



AMENDED CLINICAL STUDY PROTOCOL 4

COMPOUND: XRP9881

A randomized, open-label, phase III study of RPR109881 IV every 3 weeks versus capecitabine (Xeloda®) tablets twice daily for 2 weeks in 3-week cycles in patients with metastatic breast cancer progressing after taxanes and anthracycline therapy

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PROTOCOL OUTLINE

Study number EFC6089 [XRP9881B-3001]

Study name SOPRANO

Title

A randomized, open-label, phase III study of RPR109881 IV every 3 weeks versus capecitabine (Xeloda®) tablets twice daily for 2 weeks in 3-week cycles in patients with metastatic breast cancer progressing after taxanes and anthracycline therapy

Investigators, study sites

Approximately 250 sites worldwide: 100 North America/Latin America, 150 Europe and Australia

Estimated study duration and dates	First Patient Treated: Apr 2004 Last patient in July 2005 Primary Analysis Event (PFS): Oct 2005(20 months) Last Patient Treatment Visit: May 2006 (27 months) Survival Analysis: Nov 2007 (45 months)	Phase III
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Objectives

Primary Objective: The primary objective of this study is to compare progression free survival (PFS) in patients with metastatic breast cancer treated with RPR109881 versus capecitabine progressing after taxanes and anthracycline therapy.

Secondary Objectives: The secondary objectives are to compare survival and other measures of anti-tumor efficacy [response rate (RR), time to tumor response (TTR), duration of response (DR), single time progression rate (STPR), and time to treatment failure (TTF)] in patients treated with RPR109881 versus capecitabine; to compare the safety and tolerability of RPR109881 versus capecitabine; and to compare the quality of life and other clinical benefit measures in patients treated with RPR109881 versus capecitabine.

Study design

This will be a global multi-center, open-label, two-arm randomized, phase III clinical trial. Patients will be randomized to treatment with RPR109881 (test arm) or capecitabine (comparator arm). Patients will be stratified based on the treatment setting of prior taxane administration, prior taxane responsiveness, and region. Patients will continue to receive treatment until disease progression, patient intolerance, or withdrawal of consent. Patients who discontinue study treatment prior to disease progression will continue to have tumor assessments every 6 weeks until disease progression. Following disease progression, patients will be treated by their physicians as determined by usual medical practice and followed for survival. Patients treated on the capecitabine arm will not be eligible to receive RPR109881 in this or other clinical trials for breast cancer.

Radiological tumor assessments will be performed at baseline, at the end of every even-numbered treatment cycle (every 6 weeks), and whenever disease progression is suspected. In addition, a radiological tumor assessment to obtain a single time progression rate (STPR) will be obtained at Day 120 (+/- 7 days) for all patients. After the patient is withdrawn from study treatment, a final tumor assessment will be performed if an assessment has not been performed within the prior 6 weeks. All patients with an objective response of partial response (PR) or complete response (CR) must have the response confirmed between 4-6 weeks after the initial documentation of response. All scans will be independently reviewed in real-time to assess for response to treatment (PR or CR) and disease progression by an independent review committee (IRC). An independent data monitoring committee (IDMC) will review the data during the conduct of the trial.

Number of patients

Approximately 800 patients, 400 patients randomized to the RPR109881 treatment arm and 400 patients to the capecitabine treatment arm, are required to reach a total number of 617 progressions in order to provide 90% power to detect a 23% reduction in the hazard rates for the primary analysis of TTP. If the target number of events is attained prior to fully accruing patients to the study, the trial will be closed to further enrollment.

Inclusion eligibility criteria

Inclusion Criteria - Patients meeting all of the following criteria will be considered for enrollment into the study:

1. Histologically or cytologically proven diagnosis of breast adenocarcinoma that is now metastatic or locally recurrent and inoperable with curative intent. Patients with previously treated histo/cytologically confirmed disease who develop clinical or radiological evidence of metastatic disease do not require separate confirmation of the metastatic disease.
2. All patients must have received an anthracycline and a taxane (e.g. docetaxel and/or paclitaxel) prior to entry in the protocol. These drugs may have been given in the neoadjuvant/adjuvant or in the metastatic setting, may have been given concurrently or sequentially, and may have been given in combination with other drugs. Patients must have received a standard dose of anthracycline and of taxane expected to have potentially resulted in a response.

For taxanes

- a) Patients must have progressed while receiving paclitaxel or docetaxel therapy or at any time after having received paclitaxel or docetaxel therapy.
- b) The taxane-based treatment must have been the last chemotherapy the patient received.

For anthracyclines

Patients must have either:

- a) Progressed while on anthracycline treatment, with or without an initial response

OR

- b) Patients must have received an adequate course of anthracyclines defined as follows:

- i. In the neoadjuvant or adjuvant setting, patients must have received a regimen considered standard for adjuvant therapy, which would usually result in a cumulative dose of doxorubicin of 200-300 mg/m² or doxorubicin equivalent.
- ii. In the metastatic setting patients must have received a regimen considered standard for therapy for metastatic disease, which would usually result in a cumulative dose of doxorubicin of at least 300 mg/m² or doxorubicin equivalent.
3. Completion of all prior chemotherapy, immunotherapy (including trastuzumab [Herceptin®]), targeted non-cytotoxic therapy, and radiotherapy ≥3 weeks prior to randomization. Prior treatment with radiotherapy, chemoembolization therapy, or cryotherapy is allowed if these therapies are not directed to the areas of measurable disease being used for the purposes of this protocol. Patients on bisphosphonate therapy may continue such therapy.
4. Evidence of measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST). Measurable lesions are lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm with conventional CT. With spiral CT scan, lesion must be ≥ 10 mm in at least one dimension.
5. Male or female patients at least 18 years old.
6. ECOG (Eastern Cooperative Oncology Group) performance status of 0,1, or 2.
7. Patients must have resolution of all clinically significant toxic effects (excluding alopecia) of any prior surgery, radiotherapy, cryotherapy, chemoembolization therapy, hormone therapy, immunotherapy, targeted non-cytotoxic therapy, or chemotherapy to grade ≤1 by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, or to within the limits listed in the specific inclusion/exclusion criteria.

8. Adequate organ function as defined by:

Absolute neutrophil count (ANC)	$\geq 1,500/\mu\text{L}$
Platelets	$\geq 100,000/\mu\text{L}$
Hemoglobin	$\geq 9.0 \text{ g/dL}$ (no RBC transfusion support ≤ 2 weeks prior to the first treatment dose on study)
Prothrombin time/ International normalized ratio (PT/INR) and Partial thromboplastin time (PTT)	$\leq 1.5 \times$ upper limit of normal (ULN)
Creatinine	$\leq 1.5 \times$ ULN, or calculated creatinine clearance (CrCl) $>60 \text{ mL/min}$
Total bilirubin	Within normal limits (WNL)
Serum aspartate aminotransferase (AST; serum glutamate-oxalate transferase [SGOT] and serum alanine aminotransferase (ALT; serum glutamate-pyruvate transferase) [SGPT]	If AP is $\leq 2.5 \times$ ULN, then ALT/AST must be $\leq 2.5 \times$ ULN. If AP is $>2.5 - \leq 5.0 \times$ ULN, then ALT/AST must be $\leq 1.5 \times$ ULN
Alkaline phosphatase (AP)	$\leq 5.0 \times$ ULN

9. Patients must be either post-menopausal, surgically sterile, or using effective contraception (the definition of effective contraception will be based on the judgment of the investigator). All female patients of childbearing potential must have a negative pregnancy test (serum or urine) within the 7 days prior to randomization. The female partner of a male patient should be using effective contraception as defined above.
10. Patients (or legally acceptable representative) must agree to, sign, and date an EC/IRB-approved patient informed consent form (Ethics Committee / Institutional Review Board).
11. Patients must be willing and able to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.

Exclusion criteria - Patients presenting with any of the following will not be included in the study:

1. History of any second malignancy with the exception of adequately treated basal cell or squamous cell skin cancer, or *in situ* carcinoma of the cervix uteri. Inclusion of patients with any other *in situ* cancer or a history of an invasive cancer with complete remission for 5 or more years must be discussed with the sponsor and the principal investigators. Patients with a history of contralateral breast cancer who have been disease-free for more than 5 years prior to randomization are permitted.
2. History of hypersensitivity grade ≥ 3 to taxanes, Polysorbate-80, or to compounds with similar chemical structures. Patients with known intolerance to fluoropyrimidines or patients with known dihydropyrimidine dehydrogenase (DPD) deficiency.
3. The following breast cancer treatments:
 - Patients receiving >1 adjuvant regimen. However, patients who have received neoadjuvant therapy immediately followed by surgery and immediately followed by adjuvant therapy without intervening progression are considered to have received one adjuvant regimen and are allowed in the trial. It is not considered to be adjuvant treatment, when chemotherapy is administered after a local treatment by either surgery or radiotherapy of a single metastasis, including cutaneous metastases, since recurrence is a near certainty and not only a risk.
 - Patients receiving >1 chemotherapy regimen for metastatic or locally recurrent and inoperable breast cancer. A chemotherapy regimen is defined as a single or a combination of chemotherapy agents given until documented disease progression or relapse. For example, patients who received sequential doxorubicin and docetaxel in the metastatic setting without intervening progression are allowed in the trial.
4. Prior treatment with capecitabine or any taxane-analogs except for paclitaxel or docetaxel (eg, epothilones are not permitted, novel preparations of paclitaxel are not permitted). Generic paclitaxel and Abraxane® (nanoparticle albumin-bound paclitaxel) are permitted.
5. Concurrent treatment with potent inhibitors of cytochrome P450 3A4, such as ketoconazole, itraconazole, erythromycin, clarythromycin or patients planning to receive these treatments. For patients who were receiving treatment with such agents, a one-week washout period is required prior to randomization.
6. Concurrent treatment on another clinical trial or with any other cancer therapy including chemotherapy, immunotherapy (including trastuzumab [Herceptin®]), hormonal therapy, radiotherapy, chemoembolization therapy, cryotherapy, targeted non-cytotoxic therapies or patients planning to receive these treatments during the study.
7. HER-2 positive patients may participate in this trial. Concurrent treatment with trastuzumab [Herceptin®] is not permitted.
8. Known brain or leptomeningeal disease (CT or MRI scan of the brain required only in case of clinical suspicion of central nervous system involvement).

9. Any of the following within the 6 months prior to randomization: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft surgery, clinically symptomatic and uncontrolled cardiovascular disease, or clinically significant cardiac arrhythmias (grade 3-4).
10. History of inflammatory bowel disease or chronic diarrhea.
11. Peripheral neuropathy grade ≥ 2 .
12. Other severe acute or chronic medical or psychiatric condition, or significant laboratory abnormality requiring further investigation that may cause undue risk for the patient's safety, inhibit protocol participation, or interfere with interpretation of study results, and in the judgment of the investigator would make the patient inappropriate for entry into this study.
13. Known human immunodeficiency virus (HIV) infection requiring treatment or acquired immunodeficiency-syndrome (AIDS)-related illness.
14. Patients who are pregnant or breastfeeding.

Treatments

RPR109881: Patients randomized to the RPR109881 treatment arm will receive a starting dose of 90 mg/m² IV RPR109881 on Day 1 of Cycle 1 administered over 1-hour, with the exception of patients with known bone marrow involvement, documented by bone marrow biopsy and/or aspiration, who will receive a starting dose of 75 mg/m² IV RPR109881. Treatments will be repeated in the same manner at 3-week intervals (3-week cycles). Dose adjustment will be permitted for subsequent treatment cycles based on individual patient tolerance.

Required premedication will include: dexchlorpheniramine 5 mg, diphenhydramine 25 mg or other antihistamines; dexamethasone 8 mg or equivalent steroid. Ranitidine or other Histamine H2 antagonist is recommended **with the exception of cimetidine**. All premedications will be administered by i.v. infusion. It is recommended that infusion of these medications be completed 30 minutes or more prior to each dose of RPR109881. Anti-emetic prophylaxis with ondansetron, granisetron or dolasetron is recommended.

Capecitabine: Patients randomized to the capecitabine treatment arm will receive a starting dose of 1250 mg/m² capecitabine tablets administered orally twice daily (morning and evening, equivalent to 2500 mg/m² total daily dose) for 2 weeks followed by a 1-week rest period, to form a 3-week cycle. The dose is based on prescribing information stated in the US and EU package inserts. Dose adjustment will be permitted depending on individual patient tolerance. Capecitabine tablets should be swallowed with water within 30 minutes after a meal.

Efficacy data

The IRC (Independent Review Committee) will review the tumor assessments provided by investigators independently in a blinded fashion. The IRC will provide final assessment for responses (CR and PR), best response, date of first response, assessment of tumor progression, and the date of progression for each patient. The operational details of the review process will be provided in the IRC Charter.

Primary Efficacy Variable: Progression Free Survival (PFS) will be determined by the Independent Review Committee (IRC) and defined as the time from randomization to first documentation of objective tumor progression, according to RECIST, or death.

Secondary Efficacy Variables:

- Overall Survival (OS) defined as the time from randomization to death.
- Single Time Progression Rate (STPR) defined as the proportion of patients with objective disease progression defined by RECIST by Day 120 of treatment, or death, relative to the total number patients in the analysis population.
- Response Rate (RR) defined as the proportion of patients with confirmed complete response (CR) or confirmed partial response (PR), defined by RECIST, relative to the total number of patients in the analysis population.

Other Efficacy Variables:

- Time to Tumor Response (TTR) defined as the time from randomization to the first documentation of objective tumor response defined by RECIST.
- Time to Treatment Failure (TTF), defined as the time from randomization to the first documentation of objective tumor progression defined by RECIST, or final discontinuation of all study treatment, or death, whichever comes first.
- Duration of Response (DR) defined as the time from the first documentation of objective tumor response defined by RECIST to the first documentation of objective tumor progression defined by RECIST or death.

Quality of life data / Clinical benefit parameters

- Quality of life as assessed by the EORTC QLQ-C30 questionnaire with QLQ-BR23 breast cancer symptom module.
- The Global health status/QoL score of the QLQ-C30 will be the primary QoL endpoint. The Breast/arm symptom scores of QLQ-BR23 will be supportive.
- Change in body weight and performance status from baseline.

Safety data

Safety analyses will be performed based on incidence, severity (as graded by the NCI CTCAE, version 3.0), chronicity, and cumulative nature of treatment- emergent adverse events.

Health economic data

Health resource utilization and EQ-5D questionnaire data will be collected in applicable countries to determine the health economic impact of RPR109881. These data will be collected in order to perform an analysis by country, if necessary. Health economic data collection and analysis will be considered an adjunct study.

Statistical procedures

Three analysis populations will be defined for this study:

- The intent-to-treat (ITT) population will consist of all randomized patients. The treatment code of each patient in the ITT population is determined by the treatment code originally assigned by randomization.

This population is the primary efficacy analysis population and will be used in the analyses of all efficacy variables.

- The As-Treated (AT) population will consist of all patients who receive at least 1 partial dose of study drug. The treatment code of each patient in the as-treated population is determined by the treatment the subject actually received.

This population will be evaluated for safety as well as for demographic and background information.

- The Evaluable Patient (EP) population will consist of all randomized patients who have measurable disease of breast cancer based on RECIST criteria, have baseline and at least one post-baseline valid tumor assessment (including symptomatic deterioration defined by RECIST), and also satisfy one of the following two conditions:
 - Received at least 2 cycles of treatment at the intended dose.
 - Received less than 2 cycles of treatment at the intended dose but has evidence of disease progression or has withdrawn from study treatment due to unacceptable study drug-related toxicity.

The treatment code of each subject in the Evaluable population is determined by the treatment the subject actually received.

This population is the secondary efficacy analysis population and will be used in the analyses of the primary and selected secondary efficacy variables.

Statistical Methods: Progression free survival (PFS) will be analyzed when total 617 progressions determined by IRC are observed. The PFS will be compared between the two treatment groups using a log rank test stratified by the randomization factors “treatment setting of prior taxanes administration” and “prior taxane responsiveness” as specified at the time of randomization. The rates of PFS events will also be estimated using the Kaplan-Meier method. The analyses will be performed on the ITT population and as a secondary analysis, on the EP population.

A futility analysis of RR will be performed by the IDMC after the first 200 patients have been randomized, with a minimum of two tumor assessments, died or progressed. The futility analysis will consist of an evaluation of the objective response rate and safety data between the treatment arms for a consideration of a possible early termination for lack of efficacy or unacceptable safety. The IDMC will make a recommendation to the sponsor based on the results and the sponsor will evaluate the suggestions of the IDMC prior to making a final decision regarding continuation of the study.

Overall survival (OS) will be analyzed when total 618 deaths are observed. Time-to-death will be compared between the two treatments by the log-rank test procedure stratified by the randomization factors. The survival curves will be estimated using Kaplan-Meier estimates. The analyses will be performed on the ITT population.

An interim analysis of OS is planned at the time when the targeted number progressions are observed for the primary efficacy analysis. The nominal alpha values used for the interim analysis and final analysis will be determined by the “group sequential” approach (Lan KKG and DeMets DL, 1983) with a Gamma (-7) spending function (Hwang, IK, Shih, WJ, and DeCani, JJ, 1990).

