyperbilirubinemia occurred with a higher frequency in the combination therapy arm (9% versus 3% in the monotherapy arm). Elevation of transaminases were infrequent in both treatment groups (3% in the combination treatment arm and 5% in the monotherapy). The sponsor explored the characteristics of the patients who presented Grade ≥ 3 hyperbilirubinemia. In the combination therapy group, the incidence of adverse events was similar in patients with and without hyperbilirubinemia. However, in the monotherapy group, the incidence of adverse events was increased in patients with hyperbilirubinemia. A higher incidence of deaths during study (any reason) and adverse events were reported in patients experiencing hyperbilirubinemia compared to patients without hyperbilirubinemia in both study groups.

Table 26 Summary of the characteristics of the patients experiencing Grade ≥ 3 Hyperbilirubinemia (Modified from sponsor's table 130 Vol. 12 page 274)

	Combination Arm 251	Monotherapy Arm 255
Grade ≥ 3 hyperbilirubinemia	27 (11%)	12 (5%)
Liver metastases at baseline	13 (48%)	4 (33%)
Predominant type of Hyperbilirubinemia		
Unconjugated	9 (33%)	3 (25%)
Conjugated	3 (11%)	0
Unknown	10 (37%)	5 (42%)
Elevated Alkaline Phosphatase	5 (18%)	4 (33%)
Elevated Transaminases	9 (33%)	6 (50%)

Reviewer's Comments:

- Hyperbilirubinemia was less frequent in this trial (9% versus 3%) compared to the previous studies in patients with either metastatic breast or colorectal cancer (17%). Dose modification parameters were stricter in the current trial. Half of the patients with hepatic dysfunctions were due to liver metastases.
- Only one patient treated in the combination arm died from hepatic failure. According to the death narrative there was no history of liver metastases or other cause of liver failure.
- Safety by age will be discussed in section IX B.

Mortality:

The incidence of all deaths (related and unrelated) occurring during treatment or within 28 days after the last dose was similar in both treatment arms (12 deaths or 4.7% in the combination therapy arm and 8 deaths or 3.1% in the monotherapy arm). The incidence of treatment-related deaths occurring during study was higher (4 deaths) in the combination therapy arm (two deaths

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in the monotherapy arm). Four patients died from infections secondary to myelosuppression and one patient died from pulmonary edema. One patient treated in the combination treatment arm died from hepatic failure. A majority of deaths in both treatment groups were considered by the investigators to be due to progressive disease and unrelated to treatment. The following table summarizes key information regarding deaths in this trial:

Table 27 Mortality during treatment or within 28 days after the last dose of study drug (modified from sponsor's text table 112 and 113 Vol.12 pages 241, 242)

General Cause of Death	Specific Cause of Death	Cycle/day	Treatment Arm	
			Combination Patient ID (age)	Monotherapy Patient ID (age)
Treatment Related	Enterocolitis	C1/D14	19955/5513 (63)	
	Sepsis	C1/D23	20012/3701 (68)	
		C1/D11		19979/7904 (63)
	Pulmonary Edema	C2/D11	20017/7605 (36)	
	Hepatic Coma	C5/D33	20018/2003 (50)	
	Neutropenia/Pneumonia	C1/D9		19965/6502 (43)
Study Disease	Carcinomatosis	C4/D38	19946/4609 (53)	
	Breast Cancer	C2/D33	19949/4905 (60)	
		C4/D38	19956/5613 (49)	
		C4/D20	19962/6206 (48)	
		C12/D23	19999/2204 (55)	
		C1/D20	20014/6103 (58)	
		C1/D4	20017/7603 (26)	
		C2/D11		19949/4904 (48)
		C1/D12		19990/9009 (68)
C3/D32	19954/5408 (57)			
Other	Cachexia	C5/D14		19987/1412 (37)
	Pulmonary embolism	C3/D19		19963/6301 (61)
	Respiratory failure	C1/D13		19999/2201 (42)
	Ruptured diverticulum of colon	C2/21		19945/4509 (48)
Total Number of Deaths			12	8

Reviewer's Comments:

- Patient # 20018/2003 was a 50 year old female who died from hepatic failure after receiving 5 cycles of combination therapy. The CRF does not documented altered liver function tests at baseline or during follow-up (last blood chemistry taken 30 days before death showed a bilirubin of 2.1 mg). The only concomitant drug that the patient received for 5 days was paracetamol. According to the death narratives there was no evidence of liver metastases at baseline or at the time the patient presented with hepatic coma. There is no information of autopsy.

