CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 20-896

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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number:NDA 20-896

Trade Name: XELODA TABLETS, 150mg & 500mg

Generic Name:(capecitabine)

Sponsor:Hoffman-La Roche, Inc.

Approval Date: April 30, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20-896

APPROVAL LETTER

Please

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

NDA 20-896

APR 30 1998

Hoffman-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110-1199

Attention: Cynthia Dinella, Pharm. D.
Group Director, Regulatory Affairs

Dear Dr. Dinella:

Please refer to your new drug application dated October 28, 1997, received October 30, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xeloda (capecitabine) tablets, 150 mg and 500 mg.

We acknowledge receipt of the following amendments:

1997 November 11 and 13
December 23

1998 January 9, 27 (2), 28, and 29
February 4, 9, 12, 13, 20, 24 (2), 25, 27 (2),
March 2, 4, 5, 9, 10, 11, 12, 13, 16, 17, 18, 26, and 27
April 2, 9, 15 (2), 16 (2), 21, 23, and 27.

The User Fee goal date for this application is April 30, 1998.

This new drug application provides for the treatment of patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy may be contraindicated, e.g., patients who have received cumulative doses of 400 mg/m^2 of doxorubicin or doxorubicin equivalents. Resistance is defined as progressive disease while on treatment, with or without an initial response, or relapse within 6 months of an anthracycline-containing adjuvant regimen.

We have completed the review of this application, including the submitted draft labeling, according to the regulations for accelerated approval and have concluded that adequate information has been presented to approve Xeloda (capecitabine) tablets, 150 mg and 500 mg. for use as recommended in the enclosed marked-up draft labeling. Accordingly, the application is approved under 21 CFR 314.520. Approval is effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed revised draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-896. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of the Phase 4 commitments specified in your submission dated April 16, 1998. These commitments are listed below.

Protocols, data, and final reports, should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to this application, a status summary of each commitment. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For

administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments".
Further, we acknowledge your April 9 and 14, 1998 commitments to address the following chemistry, manufacturing and controls concerns with due diligence:

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Maureen Pelosi, Project Manager, at (301) 594-5768.

Sincerely yours,

/S/ 4/30/98

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE

cc:
Original NDA 20-896
HFD-150/Div. files
HFD-150/CSO/M.Pelosi
HFD-150/ Justice/ 4-24-98
Beitz
Martin/4-24-98
Andrews/4-23-98
McGuinn/4-23-98
Rahman/4-23-98
Ibrahims
Koutsoukos/G. Chen 4-23-98
Takeuchi
Zhou/4-23-98
Liang/ Zhou for, 4-23-98
Vaccari
Pease
Pelosi
HFD-002/ORM (with labeling)
HFD-101/Office Director
HFD-810/ONDC Division Director
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling) -
HFI-20/Press Office (with labeling)
HFD-021/ACS (with labeling)

Drafted by: Pelosi/ 4-17-98
Initialed by: Pease/4-23-98
final: by Pelosi/4-24-98 4-24-98

APPROVAL (AP) [with Phase 4 Commitments]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-896

MEDICAL REVIEW(S)

MEDICAL REVIEW OF (NDA) # 20-896: Xeloda™ (capecitabine)

Applicant: Hoffmann-La Roche Inc.
FDA Reviewer: Alison Martin, M.D.

ODAC Meeting: March 19, 1998

1.0 General Information

1.1 Name of Drug:

Established: Capecitabine (Ro 09-1978)
Proprietary: Xeloda™

1.2 Applicant:

Hoffman-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

1.3 Pharmacologic Category: Fluoropyrimidine carbamate

1.4 Proposed Indication: Xeloda™ is indicated for the treatment of patients with metastatic breast cancer after failure of paclitaxel and an anthracycline-containing chemotherapy regimen."

1.5 Dosage and Administration: "The recommended dose of Xeloda™ is 2500 mg/m^2 administered orally daily for 2 weeks followed by a 1-week rest period given as 3 week cycles. ..The Xeloda™ daily dose is given orally in two divided doses (approximately 12 hours apart) within 30 minutes after the end of a meal. Xeloda™ tablets should be swallowed with water."

1.6 How Supplied: Xeloda™ is supplied as film-coated tablets, available in two dose strengths, 150 and 500 mg.

2.0 Regulatory History

The initial IND application was filed May 20, 1994. The End of Phase I Meeting was held on 12/18/95 (see Appendix I: Summary of Clinical Trials with Xeloda™ for an overview of drug development plans). The possibility that the Phase 2 trial in refractory metastatic breast cancer, SO 14697, could support an indication was discussed. The following comments are excerpted from the minutes:

- "Concern was expressed regarding the homogeneity of the patient population. It was agreed that eligible patients will have *failed an anthracycline as well as taxol.*
- A single trial is generally not sufficient to support an indication, although it is recognized that the proposed 150 patients will narrow the confidence intervals around the response rate over the typical Phase II study...a multi-center study where sites showed replication of results might be acceptable, depending on the magnitude of effect....
- Accelerated approval is a possibility if response rate in this *failed* patient population is impressive; would then need studies linking response rate to other endpoints."

The End of Phase 2/Pre-NDA meeting was held August 6, 1997. Three issues arose concerning an NDA submission based on SO 14697: (1) Submission of a single Phase 2 trial; (2) Efficacy endpoints derived from a Phase 2 trial. The only reliable endpoint would be response rate, which is a surrogate endpoint for

efficacy or clinical benefit and would be acceptable only for accelerated, rather than full approval; and (3) Choice of an appropriate patient population for accelerated approval, i.e. patients with refractory disease who do not have adequate alternative therapies.

The Agency reiterated that SO 14697 would have to stand alone in providing efficacy data. The two other Phase 2 trials being conducted in metastatic breast cancer (SO 14799 and SO 15179– see Appendix I) were being conducted in a different patient population. It could not be assumed that a response rate in a less heavily treated patient population would carry over to the indication being sought, i.e., for those patients who have failed an anthracycline and paclitaxel. It was also discussed that while response rate could serve as a surrogate endpoint (for clinical benefit) for consideration of accelerated approval, full approval requires that clinical benefit be shown. Such endpoints would include prolongation of disease free survival or time to progression, overall survival, or improvement in quality of life (QOL). Benefit in any of these endpoints is best demonstrated in trials with comparator arms. A Phase 2 trial would be confounded by a number of factors, including issues relating to the patient selection or prognostic factors, physician bias in endpoint assessment or use of supportive care, improvements in supportive care, etc. Although protocol SO 14697 includes a clinical benefit response endpoint, the sponsor was advised that it is difficult to obtain convincing quality of life data, i.e. subjective data, without a comparator arm.

Regulatory Guidance:

- The Oncology Initiatives of March 1996 (*Reinventing the Regulation of Cancer Drugs: Accelerating Approval and Expanding Access*) state the conditions of accelerated approval: "...FDA may utilize the accelerated approval process to allow marketing of therapeutics for patients with serious and life-threatening diseases. Under existing regulations, a new drug or biologic agent that is intended to provide a meaningful therapeutic benefit over existing therapies may be approved on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint (i.e., response rate) that is reasonably likely...to predict clinical benefit...(For) patients with refractory malignant diseases or for those who have no adequate alternative, clear evidence of anti-tumor activity is a reasonable basis for approving the drug. In these cases, studies confirming a clinical benefit may appropriately be completed after approval."

- The following draft Guidance for Industry was proposed by the FDA and released for comment in March 1997: *Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products.* Although the purpose of the guidance is to describe the circumstances where a single Phase III trial may warrant full approval, the same points could be considered when any one trial is being relied upon for the basis of approval.

  "...Thirty-five years ago, when the effectiveness requirement was originally implemented, the prevailing study model was a single institution, single investigator, relatively small trial...The added rigor, power, and scope of contemporary clinical trials have made it possible to rely, in certain circumstances, on a single adequate and well-controlled study...It should be appreciated that relying on a single adequate and well-controlled study is inevitably a matter of judgment and that the conclusion based on even a highly persuasive single study will be less secure than a conclusion based on two similar studies...

  The discussion that follows identifies characteristics of a single adequate and well-controlled study that could make the study adequate...

  (a) Large multicenter study...in which (1) no single study site provided an unusually large fraction of the patients and (2) no single investigator or site was disproportionately responsible for the effect seen...

  (b) Multiple "studies" in a single study...Where the strata are randomized separately and each shows a significant effect, the study provides two or more separate estimates of the effect, albeit not by independent investigators and often not with a clear prospective intent to do so...

(c) Multiple endpoints involving different events...Where a study shows statistically persuasive evidence of an effect on more than one of such (prospectively identified) endpoints, the internal weight of evidence of the study is enhanced...
(d) Statistically very powerful finding...In a multicenter study, an extreme p-value indicates that the result is highly inconsistent with the null hypothesis of no treatment effect...

...Although acknowledging the persuasiveness of a single, internally consistent, 'strong' multicenter study, it must be appreciated that there remains a possibility that even a strong result can represent an isolated or biased result...When considering whether to rely on a single multicenter trial, it is critical that the possibility of an incorrect outcome be considered and that all the available data be examined for its potential to either support or undercut reliance on a single multicenter trial..."

3.0 Scope of Review

Medical review of NDA included:

- Regulatory history of the application;
- Initial submission of protocol SO 14697 to IND
- Initial submission of amendment to SO 14697 to IND
- Annual report for IND
- The following volumes from the 226 volume NDA submission:

1.1	Index
1.2	Proposed label
1.3	Application summary
1.105	Clinical pharmacology summary; Integrated summary of benefits and risks
1.106	Integrated summary of efficacy
1.107	Integrated summary of safety
1.182- 201	Pivotal Phase 2 trial, SO14697

- Case report forms (electronic) from the pivotal trial, SO 14697;
- Amendments with letter dates: 11/11/97 (BM), 11/13/97 (BM), 12/23/97 (BZ), 1/29/98 (BZ), 2/4/98 (BZ), 2/12/98 (BM), 2/13/98 (BM), 2/20/98 (BM), 2/24/98 (BM), 2/25/98 (BM), 2/27/98 (BM), 3/2/98 (BM), 3/9/98 (BM), 3/10/98 (BM), 3/11/98 (BM), 3/13/98 (BM), 3/17/98 (BM), 3/26/98 (BM), 3/27/98 (BM) and the Patient Package Insert with letter date 4/2/98 (BL).
- Tables of patient listings in MS Access database, which were the subject of queries.
- Safety Update, correspondence date 2/27/98, receipt date 3/2/98.

4.0 Clinical Pharmacology/Pharmacokinetics Summary (see Biopharmaceutical Review)

The following summary points are reviewed in detail in the Biopharmaceutical Review:

- Protocol BD 14823, A Pharmacodynamic/pharmacokinetic study of RO 09-1978 in plasma, tumor and healthy tissue. Nineteen patients scheduled for resection of a colorectal primary and/or liver metastasis received preoperative capecitabine (1255 mg/m^2 BID) for 5-7 days. There was a 2.5 times
- greater concentration of 5-FU in the colorectal primary than in adjacent healthy tissue. This differential is thought to be due to the four-fold difference in thymidine phosphorylase (dThdPase) activity in primary colorectal tumor vs. adjacent healthy colon tissue. In liver, a significant difference in concentration of 5-FU was not seen between healthy liver and liver metastases. The activity of

dThdPase, as well as other enzymes responsible for the activation and degradation of 5-FU, in liver and metastases to the liver appear to be similar.

- Special Populations. The sponsor performed a meta-analysis of 94 patients selected from four Phase I studies (SO 14693, SO 14794, SO 14696 and SO 14798—see Appendix I) to address the effect of age, gender, body weight (after adjustment of dose using BSA) or body surface area (after adjustment of dose using BSA) on the PK of capecitabine or its metabolites. These patients were thought to be at higher risk for adverse events for a variety of reasons. No significant effect was seen for these demographic factors. See below for a further discussion of the influence of age.

- Age. In the Phase I meta-analysis, patients ranged in age from 33 to 77 years (n = 85). An increase was seen in the AUC of α-fluoro-β-alanine (FBAL), an end product of the catabolism of 5-FU, on day 1 and day 14 of approximately 14% between the ages of 50 and 70. C_{max} of FBAL was also increased on day 1. An analysis using backward selection which included creatinine clearance and not age suggests that the effect of age on the PK of FBAL may be due to a decrease in renal function with age.

  The sponsor has performed a subgroup analysis on the safety database to investigate whether age has an influence on the incidence of grade 3-4 adverse events (AE). Results of a Cox regression analysis showed the incidence of AE is greater in the elderly (p=0.006). In the Four Month Safety Update, it is noted that the safety database has 14 patients $\geq$ 80 years of age that have been treated with capecitabine. There was a 50% incidence of grade 3-4 gastrointestinal adverse events: 21.4% diarrhea, 21.4% nausea and 7.1% vomiting. It is suggested that although PK may not be altered significantly, the elderly may be pharmacodynamically more sensitive to the toxic effects of 5-FU.

- Renal Function. A formal study evaluating the effect of creatinine clearance on the PK of capecitabine has not been performed. Data from the meta-analysis of the 4 trials as well as data from 3 additional trials (BK 14822, WP15354 and BP15572) evaluated patients with creatinine clearances as low as 30 ml/min. The AUC of FBAL increased by 45% on day 14 in patients in whom creatinine clearance was decreased by 50%.

- Hepatic Function. A formal study of the effect of hepatic dysfunction on the PK of capecitabine was conducted (BK 14822: Influence of hepatic impairment due to liver metastases on the pharmacokinetics of Ro 09-1978 in cancer patients). Thirty three adult patients with advanced or metastatic cancer were enrolled. Hepatic function was classified by a composite score based on bilirubin, SGOT/SGPT and alkaline phosphatase. Seventeen patients with normal hepatic function with or without liver metastases (group 1) and 16 patients with mild to moderate hepatic dysfunction due to metastases (group 2) were randomized to receive either a single oral dose of 1255 mg/m^2 Ro 09-1978 or 750 mg/m^2 of the metabolite, 5'DFUR, given i.v. over one hour. (The doses were predicted to provide equivalent AUCs). Following a 3-10 day washout, patients would cross-over to the other study drug. Twenty-seven patients were evaluable for PK.

  C_{max}, and AUC of capecitabine, 5'-DFUR and 5-FU were increased in patients with hepatic dysfunction. C_{max} was increased by 49, 33 and 28% and AUC by 48, 20 and 15% for intact drug, 5'-DFUR and 5-FU respectively. Patients in group 1 had approximately 40% bioavailability of 5'-DFUR while those in group 2 had 64% bioavailability.

  The Four Month Safety Update, which increases the pool of patients in the safety database to 570, notes that grade 3-4 hyperbilirubinemia occurred in 21.2% of the 339 patients with hepatic metastases at baseline and in 10.4% of the 231 patients without hepatic metastases at baseline. There was no alternative explanation for the increase in bilirubin in the patients without hepatic metastases.

- Ethnicity. The sponsor states that only 4 patients in the population used for a meta-analysis were non-Caucasian and therefore insufficient data is available to assess any effect on PK.

5.0 Related INDs

See Appendix I: Summary of Clinical Trials with Xeloda™.

6.0 SO 14697: A Phase 2 study of capecitabine (Ro 09-1978) in patients who have failed previous treatment with Paclitaxel (Taxol®) for metastatic breast cancer

6.1 Protocol Review

Principal Investigator: Aman Buzdar, M.D.
M.D. Anderson Cancer Center

Protocol Milestones:

Reviewer Table 1*
Protocol Milestones

Milestone	Dates	# Pts Entered	Comments
Draft Protocol Submission	Oct. 24, 1995	–	Telecon Nov. 17, 1995. FDA expressed concern re. Heterogeneity of "taxol failure" population and whether pts would also be anthracycline/anthracenedione resistant.
Protocol Submission	Dec. 13, 1995	–	See outline below
First Patient Enrolled	Feb. 6, 1996	1	
Amendment	July 30, 1996	64	Stricter definition of paclitaxel resistance, new grading criteria for hand-foot syndrome, clarification of the statistical test for RR, change in criteria for PD, as well as other minor changes.. *(In Section 6.1, Protocol Review, replacement text from the amendment is identified by shading. The original text is retained and can be identified by a strikethrough.)*
Last Patient Enrolled	Dec. 20, 1996	163	After the meeting the sponsor collected information on prior anthracenedione treatment.
Data Cutoff	June 12, 1997	163	
NDA Submission	Oct. 31, 1997	163	

*After Sponsor's Table 1, Summary of Protocol Amendments, vol. 1.182, p. 10

6.1.1 Objectives

Primary:

- "To determine that the overall response rate of patients with measurable metastatic breast cancer who have failed previous paclitaxel chemotherapy is in the range of 20% when given capecitabine at the proposed dose and schedule."