The following table summarizes the planned analyses

Interim and final analyses

Timing		200 patients	PFS Final	OS Final
Objective		Futility	PFS Evaluation	Final OS Evaluation
Data	PFS	-	Evaluated ($\alpha = 0.05$)	Done at PFS final
	OS	-	Evaluated (spending function based on $\alpha = 0.05$)	Evaluated (spending function based on $\alpha = 0.05$)
	RR	Evaluated (based on conditional power)	Evaluated	Done at PFS final
	Other Efficacy	-	Evaluated	Done at PFS final
	QoL	-	Evaluated	Done at PFS final
	Safety	Evaluated	Evaluated	Evaluated

Study Cut-Off / Closure

Based on the results from scheduled futility analysis and further confirmatory analysis that were performed respectively in December 2005 and April 2006, the IDMC for the trial recommended that the study be closed for randomization. The IDMC concluded that the safety profile of the study was acceptable for both arms. However, the protocol assumptions for efficacy were not met.

Randomization for the study was stopped in January 2006. A total of 438 patients were enrolled. Patients who were still on active treatment were offered by their physicians to either continue to be treated with study drugs until protocol defined discontinuation were met or to be treated as per standard medical practice.

Currently, there are 21 patients that are still on active treatment. The sponsor will continue to provide study drugs or appropriate reimbursement (for comparator drug) for those patients that are still receiving and benefitting from treatment on study.

The study cut-off date was designated to be September 15th, 2006. After this date, patients still receiving treatment may remain on their assigned treatment using Sponsor-supplied study medication -XRP9881 or commercially available capecitabine - (with Sponsor reimbursement) until one of the protocol-defined criteria for discontinuation of study treatment is met.

CRFs will be collected for all treatment cycles completed on or before the September 15th, 2006 cut-off date as well as for all follow-up visits completed prior to the database lock (estimated for 27th Oct 2006).

CRFs will not be collected for any treatment cycles completed after the study cut-off date.

However, for all patients that remain on active treatment after the cut-off date, **serious adverse events (SAEs)** occurring either while on active treatment or within 30 days after the last dose of active treatment should be reported to sanofi-aventis via the same method as during the study. Furthermore, any SAE considered (to have a reasonable possibility of being) related to study treatment should be reported to sanofi-aventis regardless of when it occurs.

Table 1 - Study schedule

Protocol Activities and Forms to Be Completed	Screening (days prior to randomization/initial dose)			Study Days ¹				End of Study (Treatment) / Withdrawal ^[19]	Follow-up	
				3-Week Repeating Cycles			Day 15-21 Even Cycles 2, 4, 6, etc.			
	≤21	≤14	≤7	Day 1 ^[2] [-1/+0]	Day 8 [-1/+1]	Day 15 [-1/+1]	All Pts. [-7/+7]		Until Disease Progression ^[20]	Until Death
Baseline Documentation										
Informed Consent and Contraceptive Counseling	X*									
Medical & Oncologic History and Demographics ³	X*									
Existing Signs and Symptoms			X							
Laboratory Studies										
Coagulation ⁴	X*									
Hematology ⁵	X*			X	X	X			X	
Blood Chemistry ⁶	X*			X ^{2,6}		X			X	
Pregnancy test ⁷			X*							
Urinalysis ⁸										
12-Lead ECG ⁹	X*									
IVRS Randomization ¹⁰				Cycle 1						
BSA, Study Drug Administration, Dispensing, and Accountability ¹¹				X ⁹⁸⁸¹						
				X ^{cape}						
				→						
Tumor Assessment										
CT abd, pelvis, chest ¹²	X*						X	X	X	X ²⁰
Bone Scan ¹²	X*						(X)		(X)	(X) ²⁰
Other Clinical Assessments										
Physical Examination ¹³		X*	X					X		
Adverse Event Assessment ¹⁴				X	X	X			X	
Assessment of Concomitant Treatments ¹⁵		X	X	X	X				X	
QLQ30/BR23 Questionnaire ¹⁶		X*	Cycles ≥2					X	X	
EQ-5D ¹⁷		X*	Odd Cycles					X	X	
Resource Utilization ¹⁸			Odd Cycles					X		
Post Study Therapy, Disease and Survival Status ²⁰									X	X

Footnotes for Study Schedule

* **Assessment must be performed prior to randomization rather than prior to initial dose for eligibility determination.**

1. **Study Days:** All assessments should be performed prior to dosing with study drug unless otherwise indicated. Acceptable time windows for performing the assessments are noted below each scheduled treatment day in the Study Schedule Table, unless otherwise noted in the footnotes below.
 2. **Day 1:** Cycle 1 Day 1 (Day 1 of the study) refers to the day the patient receives the initial dose of study medication. The Cycle 1 Day 1 Assessments noted in the Study Schedule are not required if acceptable screening for the assessment is performed within 5 days prior to the start of treatment with study drug. However, all of these assessments must be performed for subsequent cycles (eg, Cycle 2 Day 1, Cycle 3 Day 1, etc.) on Day 1 [-1/+0] and on Day 1 [-3/+0] for blood chemistry. Day 1 of each subsequent cycle is defined by the date that study drug administration is started within that cycle. Therefore, the assessment time windows (indicated in Footnote 1) for Day 1 are always relative to the date that study drug administration is started. Patients must be seen by the responsible physician on Day 1 of each cycle.
 3. **Medical & Oncologic History:** including: diagnosis; prior surgery, radiotherapy, systemic therapy, concurrent illness; history of allergy.
 4. Coagulation: PT/ INR, and PTT.
 5. **Hematology:** Hemoglobin, hematocrit, WBC with differential count, platelet count. If grade 4 neutropenia, assess ANC every 3 days [-1/+0] until ANC $\geq 1,500/\mu\text{L}$. In case of grade 1 fever, CBC should be performed.
 6. **Blood Chemistry:** Sodium, potassium, calcium, phosphate, BUN, creatinine, albumin, total protein, SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase, and glucose. For patients with extensive liver involvement, a marked increase in liver function test results warrants radiological tumor assessment to verify or refute disease progression. Perform on Day 1 [-3/+0] for cycles ≥ 2 .
 7. **Pregnancy Test:** Women of reproductive potential must have a negative pregnancy test result (serum or urine) within 7 days prior to randomization. To be repeated as clinically indicated.
 8. **Urinalysis:** As clinically indicated.
 9. **ECG:** To be repeated as clinically indicated.
 10. **IVRS Randomization:** After the patient is deemed eligible for study entry, the patient will be randomized to study treatment through IVRS.
 11. **BSA, Study Drug Administration, Dispensing, and Accountability:** At the start of each treatment cycle, the patient's BSA will be determined using the current weight and Screening height. Study drug will be administered in the clinic (RPR109881 and capecitabine). One to four cycle's-worth of capecitabine will be dispensed to patients depending on local packaging. Patients dispensed two cycles-worth of capecitabine (in bottles only) will also be dispensed a patient diary to record tablet administration. Capecitabine tablet counts will be performed at the time of resupply or withdrawal if resupply is not warranted.
 12. **Tumor Assessment:**
CT(unless contraindicated): A scan of the chest, abdomen, and pelvis to be performed during Screening, at the end of each even-numbered treatment cycle, whenever disease progression is suspected, and at the end of treatment/withdrawal visit, using the same method for each assessment. Measurable disease as defined by RECIST requires the presence of at least one measurable target lesion at baseline. Measurable lesions are lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm with conventional CT. With spiral CT scan, lesion must be ≥ 10 mm in at least one dimension. For the purpose of analysis, a CR or PR will be deemed a confirmed response if a subsequent assessment has been performed at least 4 weeks after the first assessment and the results confirm the initial finding.
Bone Scan: For patients with negative bone scan at screening, repeat bone scans should be performed as clinically indicated. For patients with positive bone scan at Screening who do not have new or worsening bone symptoms, repeat scans must be performed at the end of every 4th treatment cycle. For patients with new or worsening bone symptoms, repeat bone scans must be performed at the end of every 2nd treatment cycle. Additionally, bone scan will be performed in any patient whenever disease progression in the bone is suspected, and at the end of treatment/withdrawal visit (see relevant footnote). For all patients with positive baseline bone scan who achieve a partial or complete response on the other tumor assessment, bone scan will be repeated to confirm the response. Bone scans are not necessary if there exists clear objective evidence of progression by other assessments in sites other than bone. PET may not substitute for bone scan.
Bone marrow aspiration: Suspected bone marrow involvement at Screening (eg, due to a leukoerythroblastic peripheral blood smear), must be verified by bone marrow aspiration and documented. For patients with previously documented positive bone marrow who achieve a complete response, please contact the sponsor with respect to the need for repeat aspiration.
Day 120 Assessment: The Day 120 assessment must be performed for all patients (CT scan). If the end-of-even-numbered-cycle tumor assessment for retreatment is performed within the Day 120 window (+/-7 days), then one set of scans will suffice for both purposes. The third assessment of tumor response should be timed to correspond with the Day 120 assessment whenever possible.
-

Footnotes for Study Schedule (cont)

13. **Physical Examination:** Examination of major body systems including complete neurological exam, vital signs (temperature, blood pressure, heart rate), height (Screening only), body weight, and ECOG PS.
Results will be recorded on appropriate CRFs (eg, medical/tumor history, existing signs and symptoms, adverse events).
14. **Adverse Event Assessment:** The period of observation for collection of adverse events extends from the start of treatment with study drug (investigational agent or comparator) until 30 days after the final dose of study drug. Serious adverse events should be followed as described in the protocol.
15. **Assessment of Concomitant Medications and Treatments:** Concomitant medications and treatments will be recorded from 7 days prior to the initial dose of study drug until 30 days after the final dose of study drug. Additionally, bisphosphonate administration within the 120 days prior to study entry will be recorded.
16. **QLQ-30 / BR23 Questionnaires:** The baseline assessment must be performed before randomization but not earlier than 7 days prior to randomization. No assessment will be performed on the date of the first dose (Cycle 1 Day 1). Subsequent Day 1 assessments will begin at the start of Cycle 2. During the Follow-up period, the QLQ-30/BR23 questionnaires will be administered only to those patients being followed for disease progression at a frequency of every 6 weeks (to coincide with radiological imaging) until disease progression or start of another anticancer therapy.
17. **EQ-5D Questionnaire:** The baseline assessment will be performed before randomization but not earlier than 7 days prior to randomization. No assessment will be performed on the date of the first dose (Cycle 1 Day 1). Subsequent assessments will be performed on Day 1 of odd cycles only (eg, Cycles 3, 5, 7, etc). During the Follow-up period, the EQ-5D questionnaires will be administered only to those patients being followed for disease progression at a frequency of every 6 weeks (to coincide with radiological imaging) until disease progression or start of another anticancer therapy.
18. **Resource Utilization:** Resource Utilization data will be collected on Day 1 of odd-numbered cycles only excluding Cycle 1 (eg, Cycles 3, 5, 7, etc) until the patient discontinues study drug.
19. **End of Study (Treatment)/Withdrawal:** Obtain these assessments within 22-30 days following the final dose of study drug, CT scan (if not performed within the prior 6 weeks), and bone scan for patients with new or worsening bone symptoms and for patients with positive bone scan at Screening if not performed within the prior 12 weeks. Bone scans are not necessary if there exists clear objective evidence of progression by other assessments in sites other than bone. At the end of the 30-day post-treatment period (up to Day 37 post-treatment), assessment of adverse events, concomitant medications and any examinations or tests required to support these assessments must be performed.
20. **Post-Study Therapy, Disease and Survival Status:** During the follow-up period, patients who went off study treatment prior to documented disease progression will have tumor assessments every 6 weeks from End of Study until disease progression. For patients with bone disease at Screening, repeat bone scans will continue every 6 weeks in patients with new or worsening bone symptoms or every 12 weeks in patients who do not have new or worsening bone symptoms until tumor progression or start of other anticancer therapy. Bone scans are not necessary if there exists clear objective evidence of progression by other assessments in sites other than bone. Additionally, tumor assessments will be performed as necessary according to RECIST to confirm response and/or to document progression. Following documented disease progression, patients will be contacted every 3 months to document subsequent anti-cancer treatment and survival.

Abbreviations: ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; ANC, Absolute Neutrophil Count; BSA, Body Surface Area; BUN, Blood Urea Nitrogen; C, cycle; CBC, Complete Blood Count; CR, Complete Response; CRF, Case Report Form; CT, Computed Tomography; D, day; ECOG, Eastern Cooperative Oncology Group; HE, Health Economic; INR, International Normalized Ratio; IVRS, Interactive Voice Response System; MRI, Magnetic Resonance Imaging; PR, Partial Response; PS, Performance Status; PT, Prothrombin Time; PTT, Partial Thromboplastin Time; QoL, Quality of Life; SGOT, Serum Glutamate-Oxalate Transferase; SGPT, Serum Glutamate-Pyruvate Transferase; WBC White Blood Cell

ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ANC	Absolute Neutrophil Count
ALT	Alanine Aminotransferase
AP	Alkaline Phosphatase
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
AT	As Treated
AUC	Area Under the Time Concentration Curve
BDM	Biometrics and Data Management
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CL	Clearance
CR	Complete Response
CrCl	Creatinine Clearance
CRF	Case Report Form
CRO	Contract Research Organization
CSF	Colony-Stimulating Factor
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DLT	Dose Limiting Toxicity
DPD	Dihydropyrimidine Dehydrogenase
DR	Duration of Response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
EP	Evaluable Patient
EU	European Union
G/GM-CSF	Granulocyte/Granulocyte-Macrophage Colony Stimulating Factor
HE	Health Economic
HIV	Human Immunodeficiency Virus
h	Hour
IDMC	Independent Data Monitoring Committee
INR	International Normalized Ratio
IP	Intraperitoneal
IRB	Institutional Review Board
IRC	Independent Review Committee
ITT	Intent-to-Treat
IV	Intravenous
IVRS	Interactive Voice Response System
MBC	Metastatic Breast Cancer

MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NCIC	National Cancer Institute of Canada
NOEL	No-Observable Effect Limit
ORR	Overall Response Rate
OS	Overall Survival
PET	Positron Emission Tomography
PFS	Progression Free Survival
P-gP	P-Glycoprotein
PR	Partial Response
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
PS	Performance Status
Q	Every
QALY	Quality-adjusted life year
QoL	Quality of Life
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SGOT	Serum Glutamate-Oxalate Transferase
SGPT	Serum Glutamate-Pyruvate Transferase
STPR	Single Time Progression Rate
TEAE	Treatment Emergent Adverse Event
TTF	Time to Treatment Failure
TTP	Time to Tumor Progression
TTR	Time to Tumor Response
ULN	Upper Limit of Normal
US	United States
Vss	Steady State Volume of Distribution
WBC	White Blood Cell
WNL	Within Normal Limits

1 INTRODUCTION AND STUDY RATIONALE

Further details can be found in the Investigational Brochure [1], which contains comprehensive information on RPR109881.

1.1 BREAST CANCER

1.1.1 Medical need

Breast cancer is the most commonly diagnosed cancer in women, with approximately 207,000 new patients diagnosed each year, and accounts for 15% of all cancer deaths in women in the United States [1]. Approximately 30% of breast cancer is diagnosed with regional spread, and 5-10% with distant metastases at diagnosis, and about 41,000 women die of breast cancer each year in the United States [1]. Once the disease becomes metastatic, it is considered incurable. While multiple treatments with various chemotherapy combinations may be attempted, responses are generally short lived and the median survival is approximately 2 years. Survival at 5-years after metastases develop is only 23% [1,2,3]. There remains a large unmet medical need for this patient population and investigation for improved therapy is urgently needed.

1.1.2 Breast cancer treatment

1.1.2.1 *Chemotherapy*

The most active agents for MBC are the anthracyclines (doxorubicin, epirubicin) and the taxanes (paclitaxel, docetaxel) [2,3,4]. While monotherapy or combination of multiple agents (eg, vinorelbine, gemcitabine, mitomycin) are used in the treatment of MBC after failure of anthracyclines and taxanes with response rates for combination regimens of 0% to 62% and for single agents of 0% to 29% (reviewed in [13, 5]), only capecitabine (Xeloda[®]) is currently approved in patients with MBC resistant to paclitaxel therapy and anthracycline therapy, or for whom further anthracycline therapy is not indicated. In such patients, the development of alternative or of more effective agents is needed.

Taxanes, such as paclitaxel and docetaxel, are tubulin-binding molecules with the property of promoting the polymerization of purified tubulin *in vitro* and, at high concentrations, of enhancing the fraction of polymerized tubulin in cells.

1.1.2.2 *Drug resistance*

Over the course of treatment many tumors acquire resistance to chemotherapeutic agents, limiting further treatment options and increasing the clinical challenge of disease management. Several mechanisms for taxane resistance are possible, including the expression of P-glycoprotein (P-gp), the product of the *mdr-1* (multi-drug resistance) gene. P-gp is a drug-efflux pump that rapidly eliminates drug substrates, including taxanes, from the cell. Other proposed mechanisms of taxane

resistance include altered metabolism and/or distribution of the taxanes, changes to the interactions of taxane with tubulin including mutations in the tubulin gene or altered expression of β -tubulin isotypes, and inadequate induction of apoptotic signals [14-24]. Clinically, resistance to chemotherapy for patients with breast cancer has been defined in multiple ways (reviewed in [25]). The most important determinants of clinical resistance are the initial response to the chemotherapy, and the interval of time from the last treatment until relapse (after adjuvant treatment) or progression (after treatment for metastatic disease) [25]. Patients who progress during anthracycline treatment, and especially those whose best response to treatment was progression have lower responses to subsequent treatments, and lower survival. [25].