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- Patient # 19954 / 5408 died from progressive disease according to the death narratives. The investigator stated that repeated episodes of pleural effusion were the cause of death.
- Patient # 19956/5613 died from respiratory and hepatic failure on C4/D38. Autopsy revealed multiple lung and liver lesions.
- Patient # 19962/6206 died on C4/D20 from progressive disease. According to the death narratives, the patient presented with seizures and fell into a coma. A CSF revealed malignant cells consistent with metastatic breast cancer.
- Patient # 19999/2204 died on C12/D23 from “effusions and hypertension”. According to the investigator this event was related to progressive disease.
- Patient # 20014/6103 died on C1/D20 from progressive disease. The death narrative indicated that the patient presented with lymphangitic carcinomatosis and probable pulmonary embolism.
- Patient # 20017/7603 died on C1/D4 from respiratory failure secondary to pleural effusion.
- Patient # 19965/6502 died on C1/D9 from pneumonia. According to the death narratives the autopsy confirmed pneumonia as a cause of death secondary to breast cancer. The reviewer consider this complication could be related to study drug. Although the patient had a left lower lobe consolidation at baseline, the severe neutropenia post therapy probably contributed to the pneumonia.
- Patient # 19987/1412 died on C5/D14. According to the narratives, the patient died from cachexia which the investigator considered secondary to disease progression.
- Patient # 19999/2201 died from progressive respiratory failure secondary to pleural effusions.

D. Adequacy of Safety Testing[Note10]

- The safety data and assessments carried out in this trial are adequate. The findings are consistent with the labeling. We strongly encourage the sponsor to pursue the optimal dose of capecitabine for > 60 year old patients in prospective studies.

E. Specific Findings of Safety Review

F. Summary of Critical Safety Findings and Limitations of Data

There are no major critical differences between FDA and the sponsor assessment of data. We do not agree with the proposed initial dose reduction claiming preserved efficacy based on a retrospective subgroup analyses. This is an area that will require further assessment.

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VIII. Dosing, Regimen, and Administration Issues[Note11]

The percentage of patients requiring dose reductions and or treatment interruptions was higher in the combination therapy treatment arm (84%) compared to the monotherapy treatment arm (37%). The most common adverse event leading to dose modification were hand and foot syndrome, diarrhea and stomatitis in the combination treatment arm and neutropenic fever and diarrhea in the monotherapy treatment group. Since most of patients in the combination therapy arm were dose reduced due to adverse events, uncertainty remains about the optimal dosing. It is highly recommended that the sponsor plans future studies to explore optimal doses of xeloda to improve the safety profile. A phase 2 study in patients with metastatic breast cancer exploring reduced doses of xeloda and different schedules is recommended by the Agency.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

This study was done strictly in females since it targeted breast cancer. Colorectal studies previously submitted to support approval for metastatic breast cancer included males and females.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Age, Gender and Ethnicity: No formal studies were conducted to examine the effect of age or gender or ethnicity on the pharmacokinetics of capecitabine and its metabolites.

Safety by Age

The sponsor did a subset analysis of grade 3-4 adverse events by age. Patients > 60 years of age had a higher incidence overall of grade 3-4 adverse events and premature withdrawal due to adverse events than those who were <60 years of age in both treatment arms by 10-12%. The table below shows a comparison of the clinical adverse events by age. The more frequent adverse events among patients > 60 years of age treated in both treatment arms included stomatitis, hand-foot syndrome and neutropenia. Diarrhea was increased only in patients > 70 years old in the combination arm; however, data is limited with only 10 patients in this age group. Stomatitis was increased in older than 60 in both treatment groups especially in the combination arm. Neutropenic fever was only increased in the older population of patients who were treated in the monotherapy arm. Hand and foot syndrome was increased in the older than 70 year group in the combination arm. Creatinine clearance at baseline did not have a clinically relevant impact on safety in either treatment group. Patients with renal impairment were excluded from the study.