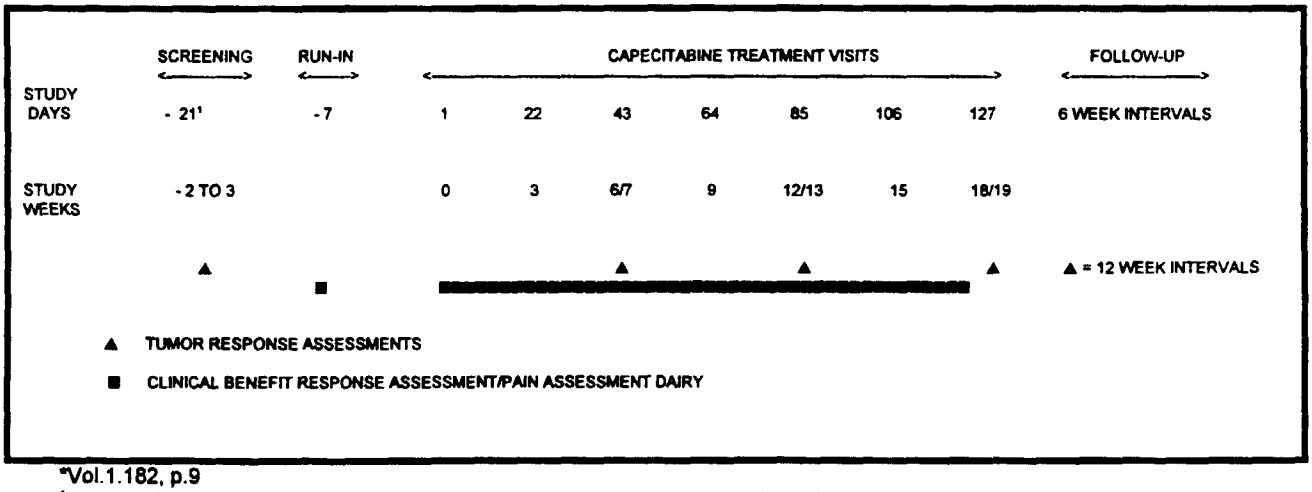
Secondary:

- To demonstrate that capecitabine is safe and tolerable;
- To determine duration of response, time to treatment failure, and overall survival;
- To evaluate subjective improvement as measured by the Clinical Benefit Response (CBR) Score.

6.1.2 Overall Design

Protocol SO 14697 was an open label, multicenter Phase 2 study to evaluate the efficacy and safety of capecitabine when given on a 3 week "intermittent schedule," i.e., 2510 mg/m^2 daily for 2 weeks followed by a 1 week rest . Target accrual was approximately 150 patients with metastatic breast cancer (2:1 ratio of patients with measurable:evaluable disease). Patients were to be assessed for tumor response every six weeks during the initial 18 weeks of treatment. If patients qualified for maintenance treatment with a CR, PR or stable disease, tumor responses would be lengthened to 12-week intervals and at the off-study date.

Sponsor's Figure 1*
Overall Study Design



*Vol.1.182, p.9
[1]Modified from Sponsor's "-14", to indicate that tumor assessments were allowed up to 3 weeks prior to treatment.

6.1.3 Eligibility Criteria

- Female ≥ 18 years old.
- KPS ≥ 70%; life expectancy ≥ 3 months.
- Histologically/cytologically confirmed advanced/metastatic breast cancer.
- Bi-dimensionally measurable or evaluable disease; ascites and pleural effusions are considered evaluable. Patients with prior XRT are allowed provided that the indicator lesion(s) is (are) are outside the field or represent a new lesion within the field.

- At least two, but not more than three previous chemotherapeutic regimens, one of which contained paclitaxel either as adjuvant therapy or for the treatment of metastatic disease.
- Failure on prior paclitaxel treatment demonstrated as either:

  (a) primary resistance [redacted];
  (b)

  (c) response followed by progression while still on therapy.

[redacted]

[redacted]

6.1.4 Exclusion Criteria

- Patients with rapidly progressing visceral involvement (e.g., liver, lymphangitic lung) or presence of CNS metastases.
- Patients with severe pain inadequately controlled by analgesics (as defined by a variation of more than 30 mm on the Visual Analogue Scale of Pain Intensity) during the run-in.
- Patients with abnormal hematologic values (ANC < 1.5 x 10^9/L, platelets < 75 x 10^9/L, Hb , 9 g/dL; impaired renal function (s.creatinine $\geq$ 1.5 x UNL); hypercalcemia (s. calcium >11.5 mg/dL); or impaired hepatic function (BR $\geq$ 1.5 x UNL, transaminases or alkaline phosphatase $\geq$ 2.5 x UNL or > 5 x UNL in case of liver or bone metastases). [redacted]
- Patients with organ grafts, with the exception of high-dose chemotherapy with autologous bone marrow transplantation
- Prior severe and unexpected reaction to fluoropyrimidine therapy or known sensitivity to 5-FU; patients with significant GI or renal disease which may in the opinion of the investigator affect the PK of capecitabine.
- Patients with clinically significant cardiac disease, mental conditions that would preclude informed consent, serious uncontrolled intercurrent infections, and patients known to be positive for hepatitis or HIV I.

6.1.5 Treatment

The daily dose of 2510 mg/m^2 was to be taken orally in two doses at approximately the same time each day within 30 minutes after the patient has eaten a meal, e.g., breakfast and dinner.

6.1.6 Concomitant Medication and Treatment

"Systematic prophylactic therapy should be avoided whenever possible as such treatment may obscure the toxicity profile." Treatment with pyridoxine 50 to 150 mg qd could be given in the event of hand-foot syndrome. Symptomatic treatment was allowed for GI symptoms. Patients requiring radiotherapy for bone lesions during the study were considered to have progressive disease.

[redacted]

are indicated, they should either be replaced by a histamine H_2 - receptor antagonist (cimetidine, ranitidine) or if possible, their administration delayed to at least 2 hours after capecitabine intake.

6.1.7 Schedule of Assessments

Reference: Appendix II: Schedule of Assessments
Clinical Benefit Response

- Pre-Study Screening: Tumor measurements were allowed up to a maximum of 21 days prior to treatment. General medical tests were to be completed within 14 days of treatment. During the week prior to treatment, patients were asked to keep a Pain Assessment Diary logging daily analgesic use and grading pain intensity as measured by the Visual Analog Scale of the Memorial Assessment Card. If the daily pain intensity score (range 0-100 mm) varied by more than 30 mm over the one week run-in period, pain was considered poorly controlled and the patients were not eligible for entry onto study.

- Visits on Study: Visits were scheduled every 3 weeks ± 3 days during the initial 18 weeks of study. Physical measurements to be obtained every 3 weeks included vital signs, weight, and the KPS. "Total body examination to be conducted only when clinically indicated." Laboratory tests to be obtained every 3 weeks were: CBC with differential, bilirubin, ASAT/ALAT, alkaline phosphatase, albumin, total protein, creatinine, electrolytes and urinalysis. Additional tests should be obtained when clinically indicated.

6.1.8 Efficacy Criteria and Study Endpoints

Reference: Appendix II: WHO Criteria (The amendment added to the definition of PD: Worsening of clearly non-measurable disease, e.g., serous effusions; bone metastases as determined by bone scan must not be the sole lesion for determination of disease progression.)
Appendix II: Clinical Benefit Response

The primary efficacy endpoint was response rate (CR + PR) in patients with measurable disease. Patients were to be assessed by the WHO criteria for measurable and evaluable lesions. Assessment of response was scheduled to occur every 6 weeks during the first 18 weeks of treatment, i.e., on days 43, 85, and 127 ± 3 days. Tumor response must be confirmed a minimum of 4 weeks after the first response has been recorded.

Secondary endpoints included:

- Time to onset of best response
- Duration of overall response. Who criteria define start date of CR as first date CR was noted; however, start date of PR is first day of treatment.
- Time to progressive (TTP) disease "from start of trial treatment. For responding patients this means time to relapse as measured from treatment start."
- Time-to-Treatment Failure (TTF) which "will be measured from the time the patient has started test drug treatment to the time the patient is first recorded as having disease progression, or the date of death, if the patient dies due to causes other than disease progression."

Reviewer Comment: *The protocol states under "Study Parameters, Efficacy" that TTF, as defined above, will be a secondary endpoint. TTP is not mentioned. However, the protocol states under*

"Statistical Considerations and Analytical Plan" that TTP will be a secondary endpoint as quoted above. TTF is not mentioned. The NDA includes both secondary endpoints. TTF is defined in the NDA as taking into account the following events: PD, death and patient withdrawal, unless clearly unrelated to treatment." TTP is not specifically defined. For further discussion, see Section 6.2.3.2 Secondary Endpoints.

- Survival
- Clinical Benefit Response Score (CBR):

The CBR is a composite score of three parameters: pain intensity, analgesic consumption, and Karnofsky PS. The definitions for a positive, negative or stable parameter are listed below. See Appendix II for details of scoring.

Positive: Pain intensity—when the pain score at baseline is ≥ 20 mm and when that score is reduced to less than 50% of baseline, maintained for ≥ 4 weeks.
Analgesic consumption—when the baseline analgesic consumption is ≥ 70 morphine equivalents per week and is reduced by at least 50%, maintained for ≥ 4 weeks.
Karnofsky PS—any improvement of ≥ 20 points maintained for ≥ 4 weeks.
Negative: If there were any deterioration, regardless of magnitude, in any of the three parameters within the first 12 weeks, maintained for ≥ 4 weeks.
Stable: Any other outcome was called a stable response.

An overall score is positive if a patient has a positive response in at least one parameter and is at least stable in the other two measures. A patient is classifed as having a negative CBR if she is negative in any one of three parameters (even if positive in the other two). A patient is classified as having a stable CBR if she is stable in all three parameters.

- Laboratory parameters
- Adverse events

6.1.9 Safety Assessments and Dose Modifications

Reference: Appendix II: NCIC Common Toxicity Criteria

Safety was evaluated by adverse event reports defined as "any adverse change from the patient's baseline condition...whether considered related to treatment or not" and were graded according to the NCIC Common Toxicity Criteria. The amended protocol provided a new grading system for the "hand-foot" syndrome (Palmar-Plantar Erythrodysesthesia):

Grade	Clinical Domain	Functional Domain
1	Minimal dysesthesia/paresthesia/tingling, pain, swelling/erythema	Discomfort which does not disrupt normal activities
2	Painful erythema with swelling	Discomfort which affects activities of daily living
3	Moist desquamation/ulceration/blister/severe pain	Severe discomfort/unable to work or perform activities of daily living

Treatment interruption and/or dose modifications were specified for grades 2 - 4 toxicity using the NCIC Common Toxicity or the Hand-Foot Syndrome Criteria:

	Grade 2	Grade 3	Grade 4
1st appearance	Interrupt treatment until resolved to grade 0-1 then continue at same dose with prophylaxis where possible	Interrupt treatment until resolved to grade 0-1, then continue at 75% of original dose with prophylaxis where possible	Discontinue treatment unless Investigator considers it to be in the best interest of the patient to continue at 50% of the original dose once toxicity has resolved to grade 0-1 (after approval of Clinical Leader)
2nd appearance of same toxicity	Interrupt treatment until resolved to grade 0-1, then continue at 75% of original dose	Interrupt treatment until resolved to grade 0-1, then continue at 50% of original dose	
3rd appearance of same toxicity	Interrupt treatment until resolved to grade 0-1, then continue at 50% of original dose	Discontinue treatment - off study	
4th appearance of same toxicity	Discontinue treatment - off study		

*Excerpted from Sponsor's protocol

The protocol specified that no dose modifications were required for toxicities unlikely to become serious or non-threatening, e.g., "alopecia, altered taste, etc." In addition, diarrhea or nausea and vomiting responding within 2 days to the addition of symptomatic treatment did not require a dose adjustment.

6.1.10 Statistical and Analytical Methods

Reference: Section 6.1.9, Efficacy Criteria and Study Endpoints.
Appendix II: Power and C.I. for Different Sample Sizes
Clinical Benefit Response Score

The following are excerpted from the protocol:

- Statistical Model

"For the analysis of efficacy, the patients will be assessed according to the WHO criteria and the best response achieved within the time from start of trial treatment to progressive disease will be reported. The overall response rate will be tested if it is in the range of 20% (primary analysis) based on the patients with objective measurable disease.

The response rates will be reported in rates with 95% Pearson-Clopper confidence intervals; subpopulation of those for the patients with objectively measurable disease as well as for the whole patients population. The survival type data will be presented by Kaplan Meier plots and estimates of the median based on the whole population (secondary analysis)."

- Hypothesis Testing

"The goal of this study is the demonstration that treatment with capecitabine produces clinical benefit in patients with taxol-resistant breast cancer. The target objective response rate (ORR) is 20%. To demonstrate achievement of the ORR in the study population of 100 patients with measurable disease, a binomial test based on the exact binomial distribution will be performed at the 2.5% α-level and the 95% Pearson-Clopper Confidence Interval will be calculated. The null hypothesis is that the overall response rate of capecitabine is lower than or equal to 10% versus the hypothesis that it is greater than 10%, i.e.:

H0 ORR ≤ 10% vs. HA ORR > 10%

The achievement of the target response rate of 20% will be demonstrated by a significant test result which basically corresponds to a lower limit of the confidence interval of the observed response rate being greater than 10%. Under the targeted response rate the study is adequately powered..."

- Types of Analysis

"All analysis of safety information will be based on the safety population.

All analysis of efficacy information will be primarily based on the Intent-to-Treat population. However, all primary and secondary analyses will be also performed for the standard population."

- Exclusion of Data from Analysis

Exclusion of Patients from Efficacy Analysis: "All eligible patients who received at least one dose of test drug will be included in an intent-to-treat analysis for efficacy. (Patients with no second tumor assessment will be treated as failures in the intent-to-treat analysis). Among these, all patients who also received at least six weeks of treatment will be included in the standard analysis."

Reviewer Comment: *The definition of standard analysis is changed in the NDA to exclude the following patients (excerpted from vol. 1.182, p. 25):*

1. *"Patients who received less than 42 days (6 weeks) of therapy (except patients who withdrew from treatment due to progressive disease). In practice, patients who were prematurely withdrawn from the study after less than 32 days on study were excluded since for this study, the six-week period corresponds to 35 days on study with a three-day time window.*
2. *Patients who missed more than 15 days of test treatment during the first 6 weeks.*
3. *Patients with a major violation of inclusion/exclusion criteria.*
4. *Patients with inadequate baseline tumor information.*
5. *Patients with inadequate follow-up tumor assessment information."*

Exclusion of Data from Safety Analysis: "Patients who received at least one dose of study medication but for whom follow-up safety information is not available will be excluded in the analysis of safety."

- Sample Size

"The sample size is based on the primary analysis using the exact distribution of the one-sided binomial test and on the necessity for safety information.

Assuming a true RR of 20% and a sample size of 100 patients with objectively measurable disease we get the power of 81% for the primary test that the overall response rate is greater than 10%. For more precise information see Table 4 and Table 5 (Appendix II). With a 20% measured response rate this number of patients gives already a reasonable size for the 95% Pearson-Clopper confidence intervals.

For safety reasons, and in order to demonstrate a similar efficacy profile, 50 patients with clinically evaluable disease will be added to the study. Hence the study will include 150 evaluable patients."

6.2 Results

6.2.1 Conduct of the Study

An independent review committee (IRC), consisting primarily of radiologists, was coordinated by World Care. An oncologist was consulted as needed. The IRC reviewed radiologic studies from patients with measurable disease who had radiographically-defined indicator lesions. Information on the location of each indicator lesion at baseline was provided to the IRC; investigator measurements and/or response assessments were not. The IRC was not asked to address the selection of indicator lesions or to determine overall response in patients who have indicator lesions followed both radiographically and clinically.

In response to an FDA fax requesting information on monitoring procedures, an amendment with letter date of 2/25/98 describes average monitoring frequency as every 4-6 weeks, unless specifically adjusted. Project specific procedures are supplied as well as discrepancy management. See amendment for further details

6.2.2 Enrollment and Disposition, Demographics and Baseline Characteristics

- **Enrollment**: A total of 163 patients were enrolled from 21 centers in the U.S. (n = 155) and 4 centers in Canada (n = 8). Enrollment ranged from 1 to 37 patients per center, with 5 centers accruing $\geq$ 10 patients. Reviewer Table 2 summarizes recruitment per center for all patients and patients with measurable disease. Accrual began February 6, 1996 and was completed by December 20, 1996.