1.2 RPR109881

RPR109881 is a novel taxoid found to be active in preclinical models of docetaxel-resistance. Clinically, this compound appears to have a safety profile similar to docetaxel, and in a phase II trial was found to be active in patients with metastatic breast cancer relapsing or progressing after docetaxel or paclitaxel and anthracycline treatment.

1.2.1 Molecular formula

RPR109881 is a taxoid derivative of the formula $C_{45}H_{53}NO_{14}$ ($Mr = 831.9$), the dihydrate of which has the formula $C_{45}H_{53}NO_{14} \cdot 2H_2O$ ($Mr = 867.9$).

1.2.2 Activity studies in preclinical models

In vitro, RPR109881 is a novel taxane found to retain the activity of docetaxel in promoting the polymerization of tubulin and in stabilizing microtubules against cold-induced depolymerization. RPR109881 and docetaxel were directly compared on a panel of murine and human cell lines from different histological types, and were found to exert identical antiproliferative activities.

1.2.2.1 In vivo schedule determination

In vivo, different schedules were tested to establish the optimal schedule of RPR109881 administration. The optimal schedule of administration was first determined by comparing three administration schedules using non tumor-bearing mice: 1) an intermittent schedule, days 1 and 5 (ie, 2 administrations), 2) a daily schedule, days 1 to 5 (ie, 5 administrations), and 3) a split dose schedule, days 1 to 5 three times a day (ie, 15 administrations).

A trend for schedule dependency on host toxicity was observed in these trials. Over the same total treatment duration, the intermittent schedule allowed administration of the highest dosage on a mg/kg basis, and produced a greater efficacy and an improved therapeutic index. This intermittent schedule was selected for testing antitumor efficacy.

1.2.2.2 Murine and human tumor models

RPR109881 i.v. was active against s.c. tumors sensitive to docetaxel such as: early stage B16 melanoma, advanced stage mammary adenocarcinoma MA13/C, colon adenocarcinoma C38 and pancreatic ductal adenocarcinoma P03.

In tumor models with less sensitivity to docetaxel such as Lewis lung carcinoma, pancreatic ductal adenocarcinoma P02, colon carcinoma C26, mammary adenocarcinoma MA44/C, Glasgow osteogenic sarcoma G0S, the activities of RPR109881 and docetaxel were similar. However, RPR109881 was more active than docetaxel in i.p. P388 leukemia.

In nude mice models of advanced human xenograft tumors of breast (Calc18), colon (HCT-8, HCT 116), pancreas (MIA PaCa-2) and lung (PC14) origin, the activities of RPR109881 and docetaxel were similar. A 2.6-fold greater efficacy was observed with RPR109881 as compared to that of docetaxel in colon HCT-8 tumors. Activity was also observed against early stage intracranial glioblastomas.

RPR109881 has been combined with several clinically available agents, such as doxorubicin, cisplatin, navelbine, 5-fluorouracil and CPT-11 in murine models. These combinations were found active, three were synergistic (doxorubicin, cisplatin and navelbine). There is only modest overlap in host toxicity with RPR109881 in combination with doxorubicin, 5-fluorouracil, or navelbine, and a marked increase in combination with CPT-11 or cisplatin.

1.2.2.3 Multidrug resistance studies

In vitro studies utilizing highly drug-resistant cell lines bearing the multidrug-resistance phenotype, such as P388/DOX and KB V1, demonstrated that RPR109881 was much less recognized than docetaxel, and was minimally recognized by moderately drug-resistant cell lines such as P388/TXT, P388/VCR, HL60/TAX and CALC 18/TXT. *In vitro* transport studies across tumor cells expressing P-gp confirmed that RPR109881 is minimally recognized by P-gp.

In vivo confirmation of the *in vitro* findings was found in 2/3 tumor models with the multidrug resistance phenotype. RPR109881 was found to be active in leukemia resistant to vincristine (P388/VCR) and in the B16 melanoma with acquired resistance to docetaxel (B16/TXT). The B16/TXT model may be more relevant to clinical situations because it is fully resistant to docetaxel, it maintains the doubling time and histological properties of B16 melanoma, and has a low over-expression of the *mdr1* murine gene.

1.2.3 Preclinical safety pharmacology studies

The receptor binding profile of RPR109881 tested up to 10 µM suggests that it is unlikely that this compound would evoke non-specific *in vivo* pharmacological effects.

No physiologically relevant effects were noted on the central nervous, respiratory and gastro-intestinal systems and on bile secretion after single intravenous administration of RPR109881 in rats or guinea-pigs and no interactions with various spasmogens were observed in *in vitro* guinea-pig ileum preparations. Slight increases in urinary Na⁺, Cl⁻, uric acid and protein concentrations

were observed following intravenous administration of RPR109881 in water-loaded rats. Slight decrease in thrombin time and slight increase in prothrombin time were noted after intravenous administration of RPR109881 in rats.

RPR109881 up to 10 µM did not modify the action potential parameters of guinea pig Purkinje fibers in *in vitro* preparations when compared to polysorbate 80. In anesthetized rats, RPR109881 infused over approximately 1 hour did not modify substantially mean carotid artery blood pressure and heart rate compared to polysorbate 80. Furthermore RPR109881 infused over approximately 1 hour in anesthetized dogs produced cardiovascular and hemodynamic changes (marked hypotension, decrease in carotid and femoral artery resistance and in carotid blood flow, increase in heart rate) similar to those noted after the administration of polysorbate 80 and were therefore likely attributable to the polysorbate 80 component of the vehicle.

1.2.4 Preclinical toxicology studies

1.2.4.1 General toxicity studies

Nonclinical toxicity studies were performed with RPR109881 using single-dose and 5-day daily intravenous administration in mice, rats and dogs and weekly intravenous administration in mice and dogs. Tissues with a high cell turnover were predominantly affected and toxicological effects of RPR109881 were similar to those observed with the other marketed taxoids. The main changes considered related to the pharmacological properties of RPR109881 (inhibition of tubulin depolymerization and therefore interference with mitosis) consisted of hair loss, decreases in circulating blood cells, hypocellularity of the bone marrow, crypt/gland cell necrosis along the intestinal tract associated clinically with diarrhea, necrosis/atrophy of lymphoid tissues and degeneration of epithelium in the testes and epididymides. In addition, increased serum levels of liver enzymes, total bilirubin, cholesterol and/or triglycerides, and microscopic liver changes (bile duct hyperplasia, bile duct necrosis, periportal fibrosis, intra-hepatic cholestasis, centrilobular inflammation) and gallbladder findings were observed in the weekly toxicity study conducted in dogs. RPR109881 produced central neurotoxicity (minimal to moderate necrosis of neurons in the brain, vacuolization and degeneration in the spinal cord) and peripheral neurotoxicity (sciatic nerve and lumbar nerve root degeneration) in mice only. The No-Observable Effect Level (NOEL) for central and peripheral neurotoxicity in mice following a single 1-minute intravenous administration was below 90 mg/m² while the NOEL for central and peripheral neurotoxicity in mice following a single 1-hour intravenous administration were 90 and 45 mg/m², respectively. Peripheral and central neurotoxicity were not observed in rats and dogs.

1.2.4.2 Mutagenicity and reproduction studies

RPR109881 was found negative in the bacterial reverse mutation test. The responses in the mouse lymphoma assay, the mouse bone marrow micronucleus test and the chromosome aberration test in CHO cells were considered to be a class effect of anticancer drugs which affect microtubules.

RPR109881 was not teratogenic in rats and rabbits and only slight developmental effects were observed. RPR109881 did not affect mating performances or fertility of the male or female rat.

1.2.4.3 Irritation and reactivity studies

RPR109881 did not show an irritation potential after intravenous, paravenous or intra-arterial administration in the ears of rabbits and did not produce antigenicity reactions in guinea pigs or in mice.

In vitro studies on hemo-compatibility suggested that solutions of RPR109881 were compatible with human plasma and serum.

1.2.5 Pharmacokinetics and metabolism studies in animals

RPR109881 pharmacokinetics after intravenous administration were characterized in tumor-free and tumor bearing mice, rats, and dogs. The decrease in plasma concentrations was consistent with a two-compartment model. The initial half-life was very short (0.05-0.22 h) and probably related to a rapid drug distribution phase in all tested species. Thereafter, RPR109881 was rapidly eliminated from dog plasma with a terminal half-life of about 0.6 h. In rats and mice, a longer elimination of the compound was observed with terminal half-lives of approximately 1.5 h and 3.2 h, respectively. The volume of distribution at steady-state was approximately five- and ten-fold lower in dogs than in mice and rats (0.5 vs. 2.4 and 5.3 L/kg, respectively). The plasma clearance was low in the mouse (0.6 L/h/kg) and high in the rat (3 L/h/kg) and dog (2.5 L/h/kg).

Area under the time concentration curve (AUCs) increased approximately proportionally to RPR109881 doses up to 182 mg/m² in tumor-bearing mice after a single intravenous infusion. In contrast, an overproportional relationship was observed in rats. Exposure remained similar after repeat administrations.

The *in vitro* binding of RPR109881 to plasma proteins was very high (96.1 to 99.6%) in mouse, rat, dog, monkey, and human plasma and non-saturable up to 30 µg/mL.

In tumor-bearing mice, the terminal half-lives observed in tissues were similar to those observed in plasma (1.6-7.5 h vs. 4.4 h), except in tumor (9.8 h) and in brain (estimated at 48 h).

Tissue/plasma AUC ratios ranged from 0.5 (heart) to about 11 (brain). In tumor, this ratio was approximately 2.

A distribution study with radiolabeled compound in rats showed rapid tissue uptake especially into the intestine, spleen, thyroid, kidneys, stomach, liver, ovary, heart, and lungs. The tissues of the central nervous system (brain, spinal cord) and the male genital organs (testis, epididymis) contained low radioactivity levels as well. Elimination of drug-related material from tissues was largely complete within 96 h. Tissue radioactivity retention at 72 h was only (0.9-1.4%) in mice and rats.

For all investigated species, radioactivity was largely excreted in the feces via the bile (83-96% of the administered dose), whereas the urinary route contributed markedly less (2-9%).

Enterohepatic recycling of radiolabeled compound was relatively low, since approximately 12% of the radioactivity excreted in bile was reabsorbed.

Almost no parent RPR109881 was excreted in urine, bile or feces (<3%) and metabolism is the main elimination pathway of RPR109881 in all species. Twelve to 36 metabolites were observed in bile, urine, and feces from mice, rats, and dogs.

In vitro, both CYP2C8 and CYP3A4 are involved in the human metabolism of RPR109881. 6α -hydroxy-RPR109881 was the main metabolite in liver microsomes from all tested species, including man. *In vivo*, parent RPR109881 was the predominant component circulating in mouse, rat, and dog plasma, based on AUC values (approximately 72%, 69-81% and 44 % of the radioactivity, respectively). As noted *in vitro*, the major metabolic pathway *in vivo*, in mice, rats, and dogs involves hydroxylation at the C6-position of the baccatin moiety to form 6α -hydroxy-RPR109881. Metabolites derived from this pathway were found to undergo further oxidation at the para-position of the phenyl group at C-3' to give 3'-(4-hydroxyphenyl) 6α -hydroxy-RPR109881 in mice and rats or by a further phase II reaction to yield the 6-O-glucuronide-RPR109881 in rats and dogs.

1.3 PRELIMINARY PHARMACOKINETICS IN HUMANS

Pharmacokinetic evaluation was performed in 129 patients from Europe, the US, Canada, and Japan over the 7.5-120 mg/m² dose range after intravenous infusion of 1 to 24 hours. Plasma samples were collected in all patients in at least one cycle and up to 5 cycles during the first 7 cycles.

RPR109881 plasma concentrations were consistent with a two- or a three- compartment open model. In 12 out of 14 patients receiving low RPR109881 doses (up to 45 mg/m²), the third phase was not observed, probably because of the limit of quantitation of the bioanalytical method (5 ng/mL). The initial phase with a half-life of approximately 2-10 minutes was not observed after a 24-hour intravenous infusion.

Table 2 - Main pharmacokinetic parameters of RPR109881

Study Number	Country	Infusion Duration	Dose Level (mg/m ²)	Number of patients with PK	Pharmacokinetic Parameters Mean ± SD [CV%]		
					CL (L/h/m ²)	V _{ss} (L/m ²)	t _{1/2 λ₃} * (h)
V101	France/Switzerland	1 h	45-105	28	33.0 ± 10.7 [33]	502 ± 364 [73]	19.7 ± 8.1 [41]
V106	Switzerland	1-3 h	75-90	26	41.4 ± 10.6 [26]	870 ± 384 [44]	25.8 ± 7.5 [29]
V102	France	6 h	60-120	21	34.4 ± 9.1 [26]	656 ± 833 [127]	29.9 ± 21.2 [71]
V103	US	24 h	30-75	13	41.7 ± 16.4 [39]	1221 ± 467 [38]	34.5 ± 16.3 [47]
V104	Canada	1 h (d1/d8)	15-52.5 (x2)	22	42.6 ± 11.8 [28]	952 ± 689 [72]	24.0 ± 15.1 [63]
V105	Japan	1 h	60-75	7	32.6 ± 8.8 [27]	654 ± 494 [76]	22.3 ± 6.4 [29]
Overall		1-24 h	15-120	117	37.9± 11.9 [31]	785±596 [76]	25.5± 14.0 [55]

* Terminal half-life, excluding patients at low doses with biphasic elimination

The plasma clearance of RPR109881 is high (mean value of 38 L/h/m²), representing about 80% of the hepatic blood flow. A large distribution volume was observed in all phase I studies (mean V_{ss} of 785 L/m²) and the terminal half-life of RPR109881 is long (approximately 26 h).

The pharmacokinetics of RPR109881 are independent of both administration schedule and dose over the investigated range (7.5-120 mg/m²). No plasma drug accumulation is observed between day 1 and day 8 (1-h i.v. infusion schedule), and plasma clearance is stable over up to 7 consecutive chemotherapy courses. No relevant pharmacokinetic differences are observed between Caucasian and Japanese cancer patients. A meta-analysis of phase I data (except Japanese Phase I data) showed that the inter-patient variability in clearance in this population is moderate (27.9%) and the intra-patient (inter-occasion) variability is low (22.5%). The inter-patient variability in clearance is significantly related to body surface area (BSA). Therefore BSA-adjusted dosing leads to a decreased variability in AUC.

In an analysis of pharmacodynamic relationships, decrease in absolute neutrophil or white blood cell count at nadir correlated with AUC of unbound RPR109881.

RPR109881 was detected in one specimen of CSF (5.3 ng/ml) and in one post-mortem brain sample (51.2 ng/g) suggesting that RPR109881 crosses the blood-brain barrier in humans.

Urinary excretion of unchanged RPR109881 is very low for all administration schedules investigated (less than 2% of the administered dose over a 0-48 h post dosing period). This finding was confirmed by the preliminary results from 7 patients included in Phase I Study XRP 9881/1001 and treated with ¹⁴C- RPR109881 at 75 mg/m², which demonstrated that the

radioactivity was largely excreted in the feces via the bile (81.4% of the administered dose), while the urinary route contributes markedly less (6.6%)..

The *in vitro* human plasma protein binding of RPR109881 is high (97-99%), and the plasma/blood cell partitioning is 0.75.

The cytochrome P450 isoforms CYP2C8 and CYP3A4 are involved in RPR109881 biotransformation *in vitro*. The main metabolite produced in human liver microsomes is 6 α -hydroxy-RPR109881. RPR109881 at concentrations up to 10 μ M (approximately 10-fold C_{max} *in vivo*) did not inhibit CYP1A2, -2A6, -2C19 or -2E1 *in vitro*. Some inhibition of CYP2C9 and CYP3A4 was observed (57% and 47%, respectively) and to a lesser extent of CYP2D6 (20-30%) at the highest concentration of RPR109881 (10 μ M).

Vinorelbine and docetaxel and acetaminophen (paracetamol) inhibited the oxidative metabolism of RPR109881 *in vitro* (5 μ M) with an IC_{50} of 2.5 μ M, 5 μ M and 1000 μ M, respectively, ie, near to their C_{max} *in vivo*. Phenytoin (IC_{50} = 200 μ M), carbamazepine (IC_{50} = 290 μ M), warfarin (IC_{50} = 61 μ M) were also found to inhibit the oxidative biotransformation of RPR109881 and this inhibition was mainly metabolism dependent. However, phenytoin and carbamazepine are known to induce CYP2C and CYP3A isoforms, which could thus counteract a possible inhibition of RPR109881 oxidative biotransformation. Omeprazole is a weak *in vitro* inhibitor of RPR109881 oxidation since the IC_{50} (50 μ M) represents 100 fold its C_{max} *in vivo*. Susceptibility to undergo to drug-drug interaction is quite minimal because of the high hepatic clearance and the i.v. administration of RPR109881. In similar experimental conditions, none of the following drugs were inhibitors: irinotecan, cisplatin, carboplatin, doxorubicin, gemcitabine, morphine, methylprednisolone, dexamethasone, valproic acid, phenobarbital, diphenhydramine, prochlorperazine, digoxin and acetyl salicylic acid. These results suggest that if acetaminophen and warfarin need to be administered to a patient receiving RPR109881, administration of the two drugs should be separated in time.

1.4 PRELIMINARY CLINICAL FINDINGS

Study 101 is a Phase I study evaluating the safety of RPR109881 administered as a 1-hour infusion every 3 weeks as a single agent. Although other studies evaluating other schedules were also performed, the dose limiting toxicity in those studies was similar to that of the 3-week schedule, and the incidence of adverse events was similar or worse compared to the 3-week regimen. Study 106 evaluated the safety of 1-hour versus 3-hour infusion of RPR109881 administered every 3 weeks, and the safety results for the 1-hour infusion arm confirmed the results obtained in Study 101. The 1-hour every 3 weeks schedule was therefore selected for Phase II studies for patient convenience. The data of Study 101 will be presented in detail.