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Table 28 Safety profile in the subgroup of patients by age. (Modified from sponsor's tables 138, 139 Vol. 12 page 290, 291)

Age Groups	Combination Arm				Monotherapy Arm			
	< 60	≥ 60 all	60 – 70	70 – 80	< 60	≥ 60 all	60 – 70	70 – 80
Number of Patients	184	67	57	10	192	63	56	7
Patients with Grade 3/4 adverse events	138(75%)	58 (87%)	48 (84%)	10 (100%)	118 (61%)	45 (71%)	39 (70%)	6 (86%)
Diarrhea: Grade 3/4	25 (14%)	10 (15%)	7 (12%)	3 (30%)	13 (7%)	2 (4%)	2 (4%)	
Stomatitis: Grade 3/4	24 (13%)	20 (30%)	17 (30%)	3 (30%)	4 (2%)	8 (13%)	7 (13%)	1 (14%)
Neutropenic Fever	32 (17%)	8 (4%)	8 (4%)	0	37 (19%)	16 (25%)	12 (21%)	4 (57%)
Hand-foot-syndrome: Grade 3	43 (23%)	18 (27%)	14 (25%)	4 (40%)	0	3 (5%)	2 (4%)	1 (14%)
Patients with Grade 4 adverse events	39 (21%)	23 (34%)	20 (35%)	3 (30%)	56 (29%)	20 (32%)	17 (30%)	3 (43%)
Patients withdrawn due to AE	50 (27%)	30 (45%)	26 (46%)	4 (40%)	40 (21%)	20 (32%)	16 (29%)	4 (57%)

The sponsor proposed to submit analyses to support a labeling change to reduce the starting dose of capecitabine in elderly patients (> 60 years of age) when used in combination with docetaxel. The proposal consisted in a reduction of the starting dose of capecitabine by 25% from 1250 mg/m² to 950 mg/m² twice daily x 14 days, with a one week rest period.

The FDA reviewers performed exploratory analyses comparing the efficacy of patients < 60 and > 60 years of age. The subgroup analyses showed that the women > 60 years of age maintain the trend for superiority in TTP and survival. Response rate was similar in both treatment groups (see table below). Therefore, the increased toxicity and treatment withdrawal did not reverse the outcome trends in the subgroup.

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Table 29 Reviewer's Table: Efficacy endpoints in women \geq 60 years old.

Survival				
ITT Population N=131	Median (95%CI) (days)	Hazard Ratio	95% CI for Hazard Ratio	Log-rank P-value
Combination	457 (323-544)	0.94	0.64-1.40	0.77
Monotherapy	390 (278-538)			
TTP				
ITT Population N=131	Median (95%CI) (days)	Hazard Ratio	95% CI for Hazard Ratio	Log-rank P-value
Combination	174 (127-204)	0.652	0.46-0.94	0.019
Monotherapy	133 (105-171)			
Response Rate				
ITT Population N=131	Overall Response Rate	χ^2 P-value		
Combination	20/68 (29%)	0.93		
Monotherapy	19/63 (30%)			

Reviewer's Comments:

- Increased adverse events were seen in women $>$ 60 year old: stomatitis in both arms, neutropenia in the monotherapy arm and hand and foot syndrome in the combination arm.
- Deaths during treatment or within 28 days after the last dose of study drug were not increased in patients $>$ 60 (3 patients of 12 in the combination arm and 3 of 8 patients in the monotherapy arm). See table 26. From the three patients who died in the combination arm; one died from enterocolitis, one from sepsis and the other from progressive disease. The causes of death from the three patients who died in the monotherapy arm were sepsis, progressive disease and pulmonary embolism.
- Toxicity did not reverse the positive outcome trends in the study endpoints.
- We can not accept an initial dose reduction claiming preserved efficacy based on a retrospective subgroup analyses; however we can review the current age-related cautions in the label.
- We strongly encourage the sponsor to pursue the optimal dose of capecitabine however, in prospective studies.