Reviewer Table 2
Accrual Per Center

Center	Pts. With Measurable Disease	All Pts.
17150	35	37
16453	18	18
17155	12	17
17043	9	10
16697	7	7
17153	7	7
16451	6	10
17044	6	6
17182	5	7
17466	4	4
17154	4	7
16643	3	3
17181	3	4
17184	3	6
17079	2	4
17152	2	2
17180	2	4
16452	1	1
17151	1	2
17183	1	2
17185	1	1
17349	1	1
17467	1	2
17468	1	1
17186	0	0
Total	**135**	**163**

- **Patients with Measurable vs. Evaluable Disease**: The investigator was responsible for identifying patients with measurable disease. Although the WHO criteria provide definitions for uni- or bidimensional measurements, the protocol required measurable disease to be bidimensional. The sponsor has identified 135 patients with measurable disease.

Reviewer Comment: *The Agency counted patients as having measurable disease if the investigator ticked the appropriate box on the CRF. By this method, 137 were listed. Two patients were excluded by the sponsor Patient indicator lesion, a peripancreatic mass, was considered poorly defined on the radiologic (CT) reports due to matting, surrounding bowel, and lack of fat planes. Patient left upper lobe nodule of approximately 1 cm^2 appears measurable, albeit small volume disease. The IRC also was able to provide measurements for the nodule on serial CT scans. Both of these patients are classified as having stable disease. Since the one patient of possible disagreement will not affect the analyses, we have accepted 135 as the denominator for patients with measurable disease.*

Since the primary objective of the protocol is response rate in patients with measurable disease, demographics, clinical descriptions and analyses will be presented for the subset of patients with measurable disease as well as the entire population.

- **Disposition**: One patient was considered ineligible during screening due to rapidly growing visceral disease and was withdrawn prior to receiving study drug. Of the remaining 162 patients, 139 (86%) had treatment discontinued prior to the data cutoff date of June 12, 1997. The reasons for discontinuation as classified by the sponsor are presented in Reviewer Table 3.

Reviewer Comment: *Review of the TTP datasets and CRFs finds 4 additional patients discontinued by June 12, 1997 for PD or an insufficient response . The sponsor's numbers are retained in parentheses. In either case, the sponsor's conclusion that the majority of patients were withdrawn due to PD rather than adverse events appears to be true. Details of the patients discontinued for reasons other than PD or an AE are reviewed in detail in Reviewer Table 12.*

Reviewer Table 3
Disposition of Patients from SO 14697*

No. of patients entered	**163**
No. of patients withdrawn[1]	1
No. of patients who received Xeloda™	162
No. of patients with measurable disease	135
No. of patients discontinued by June 12, 1997[1]	**143 (139)**
No. of patients with insufficient response	121 (117)
No. of patients with adverse event or intercurrent illness	13
No. of patients who refused treatment	3
No. of patients who failed to return	2
No. of patients who died on study	1
No. of patients discontinued for admin/other	3

*Data from Sponsor's Fig. 3, vol. 1.182, p. 36; patient listings in Appendix 8, vol. 1.182, p. 146 and pertinent case report forms.
[1]See Deaths and Dropouts, Section 6.2.4

- **Baseline Demographics and Clinical Characteristics**: The demographics and clinical characteristics of all patients (intent-to-treat, ITT) and those with measurable disease are shown in Reviewer Table 4. There were no significant differences between the two populations. The majority of women were caucasian. The median age was 56 years, with a range from years of age. The median Karnofsky Performance Status (PS) was 90. In the ITT population, 87% of patients had two or more sites of disease, with the predominant site being visceral in 68%. In patients with measurable disease, 90% had two or more sites of disease and the predominant site was visceral in 75%.

Reviewer Table 4
Baseline Demographics and Clinical Characteristics

	Patients with Measurable Disease N = 135	All Patients N = 162
Sex		
Female	135 (100%)	162 (100%)
Male	0 (0%)	0 (0%)
Age (years)		
Mean	55.4	55.8
S.D.	11.8	11.5
Median	56	55.5
Range		
Race		
Caucasian	113 (84%)	139 (86%)
African-American	13 (10%)	13 (8%)
Oriental	2 (1.5%)	2 (1%)
Hispanic	4 (3%)	5 (3%)
Other	3 (1.5%)	3 (2%)
Karnofsky P.S. [1]		
Mean	86.5	86.2
S.D.	9.7	9.7
Median	90.0	90.0
Range		
No Data	4	9
Number of Disease Sites		
1	13 (10%)	21 (13%)
2	30 (22%)	39 (24%)
3	30 (22%)	35 (22%)
4	33 (24%)	33 (20%)
5	14 (10%)	16 (10%)
>5	15 (12%)	18 (11%)
Predominant site of disease [2]		
Visceral	101 (75%)	110 (68%)
Soft Tissue	30 (22%)	35 (22%)
Bone	4 (3%)	17 (10%)

*Data derived from Sponsor's Tables 11,12 and 13, vol. 1.182, pp. 38-40 and reviewer MS Access/SAS queries.
[1] Investigator-assessed PS
[2] See Appendix III: Algorithm for Determination of Predominant Site of Disease

Of the 21 patients with a single site involved with tumor, 7 had metastatic disease to the liver, 7 to bone, 2 to lung, 2 to lymph nodes, I to the pleura, I to skin, and 1 to the breast.

Reference: Appendix III: Algorithm for Determination of Predominant Site of Disease

- **Prior Chemotherapy**

There were no significant differences in extent of exposure to prior chemotherapy between the ITT population and patients with measurable disease (see Reviewer Table 5). Greater than 90% of patients had received two or three prior chemotherapy regimens. All patients had received paclitaxel, as required by the eligibility criteria. Ninety to 91% of the patients had received an anthracenedione and 81-82% had received prior 5-fluorouracil (5-FU).

Reviewer Table 5*
Prior Chemotherapy

	Patients with Measurable Disease N = 135	All Patients N = 162
No. of Prior Chemotherapy Regimens		
1	0 (0%)	1 (1%)
2	64 (47%)	75 (46%)
3	63 (47%)	74 (46%)
4	8 (6%)	11 (7%)
5	0 (0%)	1 (1%)
Adjuvant Therapy		
Yes	73 (54%)	85 (53%)
No	56 (41%)	71 (44%)
Unknown	6 (5%)	6 (4%)
Prior Paclitaxel		
Yes	135 (100%)	162 (100%)
No	0 (0%)	0 (0%)
Prior Anthracenedione		
Yes	122 (90%)	147 (91%)
No	13 (10%)	15 (9%)
Prior 5-FU		
Yes	110 (81%)	133 (82%)
No	25 (19%)	29 (18%)

*Data derived from Sponsor's Table 14, vol. 1.182, p. 41 and reviewer MS Access/SAS queries.

- **Prior Chemotherapy: Paclitaxel or Anthracycline Resistance or Failure**

The sponsor proposes the following definitions for paclitaxel or anthracycline resistance or failure:

Resistance:

- **R1** - relapse within 6 months of completing (paclitaxel- or anthracycline-) based adjuvant therapy
- **R2** - objective response to (paclitaxel- or anthracycline-) based therapy followed by progression on therapy
- **R3** - disease progression on (paclitaxel- or anthracycline-) based therapy without improvement

Failure:

- **F1** - relapse within 6-12 months of completing (paclitaxel- or anthracycline-) based adjuvant therapy
- **F2** - objective response to (paclitaxel- or anthracycline-) based therapy followed by progression within 12 months of last (paclitaxel or anthracycline) dose
- **F3** - stable disease while on (paclitaxel- or anthracycline-) based therapy for a minimum of 4 cycles

Seventy-seven percent of patients are paclitaxel-resistant; however, less than half of patients, 41%, have disease that is considered resistant to an anthracycline. Reviewer Table 6 presents the number of patients who meet each definition.

Reviewer Table 6*
Summary of Either Paclitaxel or Anthracycline Resistance or Failure

Subgroup	Pts with Measurable Disease N = 135	All Patients N = 162
Paclitaxel-resistant		
R1	0 (0%)	0 (0%)
R2	20 (15%)	24 (15%
R3	83 (62%)	100 (62%)
Total	**103 (77%)**	**124 (77%)**
Paclitaxel-failure		
F1	1 (0.7%)	1 (0.6%)
F2	13 (10%)	16 (10%)
F3	17 (13%)	20 (12%)
Total	**31 (23%)**	**37 (23%)**
Paclitaxel-other		
Resistance/Failure not demonstrated	1 (0.7%)	1 (0.6%)
Unknown	0 (0%)	0 (0%)
Total	**1 (0.7%)**	**1 (0.6%)**
Anthracycline-resistant		
R1	15 (11%)	18 (11%)
R2	3 (2%)	3 (2%)
R3	37 (27%)	46 (28%)
Total	**55 (41%)**	**67 (41%)**
Anthracycline-failure		
F1	13 (10%)	15 (9%)
F2	15 (11%)	18 (11%)
F3	7 (5%)	9 (6%)
Total	**34 (25%)**	**42 (26%)**
Anthracycline-other		
Resistance/Failure not demonstrated	32 (24%)	38 (24%)
No anthracycline	12 (9%)	14 (8.5%)
Unknown	1 (1%)	1 (0.5%)
Total	**45 (33%)**	**53 (33%)**

***Reviewer Comment**: The protocol amendment served to enrich the study population with patients who had disease resistant to paclitaxel, as defined by R2 and R3, as well as to add a minimum "dose" to the definition to ensure an adequate trial. On the other hand, the protocol provided no criteria regarding anthracenedione resistance.*

The following 2 X 2 table presents patients with measurable disease by combined paclitaxel and anthracycline resistance or exposure. The definition of resistance, which is supported by the literature, is retained and R1-3 are collapsed into one category. The category of "failure" is replaced by the broader category of "exposure." "Failure" as a distinct category is not well defined in the literature and is weakened by the absence of a minimum dose. Use of "exposure" allows many of the 32 patients who received an anthracycline but who are categorized as having "resistance/failure not demonstrated," to count toward providing information. Most histories of anthracycline exposure from

this category involve relapse > 12 months after an accepted adjuvant anthracycline-based regimen, i.e., cumulative dose of 240 mg/m² or relapse > 12 months after multiple cycles of an anthracycline alone or in combination for metastatic disease. Four of the 32 patients

are not included because of suboptimal treatment with an anthracycline without explanation, e.g., cumulative dose < 100 mg/m² in 3 patients or < 4 cycles of adjuvant anthracycline. In addition, the 13 patients who never received an anthracycline and the one patient about whom no information is known are still not counted (18 patients excluded). Thus, a total of 62 patients are defined as anthracycline-exposed.

Reviewer Table 7: Composite Drug Resistance Profile for 135* Patients with Measurable Disease

	Anthracycline Resistance	Anthracycline Exposure
Paclitaxel Resistance	43	48
Exposure	12	14

**N = 117; a total of 18 patients have been excluded from this analysis-see paragraph above.*

6.2.3 Efficacy Results

6.2.3.1 Primary Endpoint: Response Rate

- **Response Rate in Patients with Measurable Disease**

The sponsor identifies 27 patients as responders (3 CRs and 24 PRs) in the 135 with measurable disease. Reviewer Table 8 summarizes the sponsor's response rate, the IRC's assessment of 18 of the 27 responders, and the FDA's judgement of response rate after review of the 27 CRFs (which includes the IRC review).

Reviewer Table 8
Summary of Response Rate by Sponsor, IRC and FDA

Best Response	Sponsor N = 135	IRC Review	FDA Judgement
CR	3 (2.2%)	N/A • 3 of 3 CRs had soft tissue indicator lesions	1 (0.7%) • Insufficient assessment of known baseline "evaluable" disease in 2 pts. These 2 are called PR in FDA review.
PR	24 (17.8%)	• 18 with ≥ 1 radiographic indicator lesion reviewed; 12/18 confirmed	• 24 PR
Response Rate (CR + PR) 95% Confidence Interval	27 (20.0%) 13.6 - 27.8	N/A	25 (18.5%) 12.4% - 26.1

Reviewer Comment:

CRFs from the 27 responders were checked to assure that all patients with a radiographic lesion had films reviewed the IRC. One patient who had both radiographic and clinical indicator lesions did not have her CT of the abdomen reviewed by the IRC. The investigator had selected a 1 x 1 cm lesion in the liver on screening exam. Comments in the CRF at the follow-up visit state "unable to obtain measurements of exact nodules on screening scan. Physician is calling this stable disease." Her PR is derived from following a lymph node and breast lesion by physical exam. All other 18 patients with radiographic lesions had films reviewed by the IRC.

Responses were recalculated using tumor measurements provided by the investigator and the IRC. When there were disagreements, the reviewer used the following guidelines: (a) When the difference in response between the investigator and the IRC could not be resolved by finding additional clarifying information in the CRF or a mistake in calculation, the difference was attributed to "interobserver variability or error" and the best response was accepted. (b) When the difference in response was due to a clinical lesion that could only be measured by physical examination, the investigator's measurements of the clinical lesion were summed and added to the IRC's measurement of the radiographic lesion to validate conversion to a PR. (c) CRs required assessment of all known baseline disease, per WHO criteria. (d) New lesions precluded a PR, per WHO criteria.

Reviewer Table 9 summarizes the disagreements by patient. Six patients considered to have PRs by the sponsor were assessed by the IRC as having SD. Two of these could be converted to a PR by factoring in the soft tissue responses noted by the investigator. The Agency accepted 2 additional PRs in the absence of any new clarifying information, as interobserver error. Of the 2 remaining PRs, one is considered by the Agency to have PD and the other to have stable or inevaluable disease. In addition, the Agency's review downgrades 2 CRs to PRs for insufficient information.

Reviewer Table 9
Differences in RR Assessments: Sponsor, IRC and FDA

Patient ID	Sponsor	IRC	FDA Judgement
	PR	SD	SD (inevaluable?)
	PR	SD	PR
	PR	SD	PR
	PR	SD	PR
	PR	SD	PD
	PR	SD	PR
	CR	N/A	PR
	CR	N/A	PR

Reviewer Comment: *Narratives on the 8 patients are as follows:*

1. - The patient had known disease in the liver, breast, bone and pleura at baseline. A breast lesion and multiple liver lesions were selected as indicator lesions. The breast lesion was followed by ultrasound and assessed as SD by both investigator and the IRC. Both the investigator and IRC agree that the patient's liver became extensively nodular and fibrotic on study, precluding reliable measurements. Investigator comments for week 6, 12 and 18 scans include "liver measurements unclear due to fibrosis; consensus is PR." A discrepancy report appended to the CRF states "By the time of response assessment, the lesions were too vague to be measured. By general consensus of reviewers, this vagueness was due to extensive fibrosis and reduction in size of the lesions.

Bidimensional measurements will not be possible in most of the follow-up lesions due to the fibrosis." Another discrepancy report states that one out of the five lesions is measurable from screening to assessment 4. Measurement of this lesion provides SD.

2. This is one of two patients that had lesions followed by radiograph and physical examination. She had two breast lesions, one followed by ultrasound and the other by examination. The lesion followed by exam appears to convert the stable lesion on US to an overall PR.

3. This is the second of two patients with indicator lesions followed both by radiograph and physical examination. The IRC disagrees with the investigators assessment of the liver lesions as a PR. However, the axillary mass followed by physical examination appears to convert the assessment to a PR.

4. If following the protocol's specification to assess tumor on weeks 6 and 12, this patient would be assessed as PD by the investigator, IRC and FDA by virtue of new lesions. The patient's single lung lesion was followed by CT scan, which showed shrinkage by 50% on the week 6 CT scan but progressive disease by new lung lesions on week 12 CT scan. However, a week 3 chest x-ray was submitted for comparison to the week 6 chest xray (actually a 27 day interval). The lesion shrinks to 0 on the week 3 and 6 chest xray; however, the investigator rates the overall assessment as PR, presumably because the CT scan on week 6 still shows disease. The IRC rates the chest xrays as showing a 52% and 43% decrease at 3 and 6 weeks, respectively, i.e. not meeting criteria for a PR. In the FDA review, this patient is retained as a PR.