Thirty-four patients (17 males and 17 females), median age: 59 years (range: 19-73) were included in the Phase I Study 101 of RPR109881 administered as a 1-hour infusion every 3 weeks. These patients presented with various tumor types: the most frequent were lung (7 patients), sarcoma (5 patients), stomach and kidney (4 patients). Thirty-three of 34 patients had been previously treated with chemotherapy. Twenty-five patients (73.5%) had received 1 or 2 different chemotherapy regimens. Twelve patients had received prior radiotherapy.

Premedication with oral corticosteroids (methylprednisolone 40 mg) was administered at -25 h, -13 h and -1 hour before RPR109881.

The median (range) number of cycles was 2 (1-8). Only 3 of 107 cycles were given at a dose lower than the one initially planned: one at a starting dose of 90 mg/m² because of the occurrence of grade 4 allergic reaction and two at a starting dose of 105 mg/m² because of severe hematological toxicity reported after the first cycle. Six patients had RPR109881 infusion delayed for 4 to 11 days beyond the scheduled administration date for one cycle, but in no case was the delay related to an adverse effect of the drug.

1.4.1 Safety of RPR109881 in Phase I Study 101

The most commonly reported clinical AEs by patient at all doses tested considered at least possibly related to the study drug were: gastrointestinal (67.6%), skin (58.8%), flu-like symptoms (41.2%), neurological disorders (20.6%), infections (11.8%) and fluid retention (8.8%) using the NCIC-CTC classification. Hypersensitivity was reported in 14.8% of 27 evaluable patients.

One toxic death due to septic shock was observed in a patient with metastatic gastric cancer after the first cycle at a dose of 90 mg/m².

Three patients discontinued the study treatment due to AEs at least possibly related to the study drug: grade-3 diarrhea (cycle 1) and grade-3 fluid retention (cycle 2) at 60 mg/m², and grade-4 allergy (cycle 2) at 90 mg/m².

A total of 26 serious adverse events (SAEs) were reported in 14 patients. Among them, 18 SAEs reported in 11 patients were considered as at least possibly related to the study drug. The most frequent at least possibly drug-related SAEs were febrile neutropenia (4 SAEs, in three patients), diarrhea, fever in absence of infection and infection (1 SAE in each of two patients). The other drug-related SAEs were reported in one patient each: allergy, bronchospasm, fatigue, fluid retention, flushing, nausea, neuromotor disorder and neurosensory disorder.

All except two patients [i.e., 29 patients (85.3%)] treated at doses of 60-105 mg/m² developed neutropenia of any grade. Grade-3 neutropenia was reported in seven patients (20.6%) and grade-4 neutropenia in 21 patients (61.8%). Median lowest nadirs of neutrophil count observed at 75, 90 and 105 mg/m², were $0.3 \times 10^3/\text{mm}^3$, $0.2 \times 10^3/\text{mm}^3$ and less than $0.1 \times 10^3/\text{mm}^3$, respectively. Median time to nadir ranged from 10 to 11 days. Partial or total recovery from neutropenia occurred on day 22 ± 3 after drug infusion, except in two cases (grade 3 and grade 4 in two cycles, respectively at 90 mg/m²).

The duration of grade-4 neutropenias observed in cycles with at least two blood counts between day 6 and day 15 (37 cycles = 2 at 75 mg/m², 29 at 90 mg/m² and 6 at 105 mg/m²) ranged from 2 to 18 days. The median duration of grade-4 neutropenia was 5 days at 90 mg/m² and 7 days at 105 mg/m². Grade-4 neutropenias with duration >7 days were dose-limiting toxicities. They were reported in five patients for a total of 6 cycles at 90 mg/m², and in one patient for 2 cycles at 105 g/m².

Anemia of any grade was reported in 98 of the 107 evaluable cycles (91.6%). Grade-3 and grade-4 anemias were reported each in one cycle at 90 mg/m².

The most frequently reported abnormal biochemistry test results (of any grade) were transitory increases of ALT, AST and alkaline phosphatase. All these variations recovered within one week. Grade-3 values were infrequently reported and no grade-4 value was reported. Bilirubin elevations were also noted, most commonly in patients with liver metastases. One grade 4 bilirubin elevation was noted.

The dose-limiting toxicities (DLTs) were evaluated after the first cycle to define how to escalate the dose in the subsequent patients and to establish the Maximum Tolerated Dose (MTD). The dose-limiting toxicities were defined as:

Hematologic: Neutrophils gr. 4 >7 days or Platelets gr. 4

Febrile neutropenia: Neutrophils gr. 4 with fever gr. ≥2 (38.5°C single elevation in oral temperature or 3 elevations > 38°C during a 24-hour period).

Non-hematologic: Adverse events gr. 3 or 4 excluding nausea, vomiting, and alopecia.

In this protocol that was initiated in 1996, the maximum tolerated dose (MTD) was defined as the dose expected to be the dose at which 50% of patients treated experienced a DLT. The MTD was reached at 105 mg/m² at which 2 patients out of 5 experienced DLTs. All these DLTs were related to the hematologic toxicity of the compound. In one case (patient No. 25), non-hematological DLTs (diarrhea grade-4 and lethargy grade-3) were associated with the hematological DLT. The recommended dose for Phase II trials was 90 mg/m². At the recommended dose of 90 mg/m², the number of first-cycle DLTs was 2 out of 8 (25%), which is more consistent with current definitions of MTD.

The incidence of non-hematologic toxicities at the recommended dose of 90 mg/m² for the various schedules studied listed by patient and by cycle are presented in [Table 3](#) and [Table 4](#) respectively. As can be noted, fatigue and diarrhea were the most common non-hematologic grade 3 or 4 toxicities.

Table 3 - Incidence of worst grade non-hematologic toxicities for RPR109881 90 mg/m² in study 101 tabulated by patient

Study	V-101			
Nb of patients	17			
NCIC-CTC terms	1	2	3	4
Hypersensitivity Reaction	-	1	1	1
Infection	-	1	1	1 ^a
Diarrhea	1	7	2	-
Vomiting	1	-	-	-
Nausea	2	6	-	-
Anorexia	-	3	-	-
Arthralgia	4	2	1	-
Myalgia	3	-	-	-
Fatigue	3	2	-	-
Neuromotor	-	1	-	-
Neurosensory	4	1	-	-
Alopecia*	4	4	4	-

^a Grade 5 death possibly related

* Cumulative toxicities reported only by patients

Table 4 - Incidence of non-hematologic toxicities for RPR109881 90 mg/m² in study 101 over all cycles

Study	V-101			
	1-hour infusion q 3 wks			
Nb of cycles	58			
NCIC-CTC terms	grade			
	1	2	3	4
Hypersensitivity Reaction*	1	2	1	1
Infection	-	1	1	1 ^{1a}
Diarrhea	5	9	2	-
Vomiting	2	-	-	-
Nausea	4	3	-	-
Anorexia	-	3	-	-
Stomatitis	-	-	-	-
Arthralgia	5	5	1	-
Myalgia	3	-	-	-
Fatigue	6	2	-	-
Neuromotor	-	1	-	-
Neurosensory	15	1	-	-

^a Grade 5 death possibly related

* Only 28 cycles evaluable for HSR

1.4.2 Preliminary activity of RPR109881 in patients with metastatic breast cancer after taxane therapy

Study 204, ‘A phase II multi-center, open label, non-randomized study of RPR 109881 given as a one-hour infusion at 90mg/m² every 3 weeks to female patients with metastatic breast cancer’, is a single arm, open label, multi-center, multinational study which is currently ongoing. Preliminary results after the latest interim analysis demonstrate activity of RPR109881 in patients with paclitaxel or docetaxel resistance.

Patients with metastatic breast cancer progressing after taxanes were eligible for this trial. Upon entry, patients were stratified into those patients who progressed after objective response to taxanes (non-resistant stratum) and into those patients progressing while on taxane, patients not achieving an objective response to taxane, or patients recurring within 12 months of taxane-based (neo-) adjuvant therapy (resistant stratum).

Patients were treated with RPR109881, 90 mg/m² i.v. every 3 weeks, until evidence of progressive disease, unacceptable toxicity or consent withdrawal. Thirty minutes prior to chemotherapy, patients receive premedication with dexchlorpheniramine 5 mg i.v., diphenhydramine 25 mg i.v. or other anti H1 receptor antagonist; with ranitidine 50 mg i.v., and

with dexamethasone 8 mg i.v. or other corticosteroids equivalent. Antiemetic prophylaxis was not permitted prior to the first cycle of chemotherapy. In case of nausea/vomiting, patients could receive preventive antiemetic treatment in compliance with the conventional antiemetic protocol of the center for the subsequent cycles.

1.4.2.1 Patient demographics in Study 204

The demographic characteristics of the patients are presented in [Table 5](#).

Table 5 - Demographics of patients in study 204

Characteristic	N (%)
Number of patients treated	78 (100)
Age (years)	
Median (min-max)	55 (33-74)
ECOG Performance status	
0	43 (55.1)
1	33 (42.3)
2	2 (2.6)
Previous anthracycline / anthracenedione	68 (87.2)
Previous taxane	78 (100)
Docetaxel	61 (78.2)
Paclitaxel	22 (28.2)
Organs involved ⁽¹⁾	
Any soft tissue	40 (55.6)
Any visceral	60 (83.3)
Any liver	43 (59.7)
Any bone	22(30.6)
Any brain	1 (1.4)

(1) based on 72 patients with available information

1.4.2.2 Response rate in Study 204 using definition for proposed Study 3001

Of the 47 patients progressing or relapsing within 12 months of taxanes, 4 were not evaluable for response to RPR109881 (1 patient had an early toxic death, 2 patients withdrew consent prior to response evaluation due to adverse events, 1 patient did not undergo evaluation mandated by the protocol). Two patients were found not to be eligible (1 patient pretreated with epothilone whose best response to RPR109881 was PD, 1 patient who received only 3 weeks of weekly paclitaxel whose best response to RPR109881 was SD).

Fourteen of the 45 eligible patients progressing or relapsing within 12 months were found to have partial responses (31%, 95% CI= 18,47).

1.4.2.3 Adverse events in Study 204

The median number of cycles of RPR109881 received in Study 204 was 4 (1-12). The main hematological toxicities found in patients in Study 204 are listed in [Table 6](#). The most common toxicity was neutropenia grade 3 or 4, which was found in 79% of patients (51% grade 4). The incidence of neutropenic complications is found in [Table 7](#). Febrile neutropenia was present in 4 patients (5%), and 1 patient died of septic death (1%).

Table 6 - Main hematological toxicities (study 204) – worst grade by patient

Toxicity	Number of patients with grade (%*)				Grade 3-4 n (%*)	Any n (%*)
	Gr 1	Gr 2	Gr 3	Gr 4		
Leukopenia	6 (8)	21 (29)	35 (49)	7 (10)	42 (58)	69 (96)
Neutropenia	2 (3)	8 (11)	20 (28)	36 (51)	56 (79)	66 (93)
Thrombocytopenia	7 (9)	3 (4)	1 (1)	0 (0)	1 (1)	11 (15)
Anemia	45 (60)	22 (29)	1 (1)	0 (0)	1 (1)	68 (91)

* based on 75 evaluable patients for thrombocytopenia and anemia, 72 evaluable for leukopenia and 71 evaluable for neutropenia.

Table 7 - Neutropenic complications (study 204)

Neutropenic Complication	n (%*)
Any Neutropenic complication	15 (20%)
Related Infection (Grade 3)	0 (0)
Related Infection (Grade 4)	0 (0)
Septic Death	1 (1)
Neutropenia (Grade 4) > 5 days	11 (15%)
Febrile Neutropenia	4 (5%)

* based on 76 evaluable patients

The main non-hematological toxicities are listed in [Table 8](#). Common non-hematological toxicities include diarrhea, neurosensory disorders, fatigue, nausea, vomiting, stomatitis, arthralgia and myalgia. These toxicities were mostly grades 1 or 2. The diarrhea was clinically predictable and manageable with standard supportive care consisting of loperamide or other anti-diarrheal agents. Sixty patients (77%) reported sensory neuropathy during treatment, 6 (8%) grade 3 and 0 grade 4. However, 25 patients (32%) had sensory neuropathy at baseline, perhaps due to prior taxane treatment. Five of the 6 patients who reported grade 3 sensory neuropathy during treatment had not reported neuropathy at baseline. In distinction to docetaxel, peripheral edema was rare, and hypersensitivity and nail changes were uncommon although patients received a median number of 4 cycles of RPR109881. In addition, 3 patients had hypersensitivity reactions (2 grade 1, 1 grade 2) and 3 patients had edema (breast edema (1 grade 1), lymphedema (1 grade 1, 1 grade 2), edema of upper limb (1 grade 2). As mentioned, patients did not receive anti-emetic

prophylaxis in the first cycle of treatment, and received one dose of anti-histamine and steroid prophylaxis.

Three patients died within 30 days of receiving RPR109881. Two patients died due to toxicity from study drug as reported by the investigator. One had a septic death 10 days after receiving RPR109881 treatment and one died with abdominal pain and dyspnea 10 days after receiving RPR109881. One patient died of progressive disease.

In summary, the toxicities of RPR109881 appear to be manageable and comparable to that of other approved agents used in this clinical setting.

Table 8 - Main non-hematological toxicities (study 204) – worst grade by patient

Toxicity	Number of patients with NCI/CTC grade (%*)				Grade 3-4 n (%*)	Any n (%*)
	Gr 1	Gr 2	Gr 3	Gr 4		
Abdominal pain	11 (14)	9 (12)	0 (0)	1 (1)	1 (1)	21 (27)
Alopecia	8 (10)	55 (71)	NA	NA	NA	63 (81)
Anorexia	12 (15)	6 (8)	1 (1)	0 (0)	1 (1)	20** (26)
Arthralgia	11 (14)	14 (18)	0 (0)	0 (0)	0 (0)	25 (32)
Diarrhea	34 (44)	21 (27)	6 (8)	0 (0)	6 (7)	61 (78)
Fatigue	23 (29)	24 (31)	8 (10)	2 (3)	10 (13)	57 (73)
Fever	12 (15)	4 (5)	2 (3)	0 (0)	2 (3)	18 (23)
Myalgia	12 (15)	20 (26)	2 (3)	0 (0)	2 (3)	35** (45)
Nausea	23 (29)	16 (21)	5 (6)	0 (0)	5 (6)	44 (56)
Nail changes	11 (14)	2 (3)	NA	NA	NA	13 (17)
Rash/desquamation	10 (13)	2 (3)	0 (0)	0 (0)	0 (0)	12 (15)
Sensory neuropathy	38 (49)	16 (21)	6 (8)	0 (0)	6 (8)	60 (77)
Stomatitis/pharyngitis	13 (17)	4 (5)	2 (3)	1 (1)	3 (4)	20 (26)
Vomiting	11 (14)	8 (10)	4 (5)	0 (0)	4 (5)	23 (29)

* Based on 78 treated patients

** Includes one patient with missing grade

1.4.3 Capecitabine

Capecitabine, which is the comparator treatment in the present study, is a fluoropyrimidine carbamate with antineoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is converted to 5- fluorouracil. The enzyme dihydropyrimidine dehydrogenase hydrogenates 5-FU, the product of capecitabine metabolism, to the much less toxic 5-fluoro-5, 6-dihydro-fluorouracil (FUH₂). As mentioned, capecitabine monotherapy is approved 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 is not indicated. Anthracycline therapy is not indicated in patients who have received cumulative doses of 400 mg/m² of doxorubicin or doxorubicin equivalents [12].

In the pivotal single arm Phase II trial reported in the Xeloda® label and later published (8,9), an objective response rate (RR) of 25.6%, median time to progression (TTP) of 102 days, and median overall survival (OS) of 255 days were noted in patients doubly resistant to paclitaxel and to anthracyclines (as per label). For the 135 patients with measurable disease, the RR was 18.5%, TTP was 90 days, and OS was 306 days.

In further trials of capecitabine in patients previously treated with taxanes and anthracyclines, the response rate to capecitabine has ranged from 9 to 25%, median TTP 3.0 – 4.6 months, and median OS from 10.4 – 15.2 months [6-11]. Of importance in analyzing these results, the definition of resistance to taxane was not consistent from one trial to the other. Thus, although capecitabine is an active drug in patients with metastatic breast cancer including patients previously treated with taxanes, its reported activity after resistance and failure to taxanes lies within a wide range, in part due to the variations in the population of patients studied.

The major toxicities of capecitabine in the product insert for patients treated with monotherapy for breast cancer are: diarrhea, nausea, vomiting, stomatitis, abdominal pain, constipation, hand-and-foot syndrome, dermatitis, nail disorder, fatigue, pyrexia, paraesthesia, anorexia, eye irritation, neutropenia, thrombocytopenia, anemia, lymphopenia, and hyperbilirubinemia [12].

1.4.4 Summary

The proposed trial will compare the activity of RPR109881 and capecitabine in patients with MBC progressing after taxanes and anthracycline therapy. The activity of RPR109881 in preclinical models and in a Phase II trial in this patient population, the acceptable and manageable toxicities of RPR109881, and the reported activity and toxicity of capecitabine support the conduct of the present trial.