C. Evaluation of Pediatric Program

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The sponsor applied for a waiver for pediatric study requirements. On September 23, 1999, the Agency granted a waiver for pediatric studies for metastatic breast cancer and metastatic colon cancer.

D. Comments on Data Available or Needed in Other Populations

Studies on hepatic impairment patients were previously done at the time of the first accelerated approval. The study on renal impaired patients was previously done and submitted at the time of the colorectal approval. Conclusions from these studies are already included in the label.

X. Conclusions and Recommendations

A. Conclusions

Protocol SO 14999 was a prospective randomized controlled trial of Xeloda in combination with docetaxel compared to docetaxel monotherapy for metastatic breast cancer. The populations were well balanced. Most of the patients (65% to 69%) had received previous chemotherapy for metastatic disease. Time to progression was the primary endpoint; survival and overall response rate were the secondary endpoints. The combination of xeloda and docetaxel resulted in a statistically significant prolongation of time to progression, 186 days compared to 128 days for the monotherapy patients. This difference is equivalent to a 25% reduction in the risk of tumor progression for combination therapy patients (hazard ratio 0.65, $p=0.0001$). The Xeloda docetaxel combination arm resulted in a statistically significant prolongation of overall survival by 3 months (hazard ratio=0.78, $p=0.013$). These differences are clinically significant. Overall tumor response as assessed by the reconciled tumor response data was statistically superior with the combination of xeloda docetaxel therapy ($p=0.009$).

The toxicity of the xeloda/docetaxel combination regimen was greater. The adverse events were consistent with those described in the label for xeloda and docetaxel. Gastrointestinal adverse events and hand and foot syndrome were more common in the combination therapy arm.

Treatment related neutropenia leading to medical intervention occurred with similar frequency in both treatment arms while the incidence of neutropenic fever was higher in the monotherapy treatment group. Treatment related mortality was higher in the xeloda/docetaxel arm (4 patients) compared to the docetaxel monotherapy arm (1 patient). There was a higher incidence of hyperbilirubinemia grade ≥ 3 in the combination therapy arm (11%) compared to the monotherapy arm (5%).

Overall, this study demonstrates the efficacy of xeloda and docetaxel in metastatic breast cancer. The clinical benefits observed in this study outweigh the increased but reversible toxicity associated with the combination of xeloda and docetaxel, in the opinion of the reviewer.

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B. Recommendations

The FDA review team recommends the approval of xeloda in combination with taxotere for patients with metastatic breast cancer. Since most of patients in the combination therapy arm were dose reduced due to adverse events, uncertainty remains about the optimal dosing. A phase 4 commitment will be necessary to explore optimal doses of xeloda to improve the safety profile. A phase 2 study in patients with metastatic breast cancer exploring reduced doses of xeloda and different schedules is recommended by the Agency.

XI. Appendix

A. Other Relevant Materials

Appendix I: Tumor Assessments Based on the WHO Criteria for Response

1. MEASURABILITY OF THE DISEASE

The lesions which will be used as criteria of response must be clearly defined at the entry of the patient into the trial. Ideally, all lesions should be measured at each assessment. When multiple lesions are present, this may not be possible and, under such circumstances, a representative selection of up to 7 lesions may be chosen for measurement. The same method of assessment must be used throughout the trial for each marker lesion. Measurements should be made by the same investigator for all assessments for each patient. Measurement of a tumor lesion is made in millimeters of two perpendicular diameters of marker lesions, applied at the widest portion of tumor.

1.1. Bidimensionally Measurable Disease

Malignant disease measurable (metric system) in two dimensions by ruler or calipers with surface area determined by multiplying the longest diameter by the greatest perpendicular diameter (eg. metastatic pulmonary nodules, lymph nodes and subcutaneous masses). In case of multiple lesions, the local tumor size is defined as the sum of the products of the diameters of all measured lesions.

1.2. Unidimensionally Measurable Disease

Malignant disease measurable (metric system) in one dimension by ruler or calipers (ie mediastinal adenopathy, malignant hepatomegaly or abdominal masses).

1.3. Mediastinal and Hilar Involvement

It may be measured if a pre-involvement chest X-ray is available, by subtracting the normal mediastinal or hilar width on the pre-involvement X-ray from the on-study width containing malignant disease.