5. Investigator and IRC disagreed on the indicator lymph nodes. This becomes a moot point since the week 12 CT scan, which was to be the scan confirmatory of a PR, noted a "new large' pericardial effusion on scan. The patient goes off study for PD by virtue of a new lesion identified as a pericardial effusion within the couple of weeks. Last dose of study drug was the day before CT scan. WHO criteria define PR such that no new lesion appears. (This patient was on study before the amendment. Note that the pericardial effusion is not a "worsening" of disease, but according to the CRF it represented a "new" lesion.)

6. This patient is retained as a PR in the Agency's analysis. This patient presents a difficult clinical situation wherein the liver is enlarged with tumor as noted by the investigator's examination which measures the liver 6 or 8 cm below the xiphoid or on a CT scan, down to the iliac crest. However, since bidimensional disease was required by protocol, assessments were made on two lesions measuring 1.5 x 1.5 and 1.0 x 1.1 cm, small enough to accentuate any interobserver measurement difficulties.

7. The investigator's assessment is a CR; the Agency's assessment is a PR until further information is submitted. The patient had known baseline disease in the skin, pleura and multiple lymph nodes. The multiple skin lesions represented the bidimensional disease. At time of confirmation of CR at week 12, the physical examination reported a scalene node "enlarged compared to last visit" to 2 cm and the chest xray reported "progressive sclerosis" in the thoracic spine "worrisome for metastasis." Although sclerosis may represent healing of bony metastases, the patient had no known bone metastases. The patient had undergone talc pleurodesis to the pleura, which would make this site difficult to evaluate. However, the patient was said to have progressive disease on the following visit by virtue of progressive disease in the pleura and a new bone lesion in the upper extremity. Information is not provided to indicate the extremity was the only site of disease. Information has been requested from the sponsor.

8. The investigator's assessment is a CR; the Agency's assessment is a PR until further information is submitted. The patient had known disease in the bone, lung parenchyma, skin, soft tissue, lymph nodes and pleura. The 3 skin lesions (all < 1 x 1 cm) served as the bidimensionally measurable indicator lesions. Information has not been provided on the other sites of disease to confirm a CR.

Additional Responses noted by the IRC. The IRC reviewed radiographs from a total of 101 patients: 18 from patients considered to be responders by the sponsor and the remaining 83 who were considered to have stable or progressive disease. The IRC noted 5 responses that were not called by the investigator.

***Reviewer Comment:** The FDA reviewed the IRCs responders in the same way that the sponsor's responders were reviewed: the methodology included looking for additional clarifying information, such as clinical lesions converting a PR or new lesions in sites not followed or forwarded to the IRC. All cases could not be explained by additional information. The "interobserver variability or error" is seen to go in both directions, i.e., more and less favorable than the sponsor's assessments, lending some credibility to the review panel. Narratives for the 5 patients considered responders by the IRC follow.*

1. The patient had baseline, week 6 and 12 measurements. The investigator noted a PR at week 12 while the IRC noted PR at week 6 and 12. Although the patient was considered to be responding by both the investigator and IRC at the latter timepoint, she went off study for inability to swallow the pills. Cine-esophagram revealed a distal stricture not present on prior esophagram. She did have evidence of a proximal web on both studies.

2. The patient had known disease in the lung (multiple lesions) and a solitary pleural lesion. The bidimensionally measurable lesion was a small, solitary lung lesion, ≤1 x 1 cm.

3. This disagreement in the single liver lesion is a moot point since there is evidence of PD by new pulmonary lesions the month before the last reviewed scans.

4. A single liver lesion is followed. The IRC calls a PR when the investigator assesses the tumor as SD. The IRC notes that the marked fatty change in the liver makes it difficult to be precise.

5. The reviewer cannot comment because of the extensive changes to the original CRF. No original CT reports are supplied in the CRF.

- **Duration of Response**

Sponsor Analysis. Nineteen of the sponsor's 27 responders had progressed by the data cutoff date. The median duration of response is 241 days (range days, The range for duration of CR, based on the sponsor's 3 CRs, is · days,

***Reviewer Comment:** The sponsor's analysis of response duration is based on the WHO Criteria, which counts the first day of treatment as the first day of a PR, i.e., the same definition as TTP. A CR, however, is defined as starting from the date the CR is first recorded. The duration of response for the sponsor's 27 responders calculated from the date a response was first recorded is 165 days.*

Agency Analysis. The median duration of response for the 25 patients considered responders by the Agency, calculated from first date a PR or CR was recorded, is 154 days (range days). Duration of response in patient who had a CR in 3 skin metastases, is 194 days,

- **Response Rate in Patients with Two-Drug Resistance or Exposure**

Reviewer Table 10 presents the breakdown for the 25 responders by resistance or exposure. A response rate is derived using the denominators from Reviewer Table 7, i.e., the 4 possible profiles of composite drug resistance in patients with measurable disease. All of the responders had received prior treatment with paclitaxel and an anthracycline. Sixteen patients (64% of responders) were resistant to paclitaxel; 15 (60% of responders) were resistant to an anthracycline; and 10 patients (40% of responders) were resistant to both. Responses were seen in all subgroups.

Reviewer Table 10
Response Rate among Patients with Resistance or Exposure to Two Drugs

	Anthracycline Resistance	Anthracycline Exposure
Paclitaxel Resistance	11/43 (25.6%)	6/48 (13%)
Exposure	4/12 (33%)	4/14 (29%)

It is recognized that these are subgroup analyses with broad C.I. in some of these cells. An 18% response rate (16/91) is noted among patients with paclitaxel resistance. A 27% response rate (15/55) is noted among patients with anthracycline resistance. These findings suggest that results remain fairly consistent across clinically relevant subsets.

6.2.3.2 Secondary Efficacy Endpoints

- **Time to Progression**

Sponsor Analysis. As of the data cut-off date, 135 cases of PD or death were reported for the entire patient population. The median time to disease progression (TTP) was 93 days (95% C.I. for the median is 84 - 106).

Reviewer Comment: *Information is not available regarding additional treatment after a patient comes off study. It is conceivable that patients who withdrew prematurely (see Reviewer Table 12), may have qualified for additional treatment, affecting assessment of TTP. For instance Patient withdrew after 33 days of treatment or 43 days on study. TTP is listed as 252 days.*

Agency analysis. The median TTP for all patients was 94 days (95% C.I. 84-117), i.e., close to the sponsor's result. Of the patients with measurable disease, 108 had progressed or died by the data cut-off date. The median TTP was 90 days (95% C.I. 68-100).

- **Survival**

Seventy patients had died by the data cut-off date. The median survival for all patients is 384 days. For patients with measurable disease (n = 135), 60 patients had died. The median survival is 306 days.

Reviewer Comment: *Survival for responders vs. nonresponders is not presented since the results may be misleading. It has been previously described how a response may identify patients with known or unknown prognostic factors that favor a longer survival, independent of a study drug effect. In addition there is a time bias in that patients who die early are considered nonresponders Ref. Anderson JR et al. Analysis of survival by tumor response. J Clin Oncol 1:710-719, 1983; Simon R and Makuch RW. A nonparametric graphical representation of the relationship between survival and the occurrence of an event. Stat Med 3:35-44, 1984.*

- **Clinical Benefit Response**

See Statistical Review for FDA analysis.

6.2.4 Safety Results

- **Duration of Exposure**

Reference: Appendix III: Summary of Planned vs. Received Dose Per Week

The mean duration of treatment for the population of 162 patients was 16.3 weeks (114 days, SD 86.20); the median duration of treatment was 12.3 weeks (89 days, range The mean dose (percentage of the planned dose) declined from 97% at week 3 in 162 patients to 69% at week 30 in 29 patients.

- **Overall Incidence and Intensity of Adverse Events**

Ninety-nine percent of patients (160 of 162 patients) reported adverse events (AEs). Sponsor's Table 28 (vol. 1.182, p. 73) presenting number of patients with an adverse event is reproduced on the next page.

Sponsor Table 28

Number of Patients Exhibiting One or More Adverse Events During the Study

	Capecitabine 2510 mg/sqm/day N = 162	
	No.	(%)
All Adverse Events		
Total number of patients with at least one AE	160	(98.8)
Total number of AEs*	1686	
Adverse Events Classified as Related to Treatment		
Number of patients with at least one AE	150	(92.6)
Total number of AEs**	1056	
Mild (Grade 1) Adverse Events Classified as Related to Treatment		
Number of patients with at least one AE	133	(82.1)
Total number of AEs**	517	
Moderate (Grade 2) Adverse Events Classified as Related to Treatment		
Number of patients with at least one AE	127	(78.4)
Total number of AEs**	412	
Severe (Grade 3) Adverse Events Classified as Related to Treatment		
Number of patients with at least one AE	67	(41.4)
Total number of AEs*	120	
Life-Threatening (Grade 4) Adverse Events Classified as Related to Treatment		
Number of patients with at least one AE	6	(3.7)
Total number of AEs**	7	

*Includes 16 adverse events that were ongoing at time of NDA cut-off and which therefore had missing intensities.

**Excludes the 16 AEs with missing intensities.

- **Deaths**

One patient died on treatment and 21 patients died within 28 days of study treatment. The investigators coded the causes of death as follows:

Reviewer Table 11
Cause of Death within 28 Days of Study Drug*
(N = 22)

Cause of Death	Patient Number
Cancer :"Malignant Breast Neoplasm, Metastatic Breast Cancer, Carcinomatosis"	
Cardiac Event Cardiopulmonary Arrest Cardiac Tamponade	
Cerebral Haemorrhage	
Encephalopathy NOS	

*Data from Sponsor's Table 33, vol. 1.182, p. 82

***Reviewer Comment**: Review of the CRFs supports the investigators' opinion that the causes of death are unrelated to study drug. All 22 patients were recently diagnosed with progressive disease. Patient profiles and comments for those patients who had a cause other than progressive disease listed are presented below:*

Cardiac Events Leading to Death

1. Patient died after two complicated procedures within 36 hours to relieve cardiac tamponade believed secondary to progressive disease. She entered her second surgery hypotensive, with evidence of hypokinesis by transesophageal echocardiogram and hypercarbia thought secondary to stiff lungs (lung metastases and talc pleurodesis). She developed DIC and multiorgan failure after the second procedure.

2. Patient went off study after 21 days of treatment due to development of new chest wall lesions. She was treated with talc pleurodesis as an inpatient for shortness of breath, but did not recover. She die12 days after stopping capecitabine.

3. Patient was a 75 year old woman with known bone and liver metastases who went off study for development of new ascites on study day 37. She was s/p adriamycin and taxol. No other pertinent information is available.

All three patients who died due to a cardiac event had evidence of progressive disease; two of the three had known thoracic disease and the third had developed new ascites. All three had received prior anthracenedione and paclitaxel therapy. Two patients had received chest irradiation. The extent of drug exposure in all three cases was short, ≤ 77 days.

Cerebral Haemorrhage. Patient died 25 days after her last dose of capecitabine. She was 69 years old and had risk factors of hypertension and hypercholesterolemia.

Encephalopathy. Patient had brain metastases diagnosed on study. This was not considered a failure of systemic therapy and the patient was to remain on study with drug held during

radiotherapy, to avoid inadvertent radiosensitization. She became increasingly forgetful regarding schedule of treatment and evaluation and requested to withdraw.

- **Premature Withdrawals**

For Sponsor listing of premature withdrawals, see Reviewer Table 2. Reviewer Table 12, lists the reason for withdrawal, number of days on treatment, and investigator assessment of relationship of withdrawal to treatment and outcome. CRFs were reviewed for the 13 patients who withdrew due to an adverse event or intercurrent illness, as well as for the 8 additional patients who discontinued study drug for reasons other then insufficient response or death (see preceding section for review of deaths on study or within 28 days of last dose).

Reviewer Comment: *Three additional cases could be considered as possibly related to treatment: one uncounted inability to swallow pills, one physician request to withdraw a patient for deteriorating condition in the presence of an ongoing PR, and one failure to return with the concurrent AE of life-threatening diarrhea. The premature withdrawal rate possibly related to treatment would then be 16, or 10%.*

Reviewer Table 12
Reasons for Premature Withdrawals

Reason for Withdrawal	Pt. ID	Age	# Days on Rx[1]	Relation	Outcome	Reviewer Comment
Gastrointestinal						
Diarrhea/Gastroenteritis		66	65	possible	unresolved	
		69	33	possible	resolved - no sequelae	
		62	34	possible	unresolved	
Abdominal Pain		66	65	probable	resolved - no sequelae	
		45	64	probable	unresolved	
Nausea		59	52	possible	unresolved	Assoc. w/ fatty liver & rising LFTs. Known liver mets.
Mucosal Inflammation		42	14	probable	unresolved	
Constitutional						
Weakness/Fatigue		76	211	probable	resolved - no sequelae	
		69	34	possible	resolved - no sequelae	
Weight Loss		75	14	possible	resolved - no sequelae	
Hand-Foot Syndrome		73	35	possible	unresolved	
		62	34	possible	unresolved	
Inability to Swallow Pills		58	107	unrelated	resolved - no sequelae	Distal esophageal stricture, new since study rx
		63	5			
Edema of Upper Limb		37	115	unrelated	unresolved	
Respiratory Distress		75	8	possible	unresolved	Baseline dyspnea, lung met, pleural effusion.
Pt Request to Withdraw[3]		75	13			Reason not in CRF
		56	14			Reason not in CRF
		63	53			Reason not in CRF
		55	30			Encephalopathy 2° brain mets
Failure to Return		66	10	probable	resolved - no sequelae	Life-threatening diarrhea
Physician Request to WD		61	14			Decreasing PS
		52	126			Deteriorating condition, although pt considered to be PR

[1]Number of days on treatment was calculated from the "day 1 visit date" and the "date of last dosing" from the CRF; this interval is not the same as TTP, e.g., if the investigator held treatment to allow recovery however the drug was never restarted.
[2]These 2 patients are counted twice because review of their CRF indicated that both AEs resulted in discontinuation of study drug. In other instances of multiple AEs, this did not appear to be the case.
[3]Of the 5 patients who requested to withdraw or failed to return, 1 had evidence of PD and 1 had life-threatening diarrhea requiring hydration.
[4]See Deaths on study or within 28 days of last dose of study drug.

- **Frequent Drug-Related Adverse Events**

Reviewer Table 13 summarizes the common adverse events remotely, possibly or probably related to study drug.

Reviewer Table 13
Frequent Adverse Events Considered Related to Treatment
(N = 162)

Adverse Event	Total		Grade 3		Grade 4	
	No.	(%)	No.	(%)	No.	(%)
Gastrointestinal						
Diarrhea	91	(56.2)	18	(11.1)	5	(3.1)
Nausea	85	(52.5)	7	(4.3)	–	
Vomiting	60	(37.0)	6	(3.7)	–	
Abdominal Pain	32	(19.8)	6	(3.7)	–	
Mucositis	34	(21.0)	11	(6.8)	–	
Dyspepsia	12	(7.4)	–		–	
Constipation	24	(14.8)	2	(1.2)	–	
Skin						
Hand-Foot Syndrome	99	(61.0)	16	(9.9)	–	
Other Dermatitis	8	(4.9)	1	(0.6)	–	
Photosensitivity Reaction	2	(1.2)	–		–	
Nail Disorder	8	(4.9)	–		–	
Constitutional						
Fatigue/Weakness	13	(8.0)	13	(8.0)	–	
Decr. Appetite/anorexia	30	(18.5)	4	(2.5)	–	
Pyrexia	13	(8.0)	–		–	
Other						
Paresthesia	23	(14.2)	–		–	
Dehydration	11	(6.8)	5	(3.1)	1	(0.6%)
Eye Irritation	13	(8.0)	–		–	

Reviewer Comment: *Reviewer Table 13 was generated by queries to the MS Access database of adverse events. Differences with the sponsor's numbers are seemingly due to reviewer collapse of categories as outlined in the next paragraph. Patients, however, are counted only once, by the most severe grade.*

"Diarrhea" encompasses the terms diarrhea, frequent motions, and loose stools; "abdominal pain" encompasses abdominal pain NOS, a. p. upper, a. p. lower, a. tenderness, and gastrointestinal pain NOS; "mucositis" encompasses mucosal inflammation, stomatitis, and mouth ulceration; "hand-foot syndrome" encompasses patients with any dermatitis confined to hands and/or feet; "dermatitis" encompasses dermatitis NOS, rash erythematous, dry skin, pruritus, localized exfoliation, skin hyperpigmentation, skin fissures, rash macular, rash pruritic; 'nail disorder ' also encompassess onycholysis and brittle nails; "fatigue/weakness" also encompasses malaise and lethargy; "paresthesia" also includes hypoaesthesia, and peripheral neuropathy NOS; "appetite decreased" also includes anorexia; "eye irritation" also includes eye inflammation NOS, conjunctivitis NOS, red eye, increased lacrimation and xerophthalmia.