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to compare progression free survival (PFS) in patients with metastatic breast cancer treated with RPR109881 versus capecitabine progressing after taxanes and anthracycline therapy.

2.2 SECONDARY OBJECTIVES

The secondary objectives of this study are to:

- To compare survival and other measures of anti-tumor efficacy [response rate (RR), time to tumor response (TTR), duration of response (DR), single time progression rate (STPR), and time to treatment failure (TTF)] in patients treated with RPR109881 versus capecitabine.
- To compare the safety and tolerability of RPR109881 versus capecitabine.
- To compare the quality of life and other clinical benefit measures in patients treated with RPR109881 versus capecitabine.

3 STUDY DESIGN, DURATION, AND DATES

3.1 STUDY DESIGN

This will be a global multi-center, open-label, two-arm randomized, phase III clinical trial. Patients will be randomized to treatment with RPR109881, 90 mg/m² IV administered on Day 1 of each 3-week cycle, or capecitabine, 1250 mg/m² administered orally twice daily (morning and evening, equivalent to 2500 mg/m² total daily dose) for 2 weeks followed by a 1-week rest period given as 3-week cycles. Randomization will be stratified based on the treatment setting in which taxanes were given and prior taxanes responsiveness.

Patients will continue to receive treatment until disease progression, patient intolerance, or withdrawal of consent. Patients who discontinue study treatment prior to disease progression will continue to have tumor assessments, QLQ-30/BR-23 and EQ-5D assessments every 6 weeks. Following disease progression or start of another anticancer therapy, patients will be treated by their physicians as determined by usual medical practice and followed every 3 months for start of subsequent anticancer therapy, and survival. Patients treated on the capecitabine arm will not be eligible to receive RPR109881 in this or other clinical breast cancer trials.

Radiological tumor assessments will be performed at baseline, at the end of every even-numbered treatment cycle (every 6 weeks, after Cycles 2, 4, 6, etc...), and whenever disease progression is suspected. In addition, a radiological tumor assessment to obtain a single time progression rate (STPR) will be obtained at Day 120 (+/- 7 days) for all patients. After the patient is withdrawn from study treatment, a tumor assessment will be performed if an assessment has not been performed within the prior 6 weeks. Patients who discontinue study treatment prior to disease progression will continue to have tumor assessments until disease progression or start of another anticancer therapy. In order for a response to be considered durable, all patients with an objective response of partial response (PR) or complete response (CR) must have the response confirmed between 4-6 weeks after the initial documentation of response. All scans will be independently reviewed in real-time to assess for response to treatment (PR or CR) and disease progression. An independent review committee (IRC) will review the data during the conduct of the trial.

The primary endpoint of Study 3001 will be progression free survival (PFS) with overall survival (OS) and response rate (RR) as secondary efficacy endpoints in the intent-to-treat population. Time to progression / progression free survival is defined as the time from randomization to first evidence of progression, as defined by RECIST or death. Progression free survival is the most appropriate primary endpoint for the proposed intervention and study population. Time to progression may be recorded in all randomized patients, is routinely determined as part of usual clinical oncology practice and most importantly, is not subject to the confounding influence of treatments administered subsequent to progression on protocol. This is particularly important in the proposed study as patients initially randomized to receive RPR109881 may cross-over, as part of usual clinical care, to subsequently receive capecitabine, while those patients randomized to capecitabine will not be eligible to receive RPR109881 in this or any other breast cancer clinical study protocol.

In order to minimize operational and analysis biases, careful attention to maintaining the protocol-mandated frequency of assessment in both arms will be emphasized. Regardless of randomization or subsequent off-protocol therapy, all patients will be followed after progression to determine the overall survival in both arms on an intent-to-treat basis.

3.2 STUDY DURATION AND DATES

The duration of this study is expected to be 20 months or until the observation of the required number of events needed for the final analysis of Progression free survival. The last patient treatment visit, ie, 30 days after the last patient dose, is expected to take place at month 27 (May 2006). The observation of the required event for survival is expected to take place at month 45 (November 2007). The actual overall study duration or patient recruitment period may vary, depending on the observed accrual rate and progression/survival distributions.

3.3 STUDY CUT-OFF/CLOSURE

Based on the results from scheduled futility analysis and further confirmatory analysis that were performed respectively in December 2005 and April 2006, the IDMC for the trial recommended that the study be closed for randomization. The IDMC concluded that the safety profile of the study was acceptable for both arms. However, the protocol assumptions for efficacy were not met.

Randomization for the study was stopped in January 2006. A total of 438 patients were enrolled. Patients who were still on active treatment were offered by their physicians to either continue to be treated with study drugs until protocol defined discontinuation were met or to be treated as per standard medical practice.

Currently, there are 21 patients that are still on active treatment. The sponsor will continue to provide study drugs or appropriate reimbursement (for comparator drug) for those patients that are still receiving and benefitting from treatment on study.

The study cut-off date was designated to be September 15th, 2006. After this date, patients still receiving treatment may remain on their assigned treatment using Sponsor-supplied study medication -XRP9881 or commercially available capecitabine - (with Sponsor reimbursement) until one of the protocol-defined criteria for discontinuation of study treatment is met.

CRFs will be collected for all treatment cycles completed on or before the September 15th, 2006 cut-off date as well as for all follow-up visits completed prior to the database lock (estimated for 27th Oct 2006).

CRFs will not be collected for any treatment cycles completed after the study cut-off date.

However, for all patients that remain on active treatment after the cut-off date, **serious adverse events (SAEs)** occurring either while on active treatment or within 30 days after the last dose of active treatment should be reported to sanofi-aventis via the same method as during the study. Furthermore, any SAE considered (to have a reasonable possibility of being) related to study treatment should be reported to sanofi-aventis regardless of when it occurs.

4 SELECTION OF PATIENTS

The patient population will consist of adult males or females with metastatic breast cancer that has progressed after taxane and anthracycline therapy.

4.1 NUMBER OF PATIENTS

This study will include a test arm (RPR109881) and a comparator arm (capecitabine). Approximately 800 patients, 400 patients randomized to the RPR109881 treatment arm and 400 patients to the capecitabine treatment arm,

- [REDACTED]
- | [REDACTED]
- | [REDACTED]

It is expected that each study site will enroll between 4-5 patients. No site shall enroll beyond 20 patients without written approval from the sponsor followed by notification of the IRB/IEC. Sponsor approval will be based on both consideration of the potential for statistical analysis impact and the quality of work performed to date by the site as assessed through monitoring and/or auditing. Enrollment into the screening or randomization phase of the study will be stopped when the anticipated or actual patient numbers have been achieved across all study sites. Additionally, if the target number of events is attained prior to fully accruing patients to the study, the trial may be closed to further enrollment.

The analysis of overall survival (OS) will be conducted when at least 618 deaths are observed, with a single interim analysis using a boundary determined by a Gamma(-7) function to reject the null hypothesis, to be conducted at the time of the PFS assessment. This analysis will have 90% overall statistical power (two-sided alpha level of 0.05) to detect an OS hazard ratio of 0.77, assuming a median survival of capecitabine-treated patients of 15.2 months, corresponding to an improvement of approximate 30% in median survival.

4.2 INCLUSION CRITERIA

Patients meeting all of the following criteria will be considered for enrollment into the study:

1. Histologically or cytologically proven diagnosis of breast adenocarcinoma that is now metastatic or locally recurrent and inoperable with curative intent (Appendix 1). Patients with previously treated histo/cytologically confirmed disease who develop clinical or radiological evidence of metastatic disease do not require separate confirmation of the metastatic disease.

2. All patients must have received an anthracycline and a taxane prior to entry in the protocol. These drugs may have been given in the neoadjuvant/adjuvant or in the metastatic setting, may have been given concurrently or sequentially, and may have been given in combination with other drugs. All patients must have received an anthracycline and a taxane (e.g. docetaxel and/or paclitaxel) prior to entry in the protocol.

For taxanes

- a) Patients must have progressed while receiving paclitaxel or docetaxel therapy or at any time after having received paclitaxel or docetaxel therapy.
- b) The taxane-based treatment must have been the last chemotherapy the patient received.

For anthracyclines

Patients must have either:

- a) Progressed while on anthracyclines treatment, with or without an initial response,
OR
 - b) Patients must have received an adequate course of anthracyclines defined as follows:
 - i. In the neoadjuvant or adjuvant setting, patients must have received a regimen considered standard for adjuvant therapy, which would usually result in a cumulative dose of doxorubicin of 200-300 mg/m² or doxorubicin equivalent.
 - ii. In the metastatic setting patients must have received a regimen considered standard for therapy for metastatic disease, which would usually result in a cumulative dose of doxorubicin of at least 300 mg/m² or doxorubicin equivalent.
3. Completion of all prior chemotherapy, immunotherapy (including trastuzumab [Herceptin®]), targeted non-cytotoxic therapy, and radiotherapy ≥ 3 weeks prior to randomization. Prior treatment with radiotherapy, chemoembolization therapy, or cryotherapy is allowed if these therapies did not affect the areas of measurable disease being used for the purposes of this protocol. Patients on bisphosphonate therapy may continue such therapy.
 4. Evidence of measurable disease as defined by RECIST (Appendix 3). Measurable lesions are lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm with conventional CT. With spiral CT scan, lesion must be ≥ 10 mm in at least one dimension.
 5. Male or female patients at least 18 years old.
 6. ECOG (Eastern Cooperative Oncology Group) performance status of 0,1, or 2 (Appendix 2).

7. Patients must have resolution of all clinically significant toxic effects (excluding alopecia) of any prior surgery, radiotherapy, cryotherapy, chemoembolization therapy, hormone therapy, immunotherapy, targeted non-cytotoxic therapy, or chemotherapy to grade ≤ 1 by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, or to within the limits listed in the specific inclusion/exclusion criteria.
8. Adequate organ function as defined by:

Absolute neutrophil count (ANC)	$\geq 1,500/\mu\text{L}$
Platelets	$\geq 100,000/\mu\text{L}$
Hemoglobin	$\geq 9.0 \text{ g/dL}$ (no RBC transfusion support ≤ 2 weeks prior to the first treatment dose on study)
Prothrombin time/ International normalized ratio (PT/INR) and Partial thromboplastin time (PTT)	$\leq 1.5 \times$ upper limit of normal (ULN)
Creatinine	$\leq 1.5 \times$ ULN, or calculated creatinine clearance (CrCl) $> 60 \text{ mL/min}$
Total bilirubin	Within normal limits (WNL)
Serum aspartate aminotransferase (AST; serum glutamate-oxalate transferase [SGOT] and serum alanine aminotransferase (ALT; serum glutamate-pyruvate transferase) [SGPT]	If AP is $\leq 2.5 \times$ ULN, then ALT/AST must be $\leq 2.5 \times$ ULN. If AP is $> 2.5 - \leq 5.0 \times$ ULN, then ALT/AST must be $\leq 1.5 \times$ ULN
Alkaline phosphatase (AP)	$\leq 5.0 \times$ ULN

9. Female patients must be either post-menopausal, surgically sterile, or using effective contraception (the definition of effective contraception will be based on the judgment of the investigator). All female patients of childbearing potential must have a negative pregnancy test (serum or urine) within the 7 days prior to randomization. The female partner of a male patient should be using effective contraception as defined above.
10. Patients (or legally acceptable representative) must agree to, sign, and date an EC/IRB-approved patient informed consent form.
11. Patients must be willing and able to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.

Informed consent must be obtained in writing for all patients at enrollment into the study (see Section 12.3).

4.3 EXCLUSION CRITERIA

Patients presenting with any of the following will not be included in the study:

1. History of any second malignancy with the exception of adequately treated basal cell or squamous cell skin cancer, or *in situ* carcinoma of the cervix uteri. Inclusion of patients with any other *in situ* cancer, or a history of an invasive cancer with complete remission for 5 or more years must be discussed with the sponsor and the principal investigators. Patients with a history of contralateral breast cancer who have been disease-free for more than 5 years prior to randomization are permitted.
2. History of hypersensitivity grade ≥ 3 to taxanes, Polysorbate-80, or to compounds with similar chemical structures. Patients with known intolerance to fluoropyrimidines or patients with dihydropyrimidine dehydrogenase (DPD) deficiency.
3. The following breast cancer treatments:
 - Patients receiving >1 adjuvant regimen. However, patients who have received neoadjuvant therapy immediately followed by surgery and immediately followed by adjuvant therapy without intervening progression are considered to have received one adjuvant regimen and are allowed in the trial. It is not considered to be adjuvant treatment, when chemotherapy is administered after a local treatment by either surgery or radiotherapy of a single metastasis, including cutaneous metastases, since recurrence is a near certainty and not only a risk.
 - Patients receiving >1 chemotherapy regimen for metastatic or locally recurrent and inoperable breast cancer. A chemotherapy regimen is defined as a single or a combination of chemotherapy agents given until documented disease progression or relapse. For example, patients who received sequential doxorubicin and docetaxel in the metastatic setting without intervening progression are allowed in the trial.
4. Prior treatment with capecitabine or any taxanes analogs except for paclitaxel or docetaxel (eg, epothilones are not permitted, novel preparations of paclitaxel are not permitted). Generic paclitaxel and Abraxane® (nanoparticle albumin-bound paclitaxel) are permitted.
5. Concurrent treatment with potent inhibitors of cytochrome P450 3A4, such as ketoconazole, itraconazole, erythromycin, clarythromycin or patients planning to receive these treatments. For patients who were receiving treatment with such agents, a one-week washout period is required prior to randomization.
6. Concurrent treatment on another clinical trial or with any other cancer therapy including chemotherapy, immunotherapy (including trastuzumab [Herceptin®]), hormonal therapy, radiotherapy, chemoembolization therapy, cryotherapy, targeted non-cytotoxic therapies or patients planning to receive these treatments during the study.
7. HER-2 positive patients may participate in this trial. Concurrent treatment with trastuzumab [Herceptin®] is not permitted.
8. Known brain or leptomeningeal disease (CT or MRI scan of the brain required only in case of clinical suspicion of central nervous system involvement).

9. Any of the following within the 6 months prior to randomization: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft surgery, clinically symptomatic and uncontrolled cardiovascular disease, or clinically significant cardiac arrhythmias (grade 3-4).
10. History of inflammatory bowel disease or chronic diarrhea.
11. Peripheral neuropathy grade ≥ 2 .
12. Other severe acute or chronic medical or psychiatric condition, or significant laboratory abnormality requiring further investigation that may cause undue risk for the patient's safety, inhibit protocol participation, or interfere with interpretation of study results, and in the judgment of the investigator would make the patient inappropriate for entry into this study.
13. Known human immunodeficiency virus (HIV) infection requiring treatment or acquired immunodeficiency-syndrome (AIDS)-related illness.
14. Patients who are pregnant or breastfeeding.

Any waiver of these inclusion and exclusion criteria must be approved by the investigator and the sponsor on a case-by-case basis prior to enrolling the patient. This must be documented by both the sponsor and the investigator.

No patient will be allowed to enroll in this study more than once.

4.4 PATIENTS OF REPRODUCTIVE POTENTIAL

Female patients must not be pregnant or breast-feeding while enrolled in this study, as stated in the patient eligibility criteria. Absence of pregnancy must be demonstrated in patients of reproductive potential (ie, ovulating, pre-menopausal, not surgically sterile) by serum or urine prior to exposure to the investigational product or any study procedure with potential risk to the fetus.

A patient must not become pregnant during the study. Female patients and female partners of male patients of reproductive potential must use a medically accepted contraceptive regimen. The contraceptive method(s) chosen should be medically, culturally, and geographically acceptable as well as proven to have an acceptably low failure rate, as determined by the investigator.

Repeat pregnancy tests should be performed at the discretion of the investigator during the patient's participation in the study to ensure that pregnancy has not occurred. Any pregnancy diagnosed in a female patient or in the female partner of a male patient during treatment with the study drugs RPR109881 or capecitabine, must be reported to the sponsor immediately and treatment with study drug will be permanently withdrawn. Information related to the pregnancy must be given on a "Drug Exposure Via Parent – Data Collection" form that will be provided by the sponsor and the medical management of the patient and the pregnancy will be determined on a case-by-case basis.

5 STUDY TREATMENTS

5.1 DETAILS OF STUDY TREATMENTS

Table 9 - Study treatments

	Investigational Drug	Comparator Drug
Drug Code	RPR109881	---
INN	Not yet issued	capecitabine (Xeloda®)
Formulation	<p><i>Concentrate for solution for IV infusion:</i> Single-dose vial, containing a total of 94.4 mg of RPR 109881 in 2.36 mL of polysorbate 80 VG*DF at the concentration of 40 mg/ml of RPR109881.</p> <p>The RPR109881 vial is a 15 mL clear glass vial stoppered and crimp sealed with a dark blue flip-off aluminum cap.</p> <p>* Vegetal (VG) quality for safety improvement</p> <p><i>Solvent:</i> single-dose vial containing 7.33 mL of a 13% (w/w) ethanol in water for injection solution.</p> <p>The solvent vial is a 15 mL clear glass vial stoppered and crimp-sealed with a transparent flip-off aluminum cap.</p>	<p>Xeloda®, (capecitabine) will be supplied as commercial pack as follows:</p> <p>For US:</p> <ul style="list-style-type: none">• Bottle of 60 tablets Xeloda® 150 mg• Bottle of 120 tablets Xeloda® 500 mg <p>For countries other than US or Canada:</p> <ul style="list-style-type: none">• Blister pack of 60 tablets Xeloda® 150 mg• Blister pack of 120 tablets Xeloda® 500 mg <p>For Canada:</p> <ul style="list-style-type: none">• Bottle of 60 tablets Xeloda® 150 mg• Bottle of 120 tablets Xeloda® 500 mg <p>Each pack will be over-labeled with a clinical supplies label.</p>
Manufacturer	Aventis	Roche

5.2 DOSAGE SCHEDULE

5.2.1 RPR109881 treatment

Patients randomized to the RPR109881 investigational treatment arm will receive a starting dose of 90 mg/m² IV RPR109881 on Day 1 of Cycle 1 administered over 1 hour, with the exception of patients with known bone marrow involvement, documented by bone marrow biopsy and/or aspiration, who will receive a starting dose of 75 mg/m² IV RPR109881 ([Table 10](#)). If bone marrow involvement is suspected, a bone marrow aspiration must be performed and documented during the Screening period. Treatments will be repeated in the same manner at 3-week intervals (3-week cycles). Dose adjustment will be permitted for subsequent treatment cycles based on individual patient tolerance. Treatment will continue unless any of the Withdrawal Criteria are met as described in [Section 9.1](#).