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1.4. Malignant Hepatomegaly

May be measured if the liver descends 5 cm below the costal margin by adding the measurements below the costal margins. Measurements below the costal margins will be made in the midclavicular lines or at other specifically defined points during quiet respiration.

1.5. Non-measurable, Evaluable Disease

Malignant disease evident on clinical (physical or radiographic) examination, but not measurable by ruler or calipers (ie osteolytic lesions, pelvic and abdominal masses, lymphagitic or confluent multinodular lung metastases, skin metastases, and deviated or obstructed ureters or gastrointestinal tract). Computerized tomography or radionuclide scan may be utilized for appropriate lesions and IVP for obstructed ureters if these later become unblocked. Non-measurable but evaluable lesions must not be the sole lesions for response assessment, but may be used in addition to measurable marker lesions. Document by photograph whenever possible.

2. DEFINITIONS OF OBJECTIVE RESPONSE

2.1. Measurable Disease

Complete Response (CR): The disappearance of all clinically detectable disease determined by 2 observations not less than 4 weeks apart.

Partial Response (PR): $\geq 50\%$ decreased (for bidimensional lesions) in total tumor size of the lesions (sum of the products of the two greatest perpendicular diameters of all measurable lesions) which have been measured to determine the effect of therapy by 2 observations not less than 4 weeks apart. In addition there can be no appearance of new lesions or progression of any lesion.

No Change (NC) or Stable Disease (SD): A $<50\%$ decrease in bidimensional lesions as defined above cannot be established nor has a 25% increase in the size of one or more measurable lesions been demonstrated throughout the period of treatment.

Progressive Disease (PD): A 25% or more increase in the sum of the products of perpendicular diameters of one or more measurable lesions with minimal area $>2\text{cm}^2$, or the appearance of new lesions. For malignant lesions with minimal areas of $\leq 2\text{cm}^2$, increase in size of any individual lesion of at least 1cm^2 will be required.

3. ASSESSMENT OF PATIENT'S TOTAL RESPONSE

Response must be assessed by organ site. If measurable or evaluable disease exists in more than one organ site, the response in each organ site must be recorded separately.

If both measurable and non-measurable disease is present in a given patient, the results of each should be recorded separately. Non-marker lesions should also be recorded separately, since their presence will determine overall response in the case of patients showing responses in their marker lesions.

CLINICAL REVIEW

Clinical Review Section

Complete responses imply that no new lesions have appeared and all previous existing disease has resolved for a minimal duration of at least 4 weeks.

Partial responses require $\geq 50\%$ decrease in measurable lesions and objective improvement in evaluable, but non-measurable lesions. No new lesions should have appeared. It is not necessary for every lesion to have regressed to qualify for a partial response (ie "no change") in non-measurable lesions), but no lesion should have progressed. Responses must also have lasted for at least 4 weeks.

No change responses (stable disease) show a 50% or less decrease in measurable lesions and/or objective improvement in evaluable, but non-measurable lesions. No new lesions should have appeared. It is not necessary for every lesion to have regressed to qualify for a no change response, but no lesion should have progressed.

Progression of previously measurable or evaluable malignant lesions or appearance of new malignant lesions known not to be present at the start of therapy in any site, always indicates disease progression, despite objective responses in other sites.

Organ site stabilization will not detract from CR's or PR's in measurable sites, but the patient's overall response will not be more than a PR.

The period of **overall response** lasts from the first day of treatment to the date of first observation of progressive disease.

4. DURATION OF RESPONSE

The period of **complete response** lasts from the date the complete response was first recorded to the date thereafter on which progressive disease is first noted.

In those patients who only achieve a **partial response**, only the period of overall response should be recorded.

The period of **overall response** lasts from the first day of treatment to the date of first observation of progressive disease.

(WHO handbook for reporting results of cancer treatment, World Health Organization Geneva, 1979)

B. Individual More Detailed Study Reviews (If performed)

Please refer to review of study [] entitled, "A Phase II study of capecitabine in patients who have received previous treatment with paclitaxel or docetaxel for locally advanced and/or metastatic breast cancer", submitted under IND []