- **Adverse Events Leading to Dose Modification or Treatment Interruption**

Dose modification, either a reduction or treatment interruption, was required in 89 patients (55%). The most common AEs requiring dose modification were the hand-foot syndrome (n = 44), diarrhea (n = 28), nausea (n = 15), vomiting (n = 13), stomatitis (n = 6), and reduction in hematologic parameter (6).

Treatment for an adverse event was required in 151 patients (93%). The most frequent AEs

requiring treatment included those requiring dose modification as well as others: nausea (n = 62), diarrhea (n = 61), dermatitis with the majority being hand-foot syndrome (n = 79), vomiting (n = 43), constipation (n = 24), abdominal pain (n = 19), dyspepsia (n = 14), stomatitis (n = 7)

- **Laboratory Findings**

Reference: Appendix II: NCIC Common Toxicity Criteria

Laboratory abnormalities were graded according to the NCIC Common Toxicity Criteria. Sponsor's Table 41 presents the laboratory parameters that changed during the study. Each change in grade is referred to as a "shift" such that a change from grade 0 (normal) at baseline to grade 3 during treatment would be counted as a grade 3 shift. The most common shifts occur in hematologic parameters and liver function tests. There were 32 instances of grade 2-4 shift in the direction of worsening total bilirubin levels.

Sponsor's Table 41: Summary of All Shifts from Baseline in Laboratory Parameters

(Excerpted from vol. 1.182, p. 111)

	Capecitabine 2510 (mg/sqm/day) intermittent								
Laboratory Parameter	improving by					worsening by			
	4	3	2	1	0	1	2	3	4
ALAT (SGPT)	0	0	0	9	111	19	3	1	0
ASAT (SGOT)	0	0	1	8	109	33	5	0	0
Alkaline Phosphatase	0	0	0	8	98	51	1	0	0
CALCIUM (HYPER)	0	0	0	2	152	3	1	0	1
CALCIUM (HYPO)	1	0	0	0	117	33	5	2	1
Creatinine	0	0	0	0	155	1	3	0	0
Granulocytes	0	0	0	1	5	2	0	0	0
Hemoglobin	0	0	0	9	74	64	8	2	0
Lymphocytes	0	0	2	13	56	61	14	6	0
Neutrophils	0	0	0	0	102	21	12	1	3
Platelets	0	0	0	1	121	24	5	3	2
Potassium	0	0	0	4	91	49	12	0	0
Sodium	0	0	0	0	115	38	2	1	0
Total Bilirubin	0	0	0	0	123	2	18	12	2
White blood cell (WBC)	0	0	0	1	96	44	12	3	1

Sponsor's Table 43 lists all grades 3 and 4 laboratory events. Hyperbilirubinemia and lymphopenia are the most common adverse laboratory events noted.

Sponsor's Table 43: Summary of All Grade 3 and Grade 4 Laboratory Events

(Excerpted from vol. 1.182, p. 112)

	Capecitabine 2510 (mg/sqm/day) intermittent	
Laboratory Parameter	grade 3/4 N (%)	grade 4 N(%)
ALAT (SGPT)	1 (0.62)	0 (0.00)
ASAT (SGOT)	2 (1.23)	0 (0.00)
Alkaline Phosphatase	6 (3.70)	0 (0.00)
CALCIUM (HYPER)	1 (0.62)	1 (0.62)
CALCIUM (HYPO)	3 (1.85)	1 (0.62)
Creatinine	0 (0.00)	0 (0.00)
Granulocytes	0 (0.00)	0 (0.00)
Hemoglobin	7 (4.32)	2 (1.23)
Lymphocytes	98 (60.49)	23 (14.20)
Neutrophils	5 (3.09)	3 (1.85)
Platelets	7 (4.32)	2 (1.23)
Potassium	0 (0.00)	0 (0.00)
Sodium	1 (0.62)	0 (0.00)
Total Bilirubin	17 (10.49)	3 (1.85)
White blood cell (WBC)	5 (3.09)	1 (0.62)

8.1 Background and Methodology

The Four Month Safety Update, received at the FDA 3/2/98, has increased the number of patients from 366 (204 in addition to the 162 patients in the pivotal trial) in the original submission to 570 (408 in addition to 162 patients from the pivotal trial). Data from the pool of 570 patients is used in the sponsor's new label and therefore the FDA reviewer will use the safety update for purposes of the ISS. The frequency and type of adverse events is similar between the pools of 366 and 570 patients.

The cut-off date of June 12, 1997 for the Safety Update (SU) provided for at least three months of safety follow-up for all patients. The distribution of patients by disease and trial is presented in Reviewer Table 14. The pool excludes patients from Phase I or PK/PD trials as well as one Phase 2 trial (NO15570) which has 14 patients accrued by October 12, 1997. Events in these 14 patients were

summarized separately; no new AE or change in frequency is noted. Thirty-seven patients treated in the phase 2 trials below on a *continuous* schedule of capecitabine are not included.

Reviewer Table 14: Summary of Studies Included in the 4-Month Safety Update[1]

Study	Phase	Disease	Population Characteristics	No. of Pts Receiving 2500 or 2510 mg/m2/d on Intermittent Schedule	No. Pts in the ISS of the NDA
SO14697[2]	2	Breast	1-2 prior Rx for met dis	162	162
SO15179	2	Breast	1 prior Rx for met dis	22	18
SO14799	2	Breast	No prior Rx for met dis	61	44
SO14797	2	Colorectal	No prior Rx for met dis	34	34
SO14695	3	Colorectal	No prior Rx for met dis	130	39
SO14796	3	Colorectal	No prior Rx for met dis	161	69
				Total = 570	Total = 366

[1]Modified from Sponsor's Table 1, volume 17.2 of Safety Update
[2]Pivotal Trial

The patients from the pivotal trial represent the most heavily pretreated patient population. Patients with colorectal cancer represent a majority of patients in the SU (325/570 = 57%). All of the patients in the phase 2 studies of breast cancer are women; 67% of the 570 patients are female. Dose modifications were identical to those outlined in the pivotal trial, see page 10. The mean duration of treatment was 121 days, vs 114, in the pivotal trial.

8.2 Overall Incidence and Intensity of Adverse Events (n = 570)

Reviewer Table 15 juxtaposes the overall AE profile for patients in the pivotal trial vs. all patients with breast cancer vs. patients with colorectal cancer. Patients with breast cancer, including those in the pivotal trial which represent the most heavily treated population, tend to have a higher incidence of AEs in each of the table's categories.

Reviewer Table 15: Number of Patients Exhibiting One or More Adverse Events During the Study[1]

	Pivotal Trial (n = 162)	Breast Cancer (n = 245)	Colorectal Cancer (n = 325)
All Adverse Events			
Total # pts with at least 1 AE	160 (98.8%)	223 (91.0%)	273 (84.0%)
Total # AEs	1686	1508	1496
AE Classified as Related to Rx			
# pts with at least 1 AE	150 (92.6%)	223 (91%)	273 (84.0%)
Total # AEs	1056	1508	1496
Mild (Gr. 1) AE Related to Rx			
# pts with at least 1 AE	133 (82.1%)	195 (79.6%)	238 (73.2%)
Total # AEs	517	725	788
Moderate (Gr. 2) AE Related to Rx			
# pts with at least 1 AE	127 (78.4%)	186 (75.9%)	206 (63.4%)
Total # AEs	412	590	508
Severe (Gr. 3) AE Related to Rx			
# pts with at least 1 AE	67 (41.4)	100 (40.8%)	113 (34.8%)
Total # AEs	120	177	183
L-T (Gr. 4) AE Related to Rx			
# pts with at least 1 AE	6 (3.7%)	12 (4.9%)	8 (2.5%)
Total # AE	7	16	17

[1]Modified from Sponsor's Table 28 (vol. 1.182, p. 73) and Table 54 (vol.17.2, p. 84 of SU)

8.3 Deaths

The overall incidence of deaths during treatment or within 28 days after the end of treatment in the Safety Update population (66 of 570, or 11.6%) is less than overall incidence of deaths reported in the pivotal trial (28 of 162, or 17.3%); however, the patients in the pivotal trial were more heavily

pretreated. Causes of death are presented in Sponsor's Table 18 (vol. 17.2, p. 30 from the SU).

Sponsor's Table 18: Deaths Occurring During Treatment or Within 28 Days after End of Treatment

	N = 570
Deaths probably, possibly or remotely related to treatment	**7 (1.2%)**
Pneumonia	2
Sepsis	1
Diabetes mellitus, aggravated	1
GI necrosis (Pt	1
PE	1
Cause unknown (Pt	1
Deaths reported as unrelated to treatment	**59 (10.3%)**
Progressive disease	49
CNS event: hemorrhage, subdural, CVA	4
Cardiac event: failure NOS, MI	2
PE	1
Hypokalemia	1
Septicemia NOS	2

Reviewer Comment: *Comments from review of the patient narratives are as follows:*

1. *Patient a 67 year old male with metastatic rectal cancer, died on day 21 of "massive ischemic necrosis of the colon" documented on autopsy which the investigator coded as probably related to treatment. Other AEs included epistaxis, life-threatening diarrhea, mucositis, leukopenia and "drug hypersensitivity." Previous treatment with 5-FU and potential hypersensitivity is not reported in the NDA. The sponsor will be queried further. It is possible this represents either DPD deficiency or a 5-FU typhlitis.*

2. *Patient a 61 year old female with metastatic breast cancer, was hospitalized on day 40 with a depressed level of consciousness, serum glucose of 572 mg/dl, dehydration, hypotension, diarrhea, grade 3 neutropenia and grade 2 coagulopathy. She died the following day.*

8.3 Premature Withdrawals

Seventy-one patients (12.5%) were withdrawn for adverse events or intercurrent illness. The percentage of patients withdrawn for adverse events/intercurrent illness in the pivotal trial according to the sponsor's analysis was 8%, or in the FDA's analysis, 10%. Gastrointestinal AEs and hand-foot syndrome were the primary reasons for withdrawal in both populations.

Reviewer Comment: *The significance of the apparent increase in premature withdrawal in the less heavily pretreated population is unclear at this time. Further review can be conducted when the NDA for based on two large randomized trials, is submitted within the next year. However, there does not appear to be a change in cause for withdrawal.*

Another 13 patients (2.3%) were withdrawn for reasons listed as "admin/other." This category of patients was responsible in the pivotal trial for the difference in incidence of premature withdrawal according to the sponsor (8%) and FDA (10%). It is possible that if further details were requested from the sponsor, that the incidence of premature withdrawal could rise by 2.3%.

8.4 Frequent Drug-Related Adverse Events

The Sponsor's table below depicts the percent incidence of treatment-emergent adverse events considered remotely, possibly or probably related to treatment in ≥ 5% of patients in the pivotal trial and in the pool of 570 patients. (This table was requested by the FDA for labeling purposes and is a compilation of a variety of tables from the NDA).

Sponsor's Table from Label: Percent Incidence of Treatment Emergent Adverse Events Considered Remotely, Possibly or Probably Related to Treatment in ≥ 5% of Patients

	Phase 2 Trial in Stage IV Breast Cancer (N = 162)		Pooled Safety Database (N = 570)	
Body System/Adverse Event	**Total**	**Grade 3-4**	**Total**	**Grade 3-4**
GI Disorders				
Diarrhea	54.9	14.2	50.7	12.3
Nausea	51.9	4.3	44.0	3.7
Vomiting	37.0	3.7	25.6	3.6
Stomatitis	22.3	9.3	22.8	3.9
Abdominal Pain	14.8	3.1	11.2	3.2
Constipation	15.4	--	9.3	--
Upper Abdominal Pain	5.6	--	7.4	--
Dyspepsia	8.0	--	5.6	--
Flatulence	4.9	--	4.0	--
Dry Mouth	4.3	--	3.9	--
Oral pain	3.7	--	--	--
Skin and Subcutaneous				
Hand-and-Foot Syndrome	56.2	42.0	44.6	12.8
Dermatitis	15.4	4.9	10.2	--
Rash Erythematous	10.5	4.3	7.4	--
Dry Skin	8.6	3.1	7.5	--
Alopecia	--	--	4.4	--
Pruritis	4.3	--	4.2	--
Localised Exfoliation	3.7	--	3.9	--
Skin Hyperpigmentation	3.7	--	3.2	--
Nail disorder	2.5	--	--	--
Onycholysis	2.5	--	--	--
Skin Fissures	2.5	--	2.1	--
General Disorders				
Fatigue	37.6	7.4	27.4	3.7
Pyrexia	11.1	4.3	10.0	--
Weakness	6.2	5.0	5.1	--
Asthenia	--	--	4.9	--
Pain in limb	6.2	3.1	4.0	--
Rigors	2.5	--	--	--

Percent Incidence of Treatment Emergent Adverse Events
Considered Remotely, Possibly or Probably Related to Treatment in > 5% of Patients (con't)

	Phase 2 Trial in Stage IV Breast Cancer (N = 162)		Pooled Safety Database (N = 570)	
Neurological Disorders				
Headache	9.3	–	6.7	–
Paraesthesia	9.9	–	5.6	–
Dizziness	8.0	–	4.7	–
Taste Disturbance	3.7	–	4.0	–
Hypoaesthesia	4.3	–	–	–
Insomnia	7.4	–	3.3	–
Metabolism Disorders				
Anorexia	9.3	–	10.5	–
Appetite Decreased	11.1	–	7.4	–
Dehydration	6.8	3.1	4.9	2.8
Weight Decrease	4.3	–	3.5	–
Eye Disorders				
Increased lacrimation	6.8	–	6.0	–
Eye irritation	3.7	–	–	–
Xerophthalmia	3.1	–	–	–
Respiratory Disorders				
Cough	3.1	–	–	–
Dyspnoea	4.3	–	3.9	–
Infections				
Upper respiratory tract	3.7	–	–	–
Oral candidiasis	–	–	2.1	–
Musculoskeletal Disorders				
Back pain	5.6	–	2.8	–
Muscle cramps	2.5	–	–	–
Myalgia	6.2	–	2.1	–
Cardiac Disorders				
Edema	2.5	–	–	–
Lower limb edema	5.6	–	3.9	–
Psychiatric Disorders				
Anxiety	2.5	–	–	–
Reproductive Disorders				
Intermenstrual bleeding	3.1	–	–	–
Renal and Urinary Disorders				
Dysuria	2.5	–	–	–
Blood Disorders				
Anemia			2.3	–

8.5 Adverse Events Leading to Dose Modification or Treatment Interruption

Dose modification, either a reduction or treatment interruption was required in 49% of the pooled population, compared to 55% of patients in the pivotal trial. The reasons for dose modification or treatment interruption were the same in both populations—gastrointestinal events, primarily diarrhea, nausea and vomiting, and the hand-foot syndrome.

Reviewer Comment: *The label will include incidences for both the pivotal trial and the pooled population.*

8.6 Laboratory Findings

Reference: Safety Update, Letter Date 2/27/98, vol. 17.2, p. 40

The frequency and type of laboratory abnormalities remains similar to those seen in the pivotal trial. The main clinically relevant change is hyperbilirubinemia. The incidence of grade 3-4 hyperbilirubinemia in the pivotal trial is 10% vs 14% in the pooled population. The incidence in the three trials conducted in patients with breast cancer is 7% vs 19% in the three trials conducted in patients with colorectal cancer. Grade 3-4 hyperbilirubinemia occurred in 21.1% of the 339 patients with hepatic metastases at baseline and in 10.4% of the 231 patients without hepatic metastases at baseline.

Reviewer Comment: *Further analyses have been requested from the sponsor, including association with elevation in other measures of hepatic function, duration, intervention and outcome.*

9.0 Foreign Marketing

Xeloda™ is not commercially available in other countries.

10.0 Summary

The demonstration of efficacy for NDA #20-896 is based on data from a single, uncontrolled trial: *S0 14697: A Phase 2 study of capecitabine in patients who have failed previous treatment with paclitaxel for metastatic breast cancer.* The only endpoint that could be considered robust from a Phase 2 design is response rate. From a regulatory perspective, response rate is considered a surrogate endpoint for clinical benefit and could only be considered an adequate endpoint for accelerated approval.