Body surface area (BSA) will be calculated at the start of each treatment cycle from body weight in kg, recorded prior to the start of each treatment cycle, and height in cm, recorded at baseline. The preferred Dubois and Dubois equation is below:

$$\text{BSA in units of m}^2 = \text{wgt. in kg}^{0.425} \times \text{htg. in cm}^{0.725} \times 0.007184$$

Subjects with a BSA >2.1 m² will use 2.1 m² for the determination of RPR109881 dose.

Table 10 - RPR109881 dose levels

Dose Level	RPR109881 Dose
-3 ⁰	45 mg/m ²
-2 ⁰	60 mg/m ²
-1 ^{0*}	75 mg/m ²
0 ^{**}	90 mg/m ²

⁰ Step-down dose in case of toxicity

* Starting dose level only if there is known bone marrow involvement

** Starting dose level for all other patients

Required premedication will include: dexchlorpheniramine 5 mg, diphenhydramine 25 mg or other antihistamines; dexamethasone 8 mg or equivalent steroid. Ranitidine or other Histamine H2 antagonist is recommended **with the exception of cimetidine**. All premedications will be administered by i.v. infusion. It is recommended that infusion of these medications be completed 30 minutes or more prior to each dose of RPR109881. Anti-emetic prophylaxis with ondansetron, granisetron or dolasetron is recommended.

5.2.2 RPR109881 treatment modification

Patients should be carefully monitored for toxicity. Dose modifications will be based on the worst toxicity and worst observed severity grade of the toxicity. The sponsor should be contacted for further guidance for patients requiring dosage reduction below 45 mg/m² (-3 dose level). Dose reductions for RPR109881-associated toxicity will not be re-escalated even if the toxicity has resolved.

The duration of treatment cycles must be at least 3 weeks, which will generally correspond to 21 days. Under exceptional circumstances such as legal holidays, a -1/+3 days visit window is acceptable for scheduling purposes (ie, cycle length of 20-24 days). While the presence of toxicity may result in a protocol-mandated extension of the cycle to allow sufficient time for recovery, cycle shortening (less than 20 days) days is never permitted.

Patients with bone marrow involvement who receive a starting dose of 75 mg/m² will be eligible for a 1-level dose escalation (to 90 mg/m²) at the investigator's discretion only if:

- ANC nadir from the cycle in which the patient received 75 mg/m² RPR109881 was Gr ≤2 ($\geq 1000/\mu\text{L}$) and the ANC on the expected day of retreatment is Gr ≤1 ($\geq 1500/\mu\text{L}$).

- Platelet nadir from the cycle in which the patient received 75 mg/m^2 RPR109881 was Gr ≤ 2 ($\geq 50,000/\mu\text{L}$) and the platelet count on the expected day of retreatment is $\geq 100,000/\mu\text{L}$.
- No dose reduction recommendations apply.

Unless otherwise noted in the following treatment modification sections below, patients will be allowed up to a 3-week delay in the start of a new treatment cycle in order for treatment-related toxicities to resolve. If, on the expected day of retreatment, the last tumor assessment was performed >6 weeks prior, consideration should be given to performing a tumor assessment before starting a new cycle of therapy. If the patient has not recovered sufficiently for retreatment within 3 weeks, contact the sponsor for guidance.

5.2.2.1 Status of the patient on the day of planned retreatment

In general, on the day of planned retreatment with RPR109881, patients must have resolution of all toxicities due to treatment (except alopecia) to grade ≤ 1 or baseline, if baseline was greater than grade 1.

Specific requirements apply with respect to hematologic, hepatic, and neurosensory toxicities.

5.2.2.2 Dose reduction based on maximal grade of toxicity in the previous cycle

In general, for any otherwise unspecified toxicity, the following rules apply:

- If maximal toxicities were grade ≤ 2 in the previous cycle, RPR109881 dose should be maintained.
- If maximal toxicities were grade ≥ 3 in the previous cycle, RPR109881 dose should be decreased by 1 dose level. However, in case of grade ≥ 3 adverse events such as fatigue, anorexia, pain, and accidental injuries, the relevance of dose reduction is to be evaluated by the physician at site at time of the re-administration of RPR109881.

Specific dose reduction requirements apply with respect to hematologic, hepatic, and neurosensory toxicities.

Hematologic toxicity

CBC/differential and platelet counts should be obtained weekly to monitor the effects of chemotherapy. If grade 4 neutropenia, assess ANC every 3 days [-1/+0] until grade ≤ 1 (ANC $\geq 1,500/\mu\text{L}$). In case of grade ≥ 1 fever, CBC should be performed. The absolute neutrophil count (ANC) must be $\geq 1500/\mu\text{L}$ and the platelet count must be $\geq 100,000/\mu\text{L}$ before the next cycle of study treatment is administered.

RPR109881 treatment shall be modified for neutropenia ([Table 11](#)) and thrombocytopenia ([Table 12](#)). The dose modifications based on neutropenia ([Table 11](#)) apply for patients who are not started on Granulocyte/Granulocyte Macrophage-Colony Stimulating Factor (G/GM-CSF), or for patients experiencing neutropenia despite being treated with G/GM-CSF. If neutropenia or its

complications result in the initiation of G/GM-CSF for the subsequent cycle, this dose modification ([Table 11](#)) does not apply for the initial cycle with G/GM-CSF.

No dose modification will be made for anemia; patients will be supported appropriately by the treating physician. If RPR109881 must be delayed due to hematologic toxicity, CBC/platelets will continue to be performed weekly, or more often if clinically indicated.

Table 11 - RPR109881 treatment modification based on absolute neutrophil count (ANC) for patients who are not started on G/GM-CSF or for patients experiencing neutropenia despite treatment with G/GM-CSF

ANC Nadir of the Previous Treatment Cycle	RPR109881 Treatment Modification	
	ANC on Day 1 Prior to Retreatment	
	Grade 0-1 ($\geq 1500/\mu\text{L}$)	Grade 2-4 ($< 1500/\mu\text{L}$)
Gr 3-4 febrile neutropenia of any duration [fever $\geq 38.5^\circ\text{C}$ and Grade 3/4 neutropenia (ANC $< 1000/\mu\text{L}$)]	No delay. Decrease RPR109881 by 1 dose level.	Delay retreatment with RPR109881 for up to 3 weeks until toxicity resolves to grade ≤ 1 (ANC $\geq 1500/\mu\text{L}$) and no fever, then reduce RPR109881 by 1 dose level and resume treatment.
Gr 4: $< 500/\mu\text{L}$ for < 5 days	No delay. Continue RPR109881 at the same dose level.	Delay retreatment with RPR109881 for up to 3 weeks until toxicity resolves to grade ≤ 1 (ANC $\geq 1500/\mu\text{L}$), then maintain current dose level and resume treatment.
Gr 4: $< 500/\mu\text{L}$ for ≥ 5 days	No delay. Decrease RPR109881 by 1 dose level.	Delay retreatment with RPR109881 for up to 3 weeks until toxicity resolves to grade ≤ 1 (ANC $\geq 1500/\mu\text{L}$), then reduce the dose by 1 level and resume treatment. CBC should be repeated every 3 days [-1/+0] until recovery to grade ≤ 1 .

Deaths due to sepsis following severe neutropenia have been reported in patients treated with RPR109881. Neutropenic complications should be managed promptly with antibiotic support. Initial prophylactic administration of a colony-stimulating factor (CSF) is not advised, but physicians may wish to consider CSF use in individual patients having experienced neutropenic fever or infection with prior chemotherapeutic regimens. If possible, ASCO guidelines regarding use of growth factors should be followed [[26](#)].

On-study treatment with G/GM-CSF for patients experiencing significant neutropenia (eg, neutropenia grade 4 > 5 days; febrile neutropenia - neutropenia grade ≥ 3 with related fever grade ≥ 1) and in patients with neutropenic infections may be started at that cycle, and prophylactic administration of G/GM-CSF should be considered for the subsequent cycles. If possible, ASCO guidelines regarding use of growth factors should be followed [[26](#)].

Table 12 - RPR109881 Treatment modification based on platelet count

Platelet Count Nadir of the previous treatment cycle	RPR109881 Treatment Modification	
	Platelet Count on Day 1 Prior to Retreatment	
	≥ 100,000/ μ L	<100,000/ μ L
Gr 3: ≥25,000/ μ L	No delay. Continue at the same dose level.	Delay retreatment for up to 3 weeks until recovery to ≥100,000/ μ L, then maintain current dose level and resume treatment.
Gr 4: < 25,000/ μ L	No delay. Decrease dose by 1 level.	Delay retreatment for up to 3 weeks until recovery to ≥100,000/ μ L, then reduce the dose by 1 level and resume treatment.

Non-hematologic toxicity

If RPR109881 treatment shall be modified for non-hematologic toxicity as indicated in the text and tables below. If RPR109881 must be delayed due to non-hematologic toxicity, blood counts or other clinical assessments to monitor toxicity will be performed weekly, or more often if clinically indicated.

Hepatic function

At the day of planned retreatment with RPR109881, the following laboratory parameters must be met:

- For patients who entered the trial with AP ≤2.5 x ULN, ALT/AST/AP must all be grade ≤1 (≤2.5 x ULN).
- For patients who entered the trial with AP >2.5-≤5.0 x ULN, ALT/AST must both be ≤1.5 x ULN and AP must be ≤5.0 x ULN.
- Bilirubin must be WNL.

If the above criteria are not met on the planned day of retreatment, delay retreatment with RPR109881 for up to 3 weeks until toxicity resolves to the above parameters, then reduce the dose by 1 level and resume treatment.

Renal toxicity

No dose reduction for RPR109881 will be made for renal toxicity. However, treatment with RPR109881 will be delayed for up to 3 weeks if the serum creatinine is >1.5 x ULN or ≤60 mL/min. Treatment may resume if the serum creatinine or calculated CrCl return to ≤1.5 x ULN or >60 mL/min, respectively.

Neurologic toxicity

RPR109881 treatment should be modified for neurologic toxicity as described in [Table 13](#).

Table 13 - RPR109881 Treatment modifications based on neurologic toxicity

Neurologic Toxicity on Day 1 Prior to Retreatment	RPR109881 Treatment Modification
Gr 0-2	No delay. Continue at the same dose level.
Gr 3	Delay retreatment for up to 3 weeks until recovery to grade ≤ 2 , then reduce by 1 dose level and resume treatment. If recovery to grade ≤ 2 does not occur within 3 weeks, the patient should be withdrawn from study treatment.
Gr 4	No further study treatment.

Nausea and vomiting

Nausea and/or vomiting should be controlled with adequate antiemetics. If grade 4 nausea/vomiting occurs in spite of antiemetics, the RPR109881 dose should be reduced by 1 dose level for the next cycle.

Mucositis

If mucositis is present at the time of planned treatment, study treatment is delayed until recovery to grade ≤ 1 . If acute grade 3-4 mucositis occurs at any time, the next RPR109881 dose should be reduced by 1 dose level and treatment resumed upon recovery.

Diarrhea

General Precautions:

Diarrhea can be life threatening and may lead to dehydration, electrolyte imbalance, or sepsis. Diarrhea should be treated promptly with loperamide. Patients with diarrhea should be carefully monitored and should be given fluid and electrolyte replacement if they become dehydrated.

Diarrhea in the absence of neutropenia \geq Grade 3:

In addition to the general precautions, patients should be given antibiotic support if they develop ileus, fever or neutropenic complications. Subsequent chemotherapy treatments should be delayed in patients until return of pretreatment bowel function for at least 24 hours without need for antidiarrhea medication. If grade 2, 3, or 4 diarrhea occurs, despite maximal antidiarrhea medication, subsequent doses of RPR109881 should be decreased by 1 dose level.

Diarrhea \geq Grade 3 associated with neutropenia \geq Grade 3:

In addition to prompt treatment with loperamide and fluid and electrolyte replacement, aggressive treatment with antibiotic support is recommended. CBC should be assessed every 3 days [-1/+0] until ANC resolves to $\geq 1500/\mu\text{L}$. Subsequent chemotherapy treatments should be delayed in such patients for up to 3 weeks until return of pretreatment bowel function for at least 24 hours without

need for antidiarrhea medication and until ANC resolves to $\geq 1500/\mu\text{L}$. Following recovery, the dose of RPR109881 should be reduced by 1 level.

Hypersensitivity reactions

Description and suggested management of RPR109881 hypersensitivity reactions are found in [Table 14](#).

Table 14 - Interventions based on RPR109881 hypersensitivity reaction

Symptom Severity	Intervention Recommendation
<u>Mild</u> symptoms: localized cutaneous reaction such as mild pruritus, flushing, rash	<ul style="list-style-type: none">Consider decreasing the rate of infusion until recovery of symptoms, stay at bedside,Then, complete RPR109881 infusion at the initial planned rate
<u>Moderate</u> symptoms: any symptom such as generalized pruritus, flushing, rash, dyspnea, back pain during infusion, hypotension with systolic blood pressure (BP) $> 80 \text{ mm Hg}$ not listed above (mild symptoms) or below (severe symptoms).	<ul style="list-style-type: none">Stop RPR109881 infusion,Give diphenhydramine 50 mg IV and/or IV dexamethasone 10 mg,Resume RPR109881 infusion within 3 hours following recovery of hypersensitivity reaction. Administer RPR109881 over 2 hours for all subsequent treatments.
<u>Severe</u> symptoms, such as: bronchospasm, generalized urticaria, systolic BP $\leq 80 \text{ mm Hg}$, angioedema	<ul style="list-style-type: none">Stop RPR109881 infusion;Give IV diphenhydramine 50 mg and/or IV dexamethasone 10 mg and/or epinephrine as needed.In case of severe hypersensitivity reaction, rechallenge must be performed more than 3 hours after recovery and premedication should be readministered.If severe reaction recurs despite additional premedication, the patient will go off protocol therapy.
Anaphylaxis (Grade 4 reaction)	NO FURTHER PROTOCOL THERAPY.

Management of Subsequent Treatment Cycles: The recommended pretreatment for subsequent infusions is 50 mg diphenhydramine IV and 10 mg dexamethasone IV 30 minutes prior to RPR109881 infusion. For patients who experience moderate or severe hypersensitivity reactions, the RPR109881 should be administered over 2 hours for subsequent treatment courses in addition to premedication as noted above. These patients must be informed of the potential risk of recurrent allergic reactions and must be carefully monitored.

If the initial reaction is grade 4 for Allergy, the patient will receive no further treatment and will go off protocol therapy. If a second severe reaction (grade 3) recurs despite additional premedications as outlined above, the patient will go off protocol therapy.

In case of late occurring hypersensitivity symptoms, eg, appearance within 1 week after treatment of a localized or generalized pruritus, symptomatic treatment may be given (eg, oral antihistamine). Additional oral or IV premedication with antihistamine may also be given for the

next cycle of treatment depending on the intensity of the reaction observed. No dose reductions will be made in any case.

5.2.3 Capecitabine treatment

Patients randomized to the capecitabine treatment arm will receive a starting dose of 1250 mg/m² capecitabine tablets administered orally twice daily (morning and evening, equivalent to 2500 mg/m² total daily dose) for 2 weeks followed by a 1-week rest period, to form a 3-week cycle. The dose is based on prescribing information stated in the US and EU package inserts. Dose adjustment will be permitted depending on individual patient tolerance.

Body surface area (BSA) will be calculated at the start of each treatment cycle from body weight in kg, recorded prior to the start of each treatment cycle, and height in cm, recorded at baseline. The preferred Dubois and Dubois equation is below:

$$\text{BSA in units of m}^2 = \text{wgt. in kg}^{0.425} \times \text{htg. in cm}^{0.725} \times 0.007184$$

Capecitabine tablets should be swallowed with water within 30 minutes after a meal. [Table 15](#) displays the total daily dose by body surface area and the number of tablets to be taken at each dose.

Table 15 - Capecitabine dose calculation according to body surface area, starting dose

Dose level 1250 mg/m ² twice a day		Number of tablets to be taken at each dose (morning and evening)	
Body Surface Area (m ²)	Total Daily* Dose (mg)	150 mg	500 mg
≤1.24	3000	0	3
1.25 – 1.36	3300	1	3
1.37 – 1.51	3600	2	3
1.52 – 1.64	4000	0	4
1.65 – 1.76	4300	1	4
1.77 – 1.91	4600	2	4
1.92 – 2.04	5000	0	5
2.05 – 2.17	5300	1	5
≥2.18	5600	2	5

*Total Daily Dose divided by 2 to allow equal morning and evening doses

5.2.3.1 Adjustment of starting dose in special populations

Hepatic impairment

In patients with mild to moderate hepatic dysfunction due to liver metastases, no starting dose adjustment is necessary; however, patients should be carefully monitored. Patients with severe hepatic dysfunction have not been studied.

Renal impairment

No adjustment to the starting dose of capecitabine is recommended in patients with mild renal impairment (creatinine clearance = 60-80 mL/min [Cockroft and Gault, as shown below]).

Cockroft and Gault Equation:

$$\text{Creatinine Clearance} = \frac{(140 - \text{age in yrs}) \times (\text{weight in kg})}{\text{K} \times (\text{serum creatinine})}$$

- Serum creatinine in mg/L: K = 7.2 in males; K = 8.5 in females
- Serum creatinine in µmol/L: K=0.814 in males; K= 0.96 in females

5.2.4 Capecitabine treatment modification

Dose modification of capecitabine for hematologic toxicity should follow guidance in Tables 16, 18 and 19 below. Administration of capecitabine should be interrupted during a treatment cycle if grade 3 or 4 hematologic toxicity develops. The next treatment cycle cannot start until hematologic toxicity has recovered to grade ≤ 1 .

No dose reductions or interruptions are required for anemia as it can be managed by Erythropoietin treatment or RBC transfusion.

Table 16 - Recommended capecitabine dose modifications for Hematologic Toxicities

Worst Toxicity Grade of Neutropenia and/or Thrombocytopenia Observed During the Treatment Cycle	Modification During a Treatment Cycle	Dose Adjustment for Next Cycle (% of Starting Dose)
Grade 1	No treatment interruption. Maintain dose level.	Maintain dose level
Grade 2		
1 st , 2 nd , and 3 rd appearance	Interrupt until resolved to grade ≤1	100%
Grade 3		
1 st and 2 nd appearance	Interrupt until resolved to grade ≤1	75%
3 rd appearance	Discontinue treatment permanently or If physician deems it to be in the patient's best interest to continue, at 50% of original dose after toxicity resolved to grade ≤1	--
Grade 4		
1 st appearance	Interrupt until resolved to grade ≤1	50%
2 nd appearance	Discontinue treatment permanently	
Grade 3 Febrile neutropenia		
1 st appearance	Interrupt until resolved to grade ≤1	75%
2 nd appearance	Discontinue treatment permanently or If physician deems it to be in the patient's best interest to continue, at 50% of original dose after toxicity resolved to grade ≤1	
Grade 4 Febrile neutropenia		
1 st appearance	Discontinue treatment permanently or If physician deems it to be in the patient's best interest to continue, at 50% of original dose after toxicity resolved to grade ≤1	
2 nd appearance	Discontinue treatment permanently	

Dose modifications for non-hematologic toxicities will be based on the worst toxicity and worst observed severity grade of the toxicity (Table 17, Table 18, Table 19). Toxicity due to capecitabine administration may be managed by symptomatic treatment, dose interruptions, and adjustment of capecitabine dose. Dose reductions for capecitabine-associated toxicity will not be re-escalated even if the toxicity has resolved. Patients should withdraw from treatment if toxicity occurs despite administration of capecitabine at 50% of the Starting Dose.

Unless otherwise noted in the following treatment modification sections below, patients will be allowed up to a 3-week delay in the start of a new treatment cycle in order for treatment-related toxicities to resolve. If, on the expected day of retreatment, the last tumor assessment was performed >6 weeks prior, consideration should be given to performing a tumor assessment

before starting a new cycle of therapy. If the patient has not recovered sufficiently for retreatment within 3 weeks, contact the sponsor for guidance.

Table 17 - Recommended capecitabine dose modifications for Non-Hematologic Toxicities

Worst Toxicity Grade Observed During the Treatment Cycle	Modification During a Treatment Cycle	Dose Adjustment for Next Cycle (% of Starting Dose)
Grade 1	No treatment interruption. Maintain dose level.	Maintain dose level
Grade 2		
1st appearance*	Interrupt until resolved to grade ≤ 1	100%
2nd appearance*	Interrupt until resolved to grade ≤ 1	75%
3rd appearance*	Interrupt until resolved to grade ≤ 1	50%
4th appearance*	Discontinue treatment permanently	--
Grade 3		
1st appearance*	Interrupt until resolved to grade ≤ 1	75%
2nd appearance*	Interrupt until resolved to grade ≤ 1	50%
3rd appearance*	Discontinue treatment permanently	--
Grade 4		
1st appearance*	Discontinue permanently or If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade ≤ 1	50%
1st appearance* (Cycle 1)	If a patient develops a grade 4 adverse event in the first treatment cycle, dihydropyrimidine dehydrogenase (DPD) levels should be obtained to rule out DPD deficiency.	If not DPD deficient, reduce by 50% If DPD deficient, discontinue permanently

* Appearance of any non-hematological toxicity, not necessarily the same type as previous

Dosage modifications are not recommended for grade 1 events. Therapy with capecitabine should be interrupted upon the occurrence of a grade 2 or 3 adverse experience. Once the adverse event has resolved or decreased in intensity to grade ≤ 1 , then capecitabine therapy may be restarted at full dose or as adjusted according to the above table (Table 17). The doses corresponding to 75% and 50% dose levels are found in Table 18 and Table 19. If a grade 4 adverse event occurs, therapy should be discontinued or interrupted until resolved or decreased to grade 1, and therapy should be restarted at 50% of the original dose. Doses of capecitabine omitted for toxicity or any other reason are not replaced or restored; instead the patient should resume the planned treatment cycles.

The duration of treatment cycles must be at least 3 weeks which will generally correspond to 21 days. Under exceptional circumstances such as legal holidays, a $-1/+3$ days visit window is acceptable for scheduling purposes (ie, cycle length of 20-24 days). While the presence of toxicity may result in a protocol-mandated extension of the cycle to allow sufficient time for recovery, cycle shortening (less than 20 days) is never permitted.

Table 18 - Capecitabine dose calculation according to body surface area, 75% of starting dose

Dose level 937 mg/m ² twice a day (75% of Starting Dose)		Number of tablets to be taken at each dose (morning and evening)	
Body Surface Area (m ²)	Total Daily* Dose (mg)	150 mg	500 mg
≤1.24	2300	1	2
1.25 - 1.36	2600	2	2
1.37 - 1.51	2900	3	2
1.52 - 1.64	3000	0	3
1.65 - 1.76	3300	1	3
1.77 - 1.91	3600	2	3
1.92 - 2.04	3900	3	3
2.05 - 2.17	4000	0	4
≥2.18	4300	1	4

*Total Daily Dose divided by 2 to allow equal morning and evening doses

Table 19 - Capecitabine dose calculation according to body surface area, 50% of starting dose

Dose level 625 mg/m ² twice a day (50% of Starting Dose)		Number of tablets to be taken at each dose (morning and evening)	
Body Surface Area (m ²)	Total Daily* Dose (mg)	150 mg	500 mg
≤1.24	1600	2	1
1.25 - 1.36	1600	2	1
1.37 - 1.51	1900	3	1
1.52 - 1.64	2000	0	2
1.65 - 1.76	2000	0	2
1.77 - 1.91	2300	1	2
1.92 - 2.04	2600	2	2
2.05 - 2.17	2600	2	2
≥2.18	2900	3	2

*Total Daily Dose divided by 2 to allow equal morning and evening doses

Diarrhea

If grade 2, 3, or 4 diarrhea occurs, administration of capecitabine should be immediately interrupted until the diarrhea resolves or decreases in intensity to grade ≤ 1. Following a reoccurrence of grade 2 diarrhea or occurrence of any grade 3 or 4 diarrhea, subsequent doses of capecitabine should be decreased as per the above table.

Hand-and-foot syndrome

Hand-and-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy-induced acral erythema) is a cutaneous toxicity (median time to onset of 79 days, range from 11 to 360 days) with a severity range of grades 1 to 3. Grade 1 is characterized by any of the following: numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort which does not disrupt normal activities. Grade 2 hand-and-foot syndrome is defined as painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities of daily living. Grade 3 hand-and-foot syndrome is defined as moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living. If grade 2 or 3 hand-and-foot syndrome occurs, administration of capecitabine should be interrupted until the event resolves or decreases in intensity to grade 1. Following grade 3 hand-and-foot syndrome, subsequent doses of capecitabine should be decreased.

Hyperbilirubinemia

If grade ≥ 2 drug-related elevations in bilirubin occur, administration of capecitabine should be immediately interrupted until the hyperbilirubinemia resolves or decreases in intensity to grade ≤ 1 . Dose modifications should be performed in accordance with [Table 17](#).

Renal impairment

Dose adjustment is recommended as outlined in [Table 17](#) if a patient develops a grade 2 to 4 adverse event.

5.3 TREATMENT ASSIGNMENT

The study drugs, investigational product (RPR109881) and comparator (capecitabine), will be administered only to patients included in this study following the procedures set out in the clinical study protocol. The randomization will be performed using an Interactive Voice Response System (IVRS).

After each patient has provided their written informed consent, patients will be assigned a unique 8-digit number that will incorporate the center number as well as a patient identification number. After the patient has completed the necessary Screening assessments, and is deemed eligible for study entry by the principal investigator or designated individual, the study site will contact the Clinphone IVRS. The site will need to enter the following information regarding the clinical site and study patient:

- Patient's 8-digit number (4-digit center number followed by 4-digit patient identification number)
- Patient's initials
- Gender
- Date of birth

- Prior taxanes given in the setting of:
 - Adjuvant Treatment only
 - Any Metastatic Disease with or without Adjuvant Treatment. Cancer which is locally recurrent and inoperable with curative intent should be considered metastatic for the process of stratification.

For patients who received taxanes in both the adjuvant and metastatic setting, prior responsiveness is defined relative to the metastatic setting.

- Prior responsiveness to taxanes defined by:
 - Refractory – disease progression at any time during taxane treatment or within the 30 days following the final dose of taxane.
 - Non-refractory – disease progression 31 days or more after the final dose of taxane.

Unblinded randomization to RPR109881 or capecitabine will be stratified based on treatment setting of the prior taxanes, prior responsiveness to taxanes, and region as defined below using a balancing algorithm. In order to minimize the predictability in the present open-label trial, a minimization approach with an allocation probability of 0.75 will be used to keep the balance between two treatment groups at each combination of the 3 stratification factors [27,28]. The regions are defined as follows:

North America region: United States, Canada

South America region: Mexico, South American countries

Western Europe region: Austria, Belgium, Denmark, Greenland, Finland, France, Germany, Greece, Ireland, Israel, Italy, Luxembourg, The Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom

Eastern Europe region: European countries not listed above

Southern hemisphere: Australia, New Zealand, South Africa

Rest of world: Countries not listed above

The IVRS will assign the randomized treatment arm. Details of the IVRS procedure will be provided in the IVRS Site Manual.

Study drug should begin on the same date as randomization. If not feasible, the maximum delay permitted for start of study drug is 3 working days after randomization. Clinical sites must complete the baseline case report forms (CRFs) for all randomized patients, even if the patient is not treated with study drug (RPR109881 or capecitabine). Patients who sign an informed consent but were not randomized are considered screen failures and must be documented as such in the CRF.

5.4 PACKAGING AND LABELING

The investigational medicinal product (RPR109881) will be packaged by Aventis or one of its CROs and supplied on an open label basis. The comparator (Xeloda®, capecitabine) will be supplied by Aventis as commercial pack over-labeled with a clinical supplies label. A copy of the Xeloda® product information, appropriate for each participating country, will be provided in the Study Manual.

5.4.1 Packaging of RPR109881

5.4.1.1 RPR109881 80 mg/2 ml vial (concentrate for solution for infusion)

- Single-dose vial, containing a total of 94.4 mg of RPR109881 in 2.36 ml of polysorbate 80 VG DF* at the concentration of 40 mg/ml of RPR109881.
*Vegetable origin quality for safety improvement.
- The RPR109881 vial is a 15 mL clear glass vial stoppered and crimp-sealed with a dark blue flip-off aluminum cap.
- The volume of the concentrate for solution for infusion vial has been established and validated to compensate for loss during preparation of the premix due to foaming, adhesion to walls of the vial and dead space. This overfill ensures a minimal extractable volume of 8 mL containing 10 mg/mL RPR109881 following dilution with the solvent (premix).

5.4.1.2 Solvent vial for RPR109881

- Solvent composition: 13% (w/w) ethanol in water for injection.
- The solvent vial is a 15 mL clear glass vial stoppered and crimp-sealed with a transparent flip-off aluminum cap.
- The solvent vial contains 7.33 mL of solvent. This volume has been established and validated based on the total content of the RPR109881 concentrate for solution for infusion vial and ensures a concentration of 10 mg/mL RPR109881 after preparation of the premix.

5.4.2 Packaging and dispensing of capecitabine

Xeloda® (capecitabine) will be supplied as commercial pack as follows:

For US:

- Bottle of 60 tablets Xeloda 150 mg
- Bottle of 120 tablets Xeloda 500 mg

For countries other than US or Canada:

- Blister pack of 60 tablets Xeloda® 150 mg
- Blister pack of 120 tablets Xeloda® 500 mg

For Canada:

- Bottle of 60 tablets Xeloda® 150 mg
- Bottle of 120 tablets Xeloda® 500 mg

Each pack will be over-labeled with a clinical supplies label. Capecitabine will be dispensed to the beginning of the treatment cycle, for one to four cycles-worth of medication depending on local packaging design.

5.4.3 Labeling

The clinical supplies will be labeled as follows:

- Sponsor's name and address
- Study number
- Product identification
- Content
- Dosing instructions
- Batch No.
- Kit No.

Additional statements will be printed on the label(s) as required by local regulations.

5.4.4 Study drug storage

- RPR109881 vial: +2°C to +8°C, protected from bright light.
- RPR109881 Solvent vial: room temperature or kept in the refrigerator (+2°C to +8°C).
- Capecitabine tablets: controlled room temperature, +15°C to +30°C for US and Canada, below 30°C for other countries

5.4.5 Preparation and administration of RPR109881

5.4.5.1 Preparation of the premix and infusion

RPR109881 vial should be administered only by the intravenous route, either by peripheral vein or central venous catheter. The preparation of infusion solution is indicated below:

Preparation of the premix under aseptic conditions

1. Remove the required number of RPR109881 vials from the refrigerator. The refrigerated solution may be hazy. The haziness disappears at room temperature. Consequently, it is necessary to stand the vials at room temperature (at least 60 minutes) until the solution clears.
2. Take the required number of solvent vials (one solvent vial for each RPR109881 vial).

3. Using a syringe fitted with a needle, withdraw **THE ENTIRE CONTENTS** of the solvent vial. (Taking into account the overfill adopted for the RPR109881 and solvent vials, the addition of **THE ENTIRE CONTENTS** of one solvent vial to one RPR109881 vial ensures an extractable volume of 8 ml of premix containing 10 mg of RPR109881 per mL).
4. Using the same syringe and needle, pierce the stopper of the RPR109881 vial and into it inject **THE ENTIRE CONTENTS** of the solvent vial from the syringe.
5. Remove the syringe and needle and shake the mixture manually for at least 15 seconds.
6. Allow the premix solution to stand for 5 minutes at room temperature and then check that the solution is homogeneous and clear. (It is normal for foam to persist after this rest period).

The premix obtained contains 10 mg of RPR109881 per mL.

Preparation of the infusion under aseptic conditions

WARNING: Since foam is normally present, the required dose must be accurately adjusted using a graduated syringe.

1. Using a graduated syringe fitted with a needle, pierce the stopper of the vial and, holding the vial inverted, remove the volume of premix (containing 10 mg of RPR109881 per mL) corresponding to the required dose for administration (in mg of RPR109881).
2. Inject the premix volume, so removed, into a 250 mL or 500 mL PVC free infusion bag (containing either 5% glucose solution for injection or 0.9% sodium chloride solution for injection). The concentration of the infusion solution must never be higher than 0.75 mg/mL. Therefore, the maximum amount of RPR109881 added to a 250 mL infusion container should not exceed 200 mg (or 20 mL of the premix solution). If more than 200 mg of RPR109881 is required, a larger volume of infusion vehicle (ie, 500 mL) should be used so as not to exceed the concentration limit of 0.75 mg/mL of RPR109881.
3. Mix the contents of the infusion container manually using a rocking motion.

5.4.5.2 Infusion conditions (normal lighting conditions)

When preparation of the infusion solution is finished, the infusion of RPR109881 should be completed (end of infusion) within 8 hours.

- Infusion bags and infusion administration set made of **PVC free or DEHP free** material should be used. A glass bottle could also be used.
- In line filter (with a recommended pore size of 0.22 µm) made of **PVC free or DEHP free** material should be used.

5.4.5.3 Storage period of premix and infusion solution

Since stability studies are not completed, the premix solution of RPR109881 should not be stored.

The infusion solution is stable for 8 hours from preparation to end of infusion.

5.4.5.4 Recommendation for the safe handling

- RPR109881 is an antineoplastic agent and, like other potentially toxic compounds, caution should be exercised in handling and preparing RPR109881 solutions. The use of gloves is recommended.
- If RPR109881 concentrate, premix solution or infusion solution should come into contact with skin, wash immediately and thoroughly with soap and water. If RPR109881 concentrate, premix solution or infusion solution should come into contact with mucous membranes, wash immediately and thoroughly with water.

5.4.5.5 Disposal

- All materials that have been utilized for dilution and administration should be disposed of according to standard procedures.