Accelerated approval requires a refractory patient population defined as one for whom there are no adequate alternatives or for whom the new drug provides a meaningful therapeutic benefit over existing therapies. It would be intended for the population resistant to both paclitaxel and an anthracycline. The population targeted in the pivotal trial, patients who have failed previous treatment with paclitaxel, allowed a heterogeneous group of patients from the standpoint of prior therapies. Forty-three patients were resistant to both paclitaxel and an anthracycline and 11 patients responded in this group, for a response rate of 25.6%. This is problematic in terms of being a subgroup analysis and a small sample size with broad C.I.; however, responses were also seen in patients resistant to one cytotoxic and exposed to the other, or exposed to both but not clearly resistant. Perhaps these other subgroups could be seen as supportive of the population of interest. Although the patient population entered into this Phase 2 trial is heterogeneous, the population probably accurately reflects the variety of treatments used in the community.

Although the response rate is derived from a single trial, it is a multicenter trial. A single center, accrued 37 patients (35 with measurable disease), serving as a nested Phase 2 trial and perhaps serving to confirm the overall results or provide a measure of consistency of results. Although the IRC's assessments did not confirm all of the investigator/sponsor assessments, this would not be expected. Their assessments went in both directions, i.e. more and less favorable than the sponsor's assessments, lending credibility to their review process. The concordance rate (counting the 2 patients with mixed indicator lesions) was approximately 75%.

Short term safety data with capecitabine appears tolerable and commensurate with other chemotherapy agents. The most frequent treatment-related adverse events were gastrointestinal events or the hand-foot syndrome. While 42% of patients had grade 3 or 4 treatment-related events, dose modification appears to allow patients to remain on study. No deaths were related to capecitabine. The premature withdrawal rate possibly related to treatment is 8% (sponsor) or 10% (Agency).

Should accelerated approval be considered, protocol S0 14999B has been submitted by the sponsor and could be considered for a post-marketing commitment. A synopsis of the protocol, "An open-label randomized Phase 3 study of capecitabine in combination with docetaxel (Taxotere) versus docetaxel monotherapy in patients with advanced and/or metastatic breast cancer" can be found in Appendix IV.

11.0 Oncology Drugs Advisory Committee (ODAC) Summary

ODAC, chaired by Dr. Janice Dutcher, met on March 19, 1998. The primary reviewers were Dr. Sandra Swain and Dr. George Sledge, who led the discussion of the questions posed by the FDA. The questions and count of votes are presented below.

Study SO 14697

Study SO 14697 was a non-comparative, multicenter trial in 162 women with metastatic breast cancer who had progressive disease despite treatment with paclitaxel. The primary efficacy endpoint was the objective response rate in patients with measurable disease. In the 135 women with measurable disease, the response rate was 18.5% (95% C.I.: 12.4, 26.1) with a median duration of 154 days (range . The response rate in the 43 patients who had disease resistant to both paclitaxel and an anthracycline was 25.6% (II/43; 95% C.I.: 13.5%, 41.2%), with a median duration of response of 154 days (range

*Response duration by WHO criteria starts on the first day of treatment. The Agency's analysis dates the onset of response to the first day of documented response.

Questions to the Committee

1. Of the 162 women entered into the pivotal trial, 43 had disease that was resistant to both paclitaxel and an anthracycline.

   a. In the 43 women with breast cancer resistant to both paclitaxel and an anthracycline, is an objective tumor response of 25.6% with a median duration of 154 days evidence of meaningful therapeutic benefit over existing treatments?

      YES - 11 NO - 1

      The one dissenting vote stated that no advantage was seen for capecitabine over continuous infusion 5-FU.

   b. Are the other patients in the trial supportive of the response rate in this doubly resistant population?

      YES - 12 NO - 0

2. Patients who have received certain cumulative doses of anthracyclines and/or anthracenediones could be considered to be intolerant of or poor candidates for further therapy with these agents because of the risk of cardiotoxicity with additional treatment. On 3/17/98,we received data on cumulative doses of anthracyclines and/or anthracenediones received by each patient. In addition to the 43 patients above, there are 48 patients in the paclitaxel resistant and anthracycline exposed group, some of whom could potentially meet this criteria. We are currently analyzing the number of patients and objective response rates in the following groups:

   a. In patients whose breast cancer is resistant to paclitaxel and an anthracycline, but in whom further doxorubicin may be contraindicated, e.g., patients who have already received 400 mg/m^2, would Xeloda™ represent a meaningful therapeutic gain, assuming an overall response rate of 20% when these patients are added to the 43 resistant patients (revised by the committee).

      YES - 6 NO - 5 ABSTENTION - 1

   b. In patients whose breast cancer is resistant to paclitaxel and who have received a standard adjuvant regimen resulting in a minimum cumulative dose of 240 mg/m^2 of doxorubicin equivalents, would Xeloda™ represent a meaningful therapeutic gain over additional treatment with an anthracycline, assuming an overall response rate of 20% when these patients are added to the 43 resistant patients and those described in 2a?

      YES - 0 NO - 12

3. Is the overall toxicity profile acceptable for women who have resistant disease after treatment with both paclitaxel and an anthracycline?

   YES - 12 NO - 0

4. Assuming an overall response rate of 20%, should Xeloda™ receive accelerated approval for the treatment of women with metastatic breast cancer:

   a. resistant to paclitaxel and an anthracycline-containing chemotherapy regimen?

      YES - 10 NO - 2

   b. resistant to paclitaxel and who have received a minimum cumulative dose of 400 mg/m^2 of doxorubicin equivalents?

      YES - 8 NO - 3 Abstain - 1

   c. resistant to paclitaxel and who have received a standard adjuvant regimen resulting in a minimum cumulative dose of 240 mg/m^2 of doxorubicin equivalents?

      YES - 0 NO - 11 Abstain - 1

5. The sponsor has submitted a protocol for a randomized trial, "An open-label randomized Phase 3 study of capecitabine in combination with docetaxel (Taxotere) versus docetaxel monotherapy in patients with advanced and/or metastatic breast cancer." Eligible patients would be resistant to or have recurrent disease after an anthracycline-containing therapy or have relapsed during or within 6 weeks of an adjuvant anthracycline-containing therapy. A total of 454 patients would be randomized to one of two arms. The primary endpoint is to demonstrate superiority in time to

progression in favor of the capecitabine-docetaxel combination arm.

Would a favorable result with combination therapy in this study confirm the clinical benefit of Xeloda™ in patients with prior chemotherapy?

The committee chose not to vote on Question 5. Instead, a discussion followed that suggested alternative trial designs and reminders that TTP alone would not demonstrate clinical benefit. The drug approval process depends on a full review of risk/benefit.

12.0 Recommended Regulatory Action

Recommend Accelerated Approval for: "treatment of patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy may be contraindicated, e.g., patients who have received cumulative doses of 400 mg/m^2 of doxorubicin or doxorubicin equivalents.

/S/ 4/17/98
Alison Martin, M.D.
Primary Reviewer

/S/ 4/17/98
Julie Beitz, M.D.
Team Leader, Secondary Reviewer

APPENDIX I

APPENDIX I: Phase I or PK/PD Studies Conducted with Xeloda™

STUDY	US IND	DESCRIPTION	PT #	DOSE mg/m²/d	STATUS
SO14794	No (Europe)	*Intermittent* twice daily oral therapy with Ro 09-1978 in patients with advanced and/or metastatic solid cancer		502 to 3514	Complete
SO14693	Yes	*Continuous* twice daily oral therapy with Ro 099-1978 in patients with advanced and/or metastatic solid cancer		110 to 1657	Complete
SO14694	Yes	Capecitabine (Ro 09-1978) when combined with paclitaxel (Taxol) in patients with advanced solid tumors		1004 to 1657 T:135 to 175	Complete
SO14798	No (Europe)	Capecitabine in combination with oral leucovorin in patients with advanced and/or metastatic solid cancer		1004 to 2510 + LV 60 mg/d	Complete
BD 14823	Yes	Pharmacodynamic/pharmacokinetic study of Ro 09-1978 in plasma, tumor and healthy tissue		1255 x 5-7 days	Complete
BD 14824	Yes	Exploratory clinical study: NMR Spectorscopy of Ro 09-1978 in cancer patients		1255 x 1 and 5FU 600 mg/m² x1	Complete
SO14800	No (Italy)	Pilot study of Ro 09-1978 in patients with advanced and/or metastatic solid cancer		502 x 10d	Complete
JO14865	No (Japan)	A Phase I clinical trial of Ro 09-1978		502 to 2510	Complete
BK 14822	No (Europe)	Influence of hepatic Impairment due to liver metastases on the pharmacokinetics of Ro 09-1978 in cancer patients		1255 x 1 and 5'DFUR 750 x 1	Complete
BK 14561	No (Europe)	Single dose pharmacokinetics of Ro 09-1978 and Ro 09-1979 in cancer patient volunteers		550 x 1	Complete
WP15354	Yes	Influence of Maalox on the PK of Capecitabine		1250 x 3	Complete
SO14797*	Yes	Effect of food on the PK of Capecitabine		1331(continuous) 2510 (intermittent)	Complete
BP 15572	Yes	Bioequivalence Study of two formulations of Capecitabine		2000 x 2	Complete

* Nested within another clinical study

APPENDIX I: Phase 2 or 3 Studies Conducted with Xeloda™

STUDY	US IND	DESCRIPTION	PT #*	DOSE mg/m²/d (schedule)	STATUS
SO 14697	Yes	A phase 2 study of capecitabine (Ro 09-1978) in patients who have failed previous treatment with paclitaxel (Taxol) for metastatic breast cancer		2510 (intermittent)	Complete

*As of June 12, 1997

Clinical Studies Not Reported in N20-896

N0 15542 S111 4/97 &S116 5/97	Yes	A Phase 2 study of capecitabine in patients who have failed (amended to "received") previous treatment with paclitaxel or docetaxel for locally advanced and/or metastatic breast cancer	Complete as of 1/98
So 14999	Yes	An open label randomized Phase 3 study of Capecitabine in combination with docetaxol vs. docetaxol monotherapy in patients with advanced and/or metastatic breast cancer	Planned

APPENDIX II

APPENDIX II: Schedule of Assessments

Schedule of Assessments

	Screening	Baseline Run-In	<—Initial Treatment Period—>					<– Treatment Continuation in NC/PR or CR Pts–>[c]		Off Study
Study Week	0	1	4	7	10	13	16	19	EVERY 6 WEEKS	
Study Day	-14 to 1	-7 to 1	1	22	43	64	85	106	127	EVERY 42 DAYS	
Informed Consent	•										
Demographic Data	•										
Malignancy / Treatment History	•										
Concomitant Non-Malignant Disease & Treatment	•	——Any changes throughout the study to be noted——									
ECG[a]	•		——As clinically indicated——								
Chest X-ray[a]	•										
Brain CT Scan (optional)[a]	•										
Clinical Benefit Response[d]		•	•	•	•	•	•	•			
General Physical Exam	•										
Vital Signs		•	•	•	•	•	•	•	•		
Physical Measurements	•		•	•	•	•	•	•	•		
Hematology[a]		•		•	•	•	•	•	•		
Blood Chemistry[a]		•		•	•	•	•	•	•		
Urinalysis[a]		•	——as clinically indicated——								
Pregnancy Test[a]	•										
Adverse Events			——recorded throughout study and up to 28 days after last study treatment——								
Tumor Assessments[b]	•			•		•		•		•	
Location of Metastases	•										

a – Also as clinically indicated;

b – Screening for tumor assessments can be done up to a maximum of 21 days prior to treatment by a suitable reproducible technique (to be used for the duration of the study);

c – Patients responding (complete, partial response) or in stable disease (no change) can continue to receive further treatment (see Appendix 6).

d – Daily Pain Assessment Diary + weekly assessment of Karnofsky.

Excerpted from Sponsor's Vol 1.186, p. 25

APPENDIX II: 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. 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 (ie 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.

1.4. Malignant Hepatomegaly

May be measured if the liver descends 5 cm below the costar margin by adding the measurements below the costar margins. Measurements below the costar 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 oesteolytic lesions, pelvic and abdominal masses, lymphagitic or confluent multinodular lung metastases, skin metastases, and deviated or obstructed ureters or gastrointestinal tract). Computerized tomography or radionucleide 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.

Excerpted from Sponsor's vol. 1.186, p. 59

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): 2 50% decreased (for bidimensional lesions) or 2 30% decrease (for uni-dimensional 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 (or <30% unidimensional) 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 size of one or more measurable lesions, or the appearance of new lesions.

2.2. Unmeasurable Disease

Complete Response (CR): Complete disappearance of all known disease for at least 4 weeks.

Partial Response (PR): Estimated decrease in tumor size Of 50% or more for at least 4 weeks.

No Change (NC): No significant change for at least 4 weeks. This includes stable disease, estimated decrease of less than 50%, and lesions with estimated increase of less than 25%.

Progressive Disease (PD): Appearance of any new lesion not previously identified or estimated increase of 25% or more in existent lesions.

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.

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

Partial responses require >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.

Worsening of clearly non-measurable disease (serous effusions, bone metastases as determined by bone scan) must not be the sole lesion for determination of disease progression.

Organ site stabilization will not detract from CRs or PRs 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.

(WHO Handbook for Reporting Results of Cancer Treatment. Geneva: World Health Organization, 1979)

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. Geneva: World Health Organization, 1979)

APPENDIX II: CLINICAL BENEFIT RESPONSE*

The design of this method to evaluate patients as clinical benefit responders (CBR) and nonresponders (CBNR) is based upon the symptoms most frequently experienced by patients with breast cancer, that of pain, weakness, and a decrease in Karnofsky Performance Status (KPS).

From this observation Clinical Benefit Response was used as a patient by patient determination of improvement of: PAIN, ANALGESIC CONSUMPTION; KPS.

It is a dichotomous variable and was used in this case as a Clinical Benefit Response Rate. Primary measures were pain (pain intensity and analgesic consumption) and KPS.

To have a positive response the improvement must have been substantial and sustained (for at least 4 consecutive weeks).

I. **The definition of positive, negative and stable responses in each of the four parameters is as follows:**

(a) Pain Intensity

Measurement: weekly mean of daily pain intensity scores *

Positive:

- Improvement of 50% or more over baseline, maintained for at least 4 weeks (provided baseline is $\geq$ 20 out of 100)

Negative:

- Any worsening from baseline, maintained for at least 4 weeks, occurring <12 weeks after start of treatment (provided these scores are < 20). Also, a patient who exits the study < 12 weeks after the start of treatment due to increased pain.

Stable:

- If neither positive nor negative.

* Using a "Memorial Pain Assessment Card" the patient must mark daily how much pain he/she feels on a visual analogue scale (100 mm long) from 0 (least pain) to 100 (most pain). Other details such as pain description, pain relief, mood etc. may also be recorded.

Excerpted from Sponsor's vol. 1.186, p. 64-69

(b) Analgesic Consumption

Measurement: weekly mean of daily analgesic consumption in morphine equivalent mg (see table below).

Positive:

- Improvement of 50% or more over baseline, maintained for at least 4 weeks (provided baseline is ≥ 70 mg per day) Negative:

Negative:

- Any worsening from baseline, maintained for at least 4 weeks, occurring <12 weeks after start of treatment (provided those scores are < 10 mg per day).

Stable:

- If neither positive nor negative.

Equianalgesic dose table:

Drug	SC, IM or IV (mg)	PO morphine equivalents (mg)
morphine	10	30
hydromorphone	1.5	8
levophanol	2	4
methadone	10	20
oxycodone	--	20
meperidine	75	300
fentanyl patch (TTS-100)	--	160/day
oxymorphone 25 mg supp.	--	15
acetaminophen	650	9

(c) Performance Status

Measurements: weekly measurement of KPS by self-assessment by patient.

Positive:

- Improvement of 2 20 points over baseline, maintained for at least 4 weeks (provided baseline is ≥ 70).

Negative:

- Worsening of ≥ 20 points from baseline, maintained for at least 4 weeks, occurring < 12 weeks after the start of treatment.

Stable:

- If neither positive nor negative.

II. Determining the Clinical Benefit Responders (CBRs) and Clinical Benefit Nonresponders (CBNRs)

First of all, the pain intensity and analgesic consumption responses are compared to give one of three results:

ANALGESIC CONSUMPTION

PAIN INTENSITY		Positive	Stable	Negative
	Positive	P	P	N
	Stable	P	S	N
	Negative	N	N	N

P: positive (improvement)
S: stable
N: negative

Then, this result is compared to the performance status which in most cases decides the clinical benefit response:

PERFORMANCE STATUS

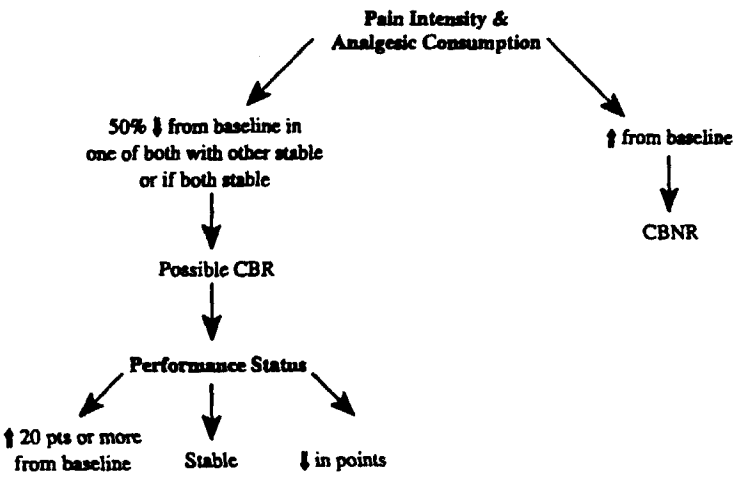
PAIN		Positive	Stable	Negative
	Positive	R	R	NR
	Stable	R	S	NR
	Negative	NR	NR	NR

R: clinical benefit responders
S: stable under primary measures
NR: clinical benefit non responders

Summary of Assessment of Clinical Benefit Response

The following flow chart diagramatically shows assignment of responses from the four parameters:

Clinical Benefit Response



CBR: Clinical Benefit Responder
CBNR: Clinical Benefit Nonresponder

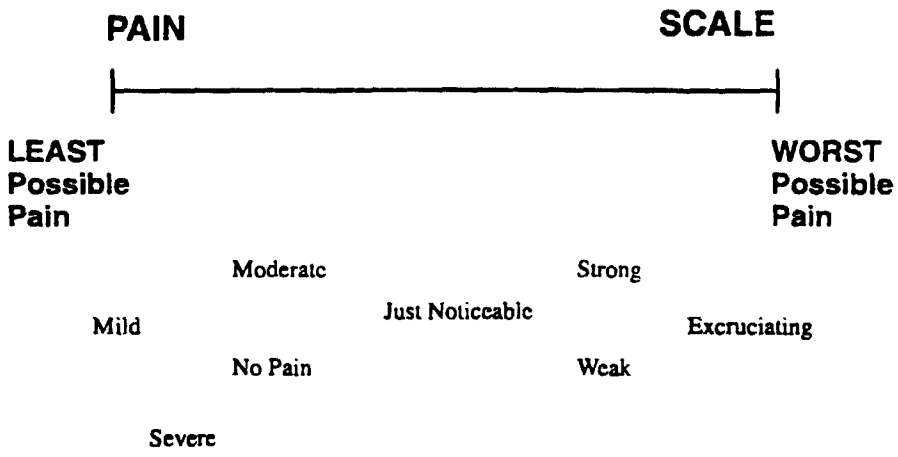
Clinical Benefit Response

The Memorial Pain Assessment Card

The Memorial Pain Assessment Card (MPAC) is a simple instrument designed to provide rapid evaluation of pain and pain relief as well as psychological distress [1]. It is an 8.5 by 11 inch card, on which is preprinted the eight pain intensity descriptors and three visual analogue scales which measure pain intensity, pain relief and mood. The card was developed by the Analgesic Studies Section of the Memorial Sloan Kettering cancer Center (MSKCC) to assess the relative potency of new and standard analgesic drugs, and in this context was found repeatedly to be a valid, reliable, efficient and sensitive measure.

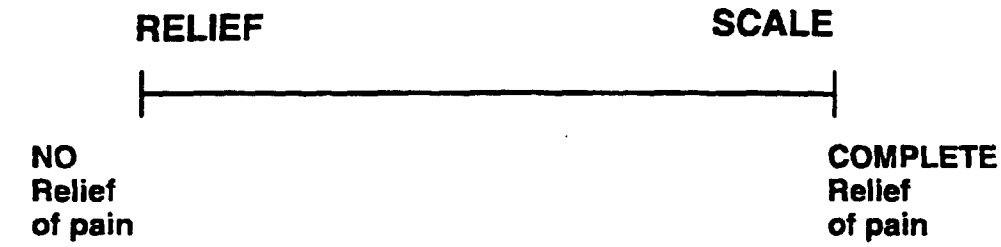
The card is folded in the middle such that four sides can quickly be presented to the patient. On each of three sides is printed a 100mm long visual analogue scale (VAS), and on the fourth is a set of adjectives adapted from the Pain Intensity VAS (VASPI), which is anchored by the terms "least possible pain" and "worst possible pain". The patient is asked to place a mark along the line to indicate his or her subjective judgment of pain intensity. The score on this and the other VAS is obtained by measuring in millimeters the distance between the left end of the line, and the patient's mark. On the second side of the MPAC is the modified Tursky pain adjectives scale, which is a categorical measure of pain intensity. Eight intensity descriptors that represent a range from "no pain" to "excruciating" are printed in a random arrangement, and the patient is asked to encircle the adjective that describes his or her subjective experience of pain severity. Side three of the MPAC is a VAS pain relief (VASPR). Patients are asked to indicate with a mark the degree of pain reduction they experience following the most recent intervention, which usually is the administration of an analgesic drug. On side four, the VAS measures the subjective experience of mood (VASMOOD), and on it patients are asked to rate their current feeling, from worst to best. The instructions for administration of these scales are simple and readily understood, and an experienced patient can complete the four ratings in less than 20 seconds with minimal effort.

Side 1:

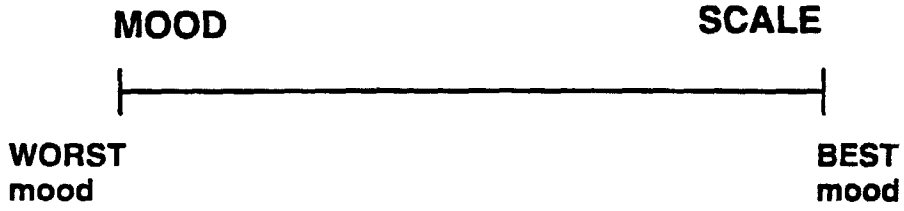


Clinical Benefit Response

Side 2:



Side 3:



APPENDIX 2: NCIC CTC GRADING SYSTEM

	Grade 0	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life threatening)
Allergy	none	transient rash, fever < 38°C, 100.4°F	urticaria, fever=38°C, 100.4°F, mild brochospasm	serum sickness, bronchospasm, req parenteral meds	anaphylaxis
BLOOD / BONE MARROW					
White Blood Cells(109A)	2 4.0	3.0 - 3.9	2.0 - 2.9	1.0-1.9	< 1.0
Platelets (109/1)	WNL	75.0 - normal	50.0 -74.9	25.0 - 49.9	c 25.0
Hemoglobin (g/dl)	WNL	10.0 - normal	8.0 - 9.9	6.5 - 7.9	< 6.5
Granulocytes (109/1) (i.e. Neuts.+baso.+eos.)	2 2.0	1.5 - 1.9	1.0-1.4	0.5 - 0.9	<05
Lymphocytes (109/1)	2 2.0	1.5 - 1.9	1.0 - 1.4	0.5 - 09	<05
Hemorrhage (clinical) (includes nosebleeds, menorrhagia etc.)	none	mild, no transfusion (includes bruise/ hematoma, petechiae)	gross, 1-2 units transfusion per episode	gross, 3-4 units transfusion per episode	massive, >4 units transfusion per episode
CARDIOVASCULAR					
Arterial	none	-	-	transient events	permanent event
Venous	none	superficial (excludes IV site reaction - code under skin)	deep vein thrombosis not requiring anticoagulant therapy	deep vein thrombosis req anticoagulant therapy	pulmonary embolism
Dysrhythmias	none	asymptomatic, transient, req no therapy	recurrent or persistent, no therapy req	req trt	req monitoring, or hypotension, or tachycardia, or fibrillation
Edema	none	I + or dependent in evening only	2+ or dependent throughout day	3+	4+, generalized anasarca

CARDIOVASCULAR (cont.)					
Function	none	asymptomatic, decline of resting ejection fraction of 10% or greater but less than 20% of baseline value	asymptomatic, decline of resting ejection fraction by >20% of baseline value	mild CHF, responsive to therapy	severe or refractory CHF
Hypertension	none or no change	asymptomatic, transient increase by >20mm Hg or to >150/100 if previously WNL. No trt req	recurrent or persistent increase by >20mm Hg or to >150/100 if previously WNL. No trt req	req therapy	hypertensive crisis
Hypotension	none or no change	changes req no therapy (incl. transient orthostatic hypotcnsion)	req fluid replacement or other therapy but not hospitalization	req therapy &	req therapy &
Ischemia	none or no change	non-specific T wave flattening	asymptomatic, ST & T wave changes suggesting ischemia	angina without evidence for infarction	acute myocardial infarction
Pain (chest)	none	mild	moderate	severe	life-threatening
Pericardial	none	asymptomatic, effusion, no intervention req	pericarditis (rub, chest pain, ECG changes)	symptomatic effusion; drainage req	tamponade, drainage urgently req; or constrictive pericarditis req surgery
COAGULATION					
Fibrinogen	WNL	0.99-0.75 x N	0.74-0.5 x N	0.49-0.25 x N	$\leq$0.24 x N
Prothrombin Time	WNL	1.101-1.25 x N	1.26-1.5 x N	1.51-2.00 x N	$\geq$ 2.00 x N
Partial Thromboplastin time	WNL	1.01-1.66 x N	1.67-2.33 x N	2.34-3.00 x N	$\geq$ 3.00 x N

ENDOCRINE					
Amenorrhea	no	yes ≥ 3 months	-	-	-
Cushingoid	normal	mild	pronounced	-	-
Hot Flashes	none	mild or <1/day	moderate &≥ 1/day	frequent & interferes with normal function	-
Gynecomastia	normal	mild	pronounced or painful	-	-
Impotence / Libido	normal	decrease in normal function	-	absence of function	-
FLU-LIKE SYMPTOMS					
Arthralgia (joint pain)	none	mild	moderate	severe	-
Diaphoresis (sweating)	none	mild	moderate	severe	-
Fever in absence of infection	none	37.1-38.0°C 98.7-100.4°F	38.1-40.0°C 100.5-104.5°F	>40.0°C >104.0°F for < 24hrs	>40.0°C (104.0°F) for > 24hrs or fever accompanied by hypotension
(includes drug fever)	Fever felt to be caused by drug allergy should be coded as **ALLERGY**. Non-allergic drug fever (e.g. as from biologics) should be coded under **FLU-LIKE SYMPTOMS**. If fever is due to infection, code **INFECTION** only.				
Hayfever (includes sneezing, nasal stuffiness, post-nasal drip)	none	mild	moderate	severe	-
Lethargy (fatigue, malaise)	none	mild,fall of 1 level in performance status	moderate, fall of 2 levels in PS.	severe, fall of 3 levels in PS	-
Myalgia (muscle ache)	none	mild	moderate	severe	-
Rigors/Chills (Gr 3 incl. Cyanosis)	none	mild or brief	pronounced and/or prolonged	cyanosis	-

GASTROINTESTINAL					
Anorexia (loss of appetite)	none	mild	moderate	severe	-
Appetite- increased	none	mild	moderate	-	-
Diarrhea	none	increase of 2-3 stools/day over pre-trt	increase of 4-6 stools/day, or nocturnal stools	increase of 7-9 stools/day, or incontinence, malabsorption	increase of ≥10 stools/day or grossly bloody diarrhea, or need for parenteral support
Esophagitis/dysphagia	none	dys. or odyn. Not req trt, or painless ulcers on esophagoscopy	dys. Or odyn. Req trt	dys. Or odyn. Lasting >14 days despite trt	dys. Or odyn. With 10% loss of body wt, dehydration, hosp. req
Mouth Dryness	none	mild	moderate	severe	-
Intestinal Fistula	no	-	-	req intervention	req operation
Heartburn (includes dyspepsia)	none	mild	moderate	severe	-
Nausea	none	able to eat reasonable intake	intake significantly decreased but can eat	no significant intake	-
Small bowel obstruction	no	-	intermittent, no intervention	req intervention	req operation
Pain/Cramping (abdominal) (includes rectal pain)	none	mild	moderate	severe	-
Proctitis (rectal)	none	-	tenesmus or ulcerations relieved with therapy	tenesmus or ulcerations or other symptoms not relieved	mucosal necrosis with hemorrhage or other life threatening
Stomatitis/oral	none	painless ulcers, erythema, or mild soreness	painful erythema, edema, or ulcers but can eat	with therapy painful erythema, edema, or ulcers, and cannot eat	Proctitis, mucosal necrosis and/or req parenteral or enteral support

GASTROINTESTINAL (cont)					
	none	mild	moderate	severe	
Taste altered					
Gastritis/ulcer	no	antacid	req vigorous medical management or non-surgical trt	uncontrolled by medical management; req surgery for GI ulceration	perforation of bleeding
Vomiting	none	1 episode in 24hrs	2-5 episodes in 24hrs	6-10 episodes in 24hrs	>10 episodes in 24hrs or req parenteral
GENITO URINARY					
Bladder changes	none	light, epithelial atrophy, or minor telangiectasia	generalized telangiectasia	severe generalized telangiectasia (often with petechiae) or reduction in bladder capacity	necrosis, or contracted bladder (capacity <100ml), or fibrosis/fistulae
Creatinine	WNL	<1.5 x N	1.5-3.0 x N	3.1-6.0 x N	>6.0 x N
Cystitis	none	mild symptoms req no intervention	symptoms relieved completely with therapy	symptoms n ot relieved despite therapy	severe (life threatening) cystitis
(non-bacterial)	Urinary tract infection should be coded under infection, not **Genitourinary**.				
Dysuria	none	dysuria not req trt	dysuria req trt	-	-
Fistula	none	-	-	yes	-
Frequency	none	freq of urination or nocturia twice pre-trt habit	freq of urination or nocturia < hourly	freq with urgency and nocturia ≥ hourly	-
Hematuria	neg	micro only	gross, no clots	gross + clots	req transfusion
	Hematuria resulting from thrombocytopenia should be coded under hemorrhage not **Genitourinary**.				

GENITO URINARY (cont)					
Ureteral obstruction	none	unilateral, no surgery req	bilateral, no surgery req	not complete bilateral, but stents, nephrostomy tubes or surgery req	complete bilateral obstruction
Proteinuria	no change	1 + or <0.3g % or <3g/L	2-3 _ or 0.3-1.0g% or 3-10g/L	4+ or >1.0g% or >10g/L	nephrotic syndrome
HEPATIC					
Alk Phos or 5'nucleotidase	WNL	≤2.5 x N	2.6-5.0 x N	5.1-20.0 x N	>2.0 x N
Transaminase ALAT (SGPT)	WNL	≤2.5 x N	2.6-5.0 x N	5.1-20.0 x N	>20.0 x N
Transaminase ASAT (SGOT)	WNL	≤2.5 x N	2.6-5.0 x N	5.1-20.0 x N	>20.0 x N
Bilirubin	WNL	—	<1.5 x N	1.5-3.0 x N	>3.0 x N
Liver (clinical)	no change from baseline	—	—	precoma	hepatic coma
LDH	WNL	<2.5 x N	2.6-5.0 x N	5.1-20.0 x N	>20.0 x N
INFECTIONS					
Infections	none	mild, no active trt	moderate, localized infect req active trt	severe, systemic infect req parenteral trt, specify site	life threatening sepsis, specify site
Febrile neutropenia	none	—	—	present	—

Fever felt to be caused by drug allergy should be coded as **ALLERGY**. Non-allergic drug fever (eg. as from biologics) should be coded under **FLU-LIKE SYMPTOMS**. If fever is due to infection, code **INFECTION** only.

METABOLIC (SI UNITS)					
Amylase	WNL	<1.5 x N	1.5-2.0 x N	2.1-5.0 x N	>5.1 x N
Hypercalcemia	<2.64mmol/L	2.64-2.88	2.89-3.12	3.13-3.37	≥3.37
Hypocalcemia	>2.10mmol/L	2.10-1.93	1.92-1.74	1.73-1.51	≤1.50
Hyperglycemia	<6.44mmol/L	6.44-8.90	8.91-13.8	13.9-27.8	>27.8 or ketoacidosis
Hypoglycemia	>3.55mmol/L	3.03-3.55	2.19-3.02	1.66-2.18	<1.66
Hypokalemia	no change or >3.5mmol/L	3.1-3.5	2.6-3.0	2.1-2.5	≤2.0
Hypomagnesemia	>0.70mmol/L	0.70-0.58	0.57-0.38	0.37-0.30	≤0.29
Hyponatremia	no change or > 135mmol/L	131-135	126-130	121-125	≤120
NEUROLOGIC					
Cerebellar	none	slight incoordination, dysdiadochokinesis	intention tremor, dysmetria, slurred speech, nystagmus	locomotor ataxia	cerebellar necrosis
Constipation	none or no change	mild	moderate	severe	ileus > 96 hrs
Cortical (includes drowsiness)	none	mild somnolence	moderate somnolence	severe somnolence, confusion, disorientation, hallucinations	coma, seizures, toxic psychosis
Dizziness (includes lightheadedness)	none	mild	moderate	severe (includes fainting)	-

NEUROLOGIC (cont)					
Extrapyramidal/Involuntary Movement	none	mild agitation (includes restlessness)	moderate agitation	torticollis, oculogyric crisis, severe agitation	-
Headache	none	mild	moderate or severe but transient	unrelenting & severe	-
Hearing	none or no change	asymptomatic, hearing loss on autiometry only	tinnitus	hearing loss interfering with function but correctable with hearing aid	deafness not correctable
Insomnia	none	mild	moderate	severe	-
Mood	no change	mild anxiety or depression	moderate anxiety or depression	severe anxiety or depression	suicidal ideation
Motor	none or no change	subjective weakness; no objective findings	mild objective weakness without significant impairment of function	objective weakness with impairment of function	paralysis
Personality Change	no change	change, not disruptive to pt or family	disruptive to pt or family	harmful to others or self	psychosis
Sensory	none or no chqange	mild paresthesias, loss of deep tendon reflexes (incl. Tingling)	mild or moderate objective sensory loss; moderate paresthesias	sensory loss or paresthesias that interfere with function	-
Vision	none or no change	blurred vision	-	symptomatic subtotal loss of vision	blindness
OCULAR					
Conjunctivitis/keratitis	none	erythema or chemosis not req steroids or antibiotics	req trt with steroids or antibiotics	corneal ulceration or visible opacification	-
Dry eye	normal	mild	req artificial tears	severe	req enucleation

OCULAR (cont)					
Glaucoma	no change	—	—	yes	-
PULMONARY					
Carbon Monoxide Diffusion Capacity (DLCO)	>90% of pretreatment value	decrease to 76-90% of pre-trt	decrease to 51-75% of pre-trt	decrease to 26-50% of pre-trt	decrease to ≤25% of pre-trt
Cough	none	mild	moderate	severe	-
Pulmonary Edema	none	—	out-pt management	in-pt management	req intubation
Pulmonary Fibrosis	normal	radiographic changes, no symptoms	—	changes with symptoms	-
Pneumonitis (non-infectious)	normal	radiographic changes, no symptoms	—	changes with symptoms	-
SOB (dyspnea) (includes wheezing)	none or no change	asymptomatic, with abnormality in PFT's	dyspnea on significant exertion	dyspnea at normal level of activity	dyspnea at rest
SKIN					
Alopecia	no loss	mild hair loss	pronounced or total head hair loss	total body hair loss	-
Skin changes	none	hyperpigmentation	atrophy	subcut, fibrosis	ulceration or necrosis
Desquamation	none	dry desquamation	moist desquamation	confluent moist desquamation	-
Flushing-facial	none	mild	moderate	severe	-
Local Toxicity (reaction at IV site)	none	pain	pain & swelling, with inflammation or phlebitis	ulceration	plastic surgery indicated

SKIN (cont)					
Rash/Itch **(not due to allergy)** **(includes recall reaction)**	**none or no change**	scattered macular or papular eruption or erythema that is asymptomatic	scattered macular or papular eruption or erythema with pruritis or other associated symptoms	generalized symptomatic macular, papular, or vesicular eruption	exfoliative dermatitis or ulceration dermatitis
WEIGHT		9			
Weight Gain	**<5.0%**	5.0-9.9%	10.0-19.9%	≥20.0%	—
Weight Loss	**<5.0%**	5.0-9.9%	10.0-19.9%	≥20.0%	—

APPENDIX II: SAMPLE SIZE

The sample size is based on the primary analysis using the exact distribution of the one-sided binomial test and on the necessity for safety information.

Assuming a true RR of 20% and a sample size of 100 patients with objectively measurable disease we get the power of 81% for the primary test that the overall response rate is greater than 10%. For more precise information see **Table 4** and **Table 5**. With a 20% measured response rates this number of patients gives already a reasonable size for the 95% Pearson-Clopper confidence intervals.

For safety reasons, and in order to demonstrate a similar efficacy profile, 50 patients with clinically evaluable disease will be added to the study. Hence the study will include 150 evaluable patients.

Table 4. Power at Different Sample Sizes for the Binomial Test at an α-level of 2.5% Using the Exact Distribution and Testing a RR of x% by Assuming a True Rate of y% (x%y%)

N	Power 10%/20%	Power 15%/20%	Power 15%/25%
80	65%	24%	64%
100	81%	26%	71%
120	85%	28%	77%
130	89%	29%	79%
140	92%	29%	81%
150	94%	37%	89%

Note that for determining the α level an actual level of e.g. 2.588% was still taken as 2.5% while 2.6% was rejected and the next lower probability was chosen.

Table 5. 95% Confidence Intervals (Pearson-Clopper) Depending on the Sample Size Assuming a Measured Response Rate of 20%

N	Lower	Upper
80		
100		
120		
130		
140		
150		

APPENDIX III

APPENDIX III: ALGORITHM FOR DETERMINATION OF PREDOMINANT SITE OF DISEASE*

The CRF collected information on the sites of disease as: skin, soft tissue, lymph nodes, bone, liver, lung, pleura, peritoneum, as well as a category of "other", which required filling in a blank. Each site of disease had a box checked to indicate presence of a solitary metastasis, multiple metastases, no involvement or whether the information was not known.

The following table provides the algorithm by which a predominant site of disease was chosen.

Site of Metastatic Disease			Predominant Site of Metastatic Disease
Visceral lung, liver, pleura, peritoneal disease	**Soft Tissue** = skin, lymph nodes, soft tissue	**Bone**	
Multiple	Multiple/Solitary/None	Multiple/Solitary/None	Visceral
Solitary	Solitary	Solitary	Visceral
None	Multiple	Multiple/Solitary/None	Soft Tissue
None	Solitary	Solitary	Soft Tissue
None	None	Multiple/Solitary	Bone
Solitary**	Solitary***	Multiple	Bone

*Excerpted from sponsor's table 7, p26, vol. 1.182.
**No more than one organ site
***No more than two organ sites

Sponsor's Table 27: Summary of Planned Versus Received Dose Per Week (excerpted from vol. 1.182, p. 71)

Program ED12 produced by on 31JUL97 - 20:34

Week			Capecitabine 2510 (mg/sqm/day) intermittent
Total		N	162
		Mean	0.87
		Std	0.16
		Min	
		Max	
		Med	0.92
Week	3	N	162
		Mean	0.97
		Std	0.11
		Min	
		Max	
		Med	1.00
Week	6	N	144
		Mean	0.89
		Std	0.20
		Min	
		Max	
		Med	1.00
Week	9	N	100
		Mean	0.81
		Std	0.25
		Min	
		Max	
		Med	1.00
Week	12	N	90
		Mean	0.78
		Std	0.26
		Min	
		Max	
		Med	0.88
Week	15	N	75
		Mean	0.72
		Std	0.28
		Min	
		Max	
		Med	0.75
Week	18	N	62
		Mean	0.72
		Std	0.26
		Min	
		Max	
		Med	0.72
Week	21	N	48
		Mean	0.70
		Std	0.28
		Min	
		Max	
		Med	0.72

Table 27 (cont.) Summary of Planned Versus Received Dose Per Week

Program ED12 produced by on 31JUL97 - 20:34

Week			Capecitabine 2510 (mg/sqm/day) intermittent
Week	24	N	38
		Mean	0.71
		Std	0.25
		Min	
		Max	
		Med	0.72
Week	27	N	33
		Mean	0.66
		Std	0.25
		Min	
		Max	
		Med	0.68
Week	30	N	29
		Mean	0.69
		Std	0.21
		Min	
		Max	
		Med	0.70

APPEARS THIS WAY
ON ORIGINAL

APPENDIX IV

APPENDIX IV: SPONSOR'S SYNOPSIS OF PROTOCOL SO14999		
COMPANY: F. Hoffman-La Roche, Ltd NAME OF ACTIVE INGREDIENT: CAPECITABINE		
TITLE OF PROTOCOL	An open-label randomized phase III study of capecitabine in combination with docetaxel (Taxotere®) versus docetaxel monotherapy in patients with advanced and/or metastatic breast cancer.	
INDICATION	Treatment of locally advanced metastatic breast cancer resistant to or recurring after an anthracycline-containing therapy, or relapsing during an anthracycline-containing adjuvant therapy.	
CLINICAL PHASE	Phase III	
OBJECTIVES	Primary: To demonstrate superiority in time to progression in favor of the capecitabine-docetaxel combination arm. Secondary: To demonstrate superiority of the capecitabine-docetaxel combination arm over docetaxel monotherapy in terms of overall response rate (complete and partial responses). To observe at least equivalent survival curves for the two treatment groups. To evaluate and compare the safety profile of each treatment arm. To evaluate and compare changes from baseline in the quality of life of the two treatment groups. To collect data on medical care utilization in the two treatment groups. To describe the pharmacokinetics of capecitabine in 16 patients randomized tot he combination arm.	
METHODOLOGY [STUDY DESIGN]	Open-label randomized multi-center multinational comparative study of capecitabine administered as an oral twice daily outpatient intermittent treatment (2 weeks treatment, I week rest period) combined with a 3 weekly i.v. 100 mg/m^2 docetaxel dose as an outpatient treatment for at least 6 weeks. Randomization will be done by country; stratification will be done by previous paclitaxel (Taxol®) treatment or not. Patients responding (complete or partial response) or with stable disease (no change) at the end of 6 weeks of treatment continue to receive treatment until disease progression in patients who stop study treatment for other reasons. Patients with documented progressive disease will go off study at that time.	
DURATION	Patients will be evaluated for response at 6-week intervals. Patients with complete or partial response and patients with stable disease will be treated until disease progression (followed by a 4-week follow-up period after the end of the treatment). The study formally ends with the last patients stopping study medication (plus 28 days follow-up). Clinical cut-off for the study analysis will be 9 months after the last patient enrolled. Further data collected after the clinical cut-off will be reported in an addendum to the study report.	
PLANNED TOTAL SAMPLE SIZE	454 evaluable patients: 227 patients in the combination arm, 227 in the docetaxel monotherapy arm; approximately 80 centers.	

SYNOPSIS OF PROTOCOL SO14999 CONTINUED	
PATIENT SELECTION CRITERIA	Treatment of patients with locally advanced or metastatic cancer who are resistant to or have recurrent disease after an anthracycline-containing therapy, or who have relapsed during an adjuvant anthracycline-containing therapy. Female out-patients 18 years of age or older with histologically or cytologically confirmed breast cancer. Patients should not have been previously treated with a docetaxel-containing regimen either in the adjuvant or advanced disease setting. Patients must have at least one bidimensionally measurable lesion. Marker lesions which are solely bone lesions, ascites or pleural effusions will not be accepted.
FORMULATIONS	**Capecitabine (Ro 09-1978)**: film-coated tablets is strengths of 150 mg and 500 mg. **Docetaxel**: IV 80 mg and 20 mg vials.
TEST DRUG DOSAGE	**Capecitabine - docetaxel combination arm:** **Capecitabine intermittent schedule**: Twice daily oral treatment (2 weeks treatment, 1 week rest) at a dose of 2500 mg/m^2/day (split into two equal doses to be taken in the morning and evening) on days 1 to 14 of each 3 week treatment cycle. **Docetaxel**: 75 mg/m^2 given intravenously over 1 hour (with appropriate comedication) every 3 weeks, given on the 1st day of each 3 week treatment cycle.
ROUTE OF ADMINISTRATION	**Capecitabine**: Oral within 30 minutes after ingestion of food. **Docetaxel**: Intravenous infusion over 1 hour.
MAIN PARAMETERS OF: -EFFICACY -SAFETY -PHARMACOKINETICS -QUALITY OF LIFE -MEDICAL CARE	Tumor measurement/assessment (based on WHO criteria) Survival Adverse events, laboratory parameters C_{max}, t_{max}, AUC and $t_{1/2}$ capecitabine and its metabolites EORTC QLQ-C30 (v.2.0) and Breast Cancer module BR23 Hospitalization, treatment of adverse events, consultations, diagnostic procedures or tests

PROCEDURES

Informed consent:
Written informed consent should be obtained before any study-specific procedures.

Screening: The screening may be made in two stages.

- Assessments which can be made up to 14 days before treatment start will include: demographic data; medical history;
  physical examination including a general neurologic examination; pregnancy test (for all premenopausal women and
  women less than 1 year after menopause) and special tests (chest X-ray, ECG, and bone scans/X-rays of hot spots and
  brain CT scan if clinically indicated). Tumor assessments should be made within 14 days prior to treatment start (although up to a maximum of 21 days is acceptable in exceptional circumstances) by a suitable reproducible technique (MRI, CT scan, X-rays or photograph), however, the same procedure, technique and protocol should be
  used throughout the study for evaluation of indicator lesions.

- Assessments to be made within 7 days prior to the start of treatment: vital signs and physical measurements (including Karnofsky performance status, height and weight), hematology, blood chemistry, urinalysis.

- Assessment on treatment day 1 before treatment starts: quality of life questionnaire.

During Treatment:
Visits are foreseen on days 1, 8 (to check the neutrophil count nadir in both arms), 22, and then on a 3 weekly basis, with the visit normally occurring on the same day of the week. The third and subsequent visits can take place on the scheduled day ± 3 days. Two additional visits are planned on days 14 and 77 for PK sampling for 16 selected patients.

Parameters:

- Assessments of tumor response on days 43, 85, 127 and every 6 weeks until week 48 and then every 12 weeks until
  PD. When applicable, responses should be confirmed at least 4 weeks after having first been reported.

- Adverse Events and medical care utilization are monitored continuously during treatment and for 28 days after the
  last intake/infusion of study drug.

- ECG/Chest X Ray
  Bone scans/X-rays of hot spots and brain CT scan if clinically indicated.

- Vital signs and physical examination including weight and Karnofsky Performance Status.

- Quality of life Questionnaire on the first treatment day and every 6 weeks, before the new treatment course starts and
  when the patient goes off study.

- Nature and duration of any hospitalization, treatment of any adverse event, nature and duration of any home care and
  support, consultations.

- Pharmacokinetics of capecitabine: In the first 16 patients allocated to the combination arm in 6 selected sites, blood
  samples will be taken on days 14 and 77 at the following timepoints: predose, 0.5, 1, 2, 3, 4, 5, 7 and 10 hours after capecitabine administration.

Follow-up:

- Time to disease progression and survival status census will be performed on a 6 weekly basis to week 48 and thereafter every 12 weeks for those patients who stop treatment due to reasons other than progressive disease. Survival status census will be performed on a 12 weekly basis after disease progression.

STATISTICAL ANALYSIS

Efficacy

The statistical analyses will comprise:

Primary analysis

Time to progression
-Testing for difference
-Logrank test two-sided at alpha=5%
-Secondary: Cox regression with previous paclitaxel treatment as additional factor

Secondary analysis

Time progression
-Testing for difference
-Chi square test with Shouten correction two-sided at alpha=5%

Survival
-Testing for at least equivalence based on estimate of risk or hazard ration of docetaxel versus docetaxel
+ capecitabine in Cox regression model with previous paclitaxel treatment as additional factor.

Safety Parameters

The standard safety analysis will include listings, frequency and shift tables of adverse events and laboratory data of all patients receiving at least one dose of either treatment. Cox regression to compare time to onset of adverse events.

Quality of Life

A comparison of the two treatments will be made using a two-sided Van der Waerden test in order to look for differences in favor of the combination treatment.

Medical Care Utilization

Listing and summary tables of medical care parameters.

Pharmacokinetics

PK parameters obtained in this patient population (n=16) will be compared to those obtained in other studies (e.g. in patients with colorectal cancer).
PK parameters obtained on days 14 and 77 will be compared.

Stratification

-Previous treatment or not with paclitaxel (Taxol®)