5.5 SUPPLIES AND ACCOUNTABILITY

The investigator or pharmacist will inventory and acknowledge receipt of all shipments of the study drugs, investigational product (RPR109881) and comparator (capecitabine). The study drugs must be kept in a locked area with restricted access. The study drugs must be stored and handled in accordance with the manufacturer's instructions. The investigator or pharmacist will also keep accurate records of the dates and quantities of the study drugs dispensed, used, and returned by each patient, and destroyed. The study monitor will periodically check the supplies of study drugs held by the investigator or pharmacist to verify accountability of all study drugs used. At the conclusion of the study, all unused study drugs and all medication containers will be destroyed at the investigational site (at a locally authorized facility) according to local regulation unless other arrangements have been approved by the sponsor. Destruction of unused vials will occur only after drug accountability has been performed or written permission for destruction has been obtained from the study monitor. Used medication containers may be destroyed during the conduct of the study if required by the institution. The sponsor will verify that a final report of drug accountability to the unit dose level is prepared and maintained in the investigator study file.

Drug vials must not be used outside the frame of this protocol.

5.6 COMPLIANCE

Administration of the study drugs, investigational drug (RPR109881) and comparator (capecitabine) will be supervised by the investigator or subinvestigator. Any delegation of this responsibility must follow Section [12.2](#).

The person responsible for drug dispensing is required to maintain adequate records of all study drugs. The fixed labels and the tear off parts of the vials, bottles, or blister packs administered or dispensed to patients must be completed (subject number, and date of infusion , respectively). The tear off parts must be maintained by the site and data will be transcribed onto the CRF. The lot number of investigational drug (RPR109881 and solvent) and comparator (capecitabine) must be recorded in the CRF.

The person responsible for drug administration to the patient will record precisely the date the drug is administered to the patient. Interruption of the 1-hour RPR109881 infusion or 14-day course of capecitabine along with reason for the interruption will be recorded in the CRF.

Patients will be instructed to bring their unused capecitabine at the time of resupply. For patients administered capecitabine in blister-packs and bottles packaged as one-cycles worth, this will occur at the end of each treatment cycle. Compliance will be assessed by tablet counts. For patients who are dispensed two-cycles worth of capecitabine in bottles only, a patient diary to record capecitabine administration will be kept. The diary will be reviewed at the end of each treatment cycle for compliance, and the tablets will be counted at the time of re-supply. Details will be recorded in the CRF.

6 PRIOR AND CONCOMITANT ILLNESSES AND TREATMENTS

6.1 PRIOR AND CONCOMITANT ILLNESSES

Additional illnesses present at the time informed consent is given are regarded as concomitant illnesses and must be documented in the CRF. Relevant past illnesses must also be documented in the CRF.

Illnesses first occurring or detected during the study, and worsening of a concomitant illness during the study, are to be regarded as adverse events and must be documented as such in the CRF (see Section 8).

6.2 PRIOR AND CONCOMITANT TREATMENTS

All treatments being taken by the patient on entry to the study or at any time during the study in addition to the investigational product are regarded as concomitant treatments and must be documented on the appropriate pages of the CRF.

Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the patient's welfare and are unlikely to interfere with the investigational product, they may be given at the discretion of the investigator and recorded in the CRF.

The following concomitant treatments are not permitted during this study:

- Concurrent treatment with other investigational drugs.
- Concurrent treatment with any other anticancer therapy including immunotherapy, targeted therapy or biological therapies.
- Initial prophylactic use of growth factors except for erythropoietin.
- Concurrent treatment with potent inhibitors of cytochrome P450 3A4, such as ketoconazole, itraconazole, erythromycin, clarythromycin. For patients who were receiving treatment with such agents, a one-week washout period is required prior to randomization.

The following concomitant treatments should be administered with caution during this study:

- **For both arms, due to drug interaction with warfarin,** when oral anticoagulants are necessary, it is recommended to use low molecular weight heparin rather than warfarin. However, if treatment with coumadin-derivative is needed, INR should be closely monitored.
- Capecitabine Treatment Arm:
 - The dose of phenytoin and the dose of coumarin-derivative anticoagulants may need to be reduced when either drug is administered concomitantly.

- RPR109881 Treatment Arm:
 - Coumarin-derivative anticoagulant inhibits the oxidative metabolism of RPR109881 in vitro. If the patient requires a coumarin-derivative anticoagulant, the drug should be given 2 hours or more after the end of infusion of the RPR109881. Monitoring of the coagulation factors or INR (International Normalized Ratio) is required.
 - If acetaminophen (paracetamol) is required, it should be administered 2 h or more before the start of the infusion with RPR109881 or 2 h or more after the end of infusion of the RPR109881. Due to the possibility of an interaction between acetaminophen (paracetamol) and RPR109881 co-administered within this time window, the drug administrator must inquire if the patient has received acetaminophen (paracetamol) prior to administering RPR109881.
 - Concurrent treatment with potent inducers of cytochrome P450 3A4, such as the antiepileptic drugs carbamazepine, phenytoin, and phenobarbital.

The following concomitant treatments are permitted during this study:

- G/GM-CSF administration will be permitted for the treatment of severe neutropenia at the discretion of the investigator. If possible, the ASCO guidelines regarding use of growth factors should be followed [26].
- Capecitabine can induce diarrhea, sometimes severe. Patients with severe diarrhea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. Standard antidiarrheal treatments (eg, loperamide) are recommended.
- Bisphosphonate therapy.
- Palliative radiotherapy may be given for control of pain for palliative intents. The sponsor should be notified to obtain prior approval prior to treatment if palliative radiotherapy is being considered, and prior to resuming therapy on the study.
- The irradiated area should be as small as possible and should never involve more than 20% of the bone-marrow in any given 3-week period. In all such cases, the possibility of tumor progression should be ruled out by physical, biological and radiological assessments of the tumor. If the only evaluable lesions are to be irradiated, the patient will be removed from the study. The irradiated area cannot be used as a parameter for response assessment. Treatment with RPR109881 and radiation therapy should not be given concurrently.
- Supportive treatment as medically indicated for the patient's well-being may be prescribed at the investigator's discretion. Every medication or treatment taken by the patient during the trial and the reason for its administration must be recorded on the CRF.
- Use of erythropoietin for chemotherapy-related anemia.

7 STUDY PROCEDURES AND SCHEDULE

7.1 OVERVIEW OF DATA COLLECTION

Details of the primary, secondary, and other efficacy variables are found in Section [11.1](#).

7.1.1 Primary efficacy data

- Progression free survival: date of tumor progression (RECIST) or death

7.1.2 Secondary and other efficacy data

- Tumor response PR/CR (RECIST)
- Date of initial tumor response PR/CR (RECIST)
- Date of confirmed tumor response PR/CR (RECIST)
- Progression (RECIST) by Day 120
- Date of Progression following confirmed PR/CR (RECIST)
- Date other anti-tumor therapy started
- Date of death

7.1.3 Safety

- Adverse events
- Serious adverse events
- Standard clinical chemistry and hematological findings
- Vital signs (heart rate, blood pressure, temperature)
- Body weight
- Other tests as clinically indicated (eg, ECG)
- Date of treatment withdrawal

7.1.4 Quality of life / clinical benefit

- EORTC QLQ-30 Questionnaire
- EORTC QLQ BR-23 Breast cancer symptom module
- Body weight and Performance Status

7.1.5 Health economics

- Resource Utilization
- EQ-5D Questionnaire

7.2 DESCRIPTION OF STUDY DAYS

7.2.1 Screening

The Screening period is from Day -21 to randomization/initial dose of study drug, although some Screening assessments and activities must be performed within 14 or 7 days prior to randomization/initial dose of study drug as indicated below or in the Study Schedule. The Screening assessments listed below marked with the superscript "*" must be performed prior to randomization as these assessments are required to determine patient eligibility.

7.2.1.1 Day –21 to Randomization/initial dose of study drug (* required prior to randomization)

- Informed Consent and Contraceptive Counseling*
- Tumor Assessment: CT Scan of chest, abdomen and pelvis; and Bone Scan. For patients with suspected bone marrow involvement (eg, due to a leukoerythroblastic peripheral blood smear), a bone marrow aspiration must be performed and documented.*
- Medical & Oncologic History and Demographics*

7.2.1.2 Day –14 to Randomization/initial dose of study drug (* required prior to randomization)

- Coagulation, Hematology, Blood Chemistry*
- 12-Lead ECG*

7.2.1.3 Day –7 to Randomization/initial dose of study drug (* required prior to randomization)

- Physical Examination [examination of major body systems including complete neurological exam, vital signs (heart rate, blood pressure, temperature) height, body weight, and ECOG performance status]*
- Pregnancy Test (for women of reproductive potential)*
- EQ-5D Questionnaire*
- Existing Signs and Symptoms

- Assessment of Concomitant Treatments, including medication use, administered within the 7 days prior to the initial study drug dose will be recorded.
- EORTC QLQ-30 and BR-23 Quality of Life Questionnaires*

7.2.2 Study days

The period called Study Days begins when the patient receives the initial dose of study drug (Cycle 1 Day 1). Each cycle consists of 21 days and assessments are scheduled on a weekly basis (Day 1, Day 8, Day 15) but may be repeated more often, as clinically indicated. Cycle lengths may be extended if additional time is required for resolution of study drug-related toxicities or other adverse events, but cycle shortening to less than 20 days is never permitted. A maximum 3-week delay for resolution of study drug-related toxicities is allowed. Beyond this, the sponsor should be contacted for guidance. In the case of treatment delay, safety assessments (eg, laboratory assessments) should continue, minimally, at the frequency outlined in the Study Schedule for the cycle in which the delay took place. A patient diary will be provided to patients who are dispensed capecitabine in bottles. Patients who are dispensed capecitabine in blister packs will have the packs analyzed and will not require a diary.

If the assessment is scheduled for a day in which the patient is also scheduled to receive study drug, the assessment must be performed prior to the study drug administration unless otherwise indicated in the Study Schedule and not precluding additional assessments where necessary, eg, monitoring and recording any adverse events during and after study drug treatment.

7.2.2.1 Cycle 1 Day 1

- IVRS Randomization after review of the Screening assessments and the patient is deemed eligible for study entry.

Typically, randomization will occur on Cycle 1 Day 1 which is defined as the day the patient receives the initial dose of study drug. If this is not possible due to scheduling conflicts, site holidays, or other unforeseen circumstances, the maximum delay between randomization and the start of study medication is 3 working days.

- All assessments indicated in “Day 1 of Each Cycle” below

On Cycle 1 Day 1 only, the required assessment may be omitted if an acceptable screening assessment was performed within 5 days prior to Cycle 1 Day 1.

7.2.2.2 Day 1 of each cycle

Day 1 of each cycle is dictated by the day the patient receives the first dose of study drug for any given cycle. For all cycles of treatment, the Day 1 assessment has a [-1/+0] window except as otherwise specified below, meaning that the assessment may be performed 1 day prior to Day 1, on Day 1, but not after Day 1.

- Physical Examination [complete neurological exam (both treatment arms), vital signs (heart rate, blood pressure, temperature) body weight, and ECOG performance status]
- Hematology, Blood Chemistry ([-3/+0] window for cycles ≥ 2)
- Determination of BSA, Study Drug Administration, Dispensing of Drug and Patient Diary (for patients who are dispensed two-cycles worth of capecitabine in bottles only), and Drug Accountability (capecitabine only, at the time of re-supply)
- Assessment of Adverse Events
- Assessment of Concomitant Treatments including medication use
- QLQ-30/BR-23 Quality of Life Questionnaires
- EQ-5D Questionnaire (odd cycles only)
- Resource utilization (odd cycles only and not during the first cycle)

7.2.2.3 Day 8 of each cycle

For all cycles of treatment, the Day 8 assessment has a [-1/+1] window, meaning that the assessment may be performed 1 day prior to Day 8, on Day 8, or 1 day after Day 8.

- Hematology
- Assessment of Adverse Events
- Assessment of Concomitant Treatments including medication use

7.2.2.4 Day 15 of each cycle

For all cycles of treatment, the Day 15 assessment has a [-1/+1] window, meaning that the assessment may be performed 1 day prior to Day 15, on Day 15, or 1 day after Day 15.

- Hematology, Blood Chemistry
- Assessment of Adverse Events
- Assessment of Concomitant Treatments including medication use

7.2.2.5 End of even-numbered cycles

During all even-numbered cycles (eg, Cycles 2, 4, 6, etc.) Days 15-21, CT imaging of tumor will be performed and assessed. The Cycle 6 assessment must be performed on Day 120, whenever possible.

For patients with bone disease at Screening, repeat scans must be performed at the end of all even-numbered treatment cycles (eg, Cycles 2, 4, 6, etc.) Days 15-21 inpatients experiencing new or worsening bone symptoms or at the end of every 4th treatment cycle (eg, Cycles 4, 8, 12, etc.) Days 15-21 in patients not experiencing new or worsening bone symptoms. Bone scans are not necessary if there exists clear objective evidence of progression by other assessments in sites other than bone.

For patients with previously documented positive bone marrow who achieve a complete response, please contact the sponsor with respect to the need for repeat aspiration.

7.2.2.6 Day 120

The Day 120 assessment has a (+/-7 days) window, ie, Day 113-Day 127. If the end-of-even-numbered-cycle tumor assessment for retreatment is performed within the Day 120 window, then one set of scans will suffice for both purposes.

- Tumor Assessment: CT Scan
- Body weight and ECOG performance status

7.2.3 End of study (treatment) / withdrawal

All patients must continue to be observed for 30 days after the final dose of study treatment as follows:

At the end of the study treatment, the following procedures should be performed within the 22-30 days following the final dose of study drug.

- Physical Examination [complete neurological exam (both treatment arms), vital signs (heart rate, blood pressure, temperature) body weight, and ECOG performance status]
- Hematology, Blood Chemistry
- Tumor Assessment: CT Scan (if not performed within the prior 6 weeks) and Bone Scan (if not performed within the prior 6 weeks for patients experiencing new or worsening bone symptoms, or within the prior 12 weeks for patients with positive bone scan at Screening who are not experiencing new or worsening bone symptoms). Bone scans are not necessary if there exists clear objective evidence of progression by other assessments in sites other than bone.
- Assessment of Adverse Events
- Assessment of Concomitant Treatments
- Drug Accountability (capecitabine only)
- EORTC QLQ-30 and BR23 Quality of Life Questionnaires
- EQ-5D Questionnaire
- Resource utilization

At the end of the 30-day post-treatment period (up to Day 37 post-treatment), the following assessments must be performed:

- Assessment of Adverse Events
- Assessment of Concomitant Treatments
- If clinically indicated, physical examination, laboratory assessments, or other tests necessary to follow unresolved or evaluate new adverse events

During this period, the outcome of adverse events with a date of onset during the study period should be re-evaluated, and any new adverse events should be recorded. Serious adverse events should be followed as described in Sections [8.1.2](#), [8.2](#), and [8.4](#) of the protocol.

7.2.4 Follow-up

7.2.4.1 Adverse events

All patients who have adverse events, whether considered associated with the use of the investigational products or not, must be monitored to determine the outcome. The clinical course of the adverse event will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate follow-up. Should the adverse event result in death, a full pathologist's report should be supplied, if possible.

If the investigator detects a serious adverse event in a study patient after the end of the period of observation, and considers the event possibly related to prior study treatment, he or she should contact the sponsor to determine how the adverse event should be documented and reported.

7.2.4.2 Post-study therapy, disease status, and survival

After withdrawal from study treatment, further treatment, if any, is at the discretion of the investigator. Please note that in the absence of PD or of symptoms requiring anti-cancer treatment, follow-up without such treatment should be considered.

Patients who discontinue study treatment prior to disease progression will continue to have tumor assessments every 6 weeks until disease progression. For patients with bone disease at Screening, repeat bone scans will continue every 6 weeks in patients experiencing new or worsening bone symptoms or every 12 weeks in patients not experiencing new or worsening bone symptoms. Bone scans are not necessary if there exists clear objective evidence of progression by other assessments in sites other than bone. Additionally, tumor assessments will be performed as necessary according to RECIST to confirm response (PR/CR) and/or to document progression.

Following documented disease progression, patients will be contacted every 3 months to document subsequent anti-cancer treatment and survival.

7.2.4.3 Quality of life

The QLQ-30/BR23 questionnaires should continue to be completed every 6 weeks by the patient either in the clinic if the patient is returning for reasons other than questionnaire completion, or by completion of the questionnaires at the patient's home and return by mail until one of the following three scenarios:

- Progression
- Initiation of another chemotherapy
- Death

Health economic data

The EQ-5D questionnaire should continue to be completed every 6 weeks by the patient either in the clinic if the patient is returning for reasons other than questionnaire completion, or by completion of the questionnaires at the patient's home and return by mail until one of the following three scenarios:

- Progression
- Initiation of another anticancer therapy
- Death

7.3 METHODS

7.3.1 Efficacy data

At baseline, all known and suspected sites of disease should be imaged using optimal techniques, including, but not limited to, CT scan (unless CT contrast is contraindicated) of the chest, abdomen, and pelvis and bone scan. To ensure comparability, the imaging methods utilized at baseline should be performed in subsequent assessments using identical techniques (ie, scans performed immediately following bolus contrast administration using a standard volume of contrast, to identical contrast agent, and preferably the same scanner). Chest X-ray for the purposes of efficacy assessment is discouraged. Ultrasound and PET may only be utilized as a diagnostic or screening tool, not for purposes of assessing efficacy. Whenever possible, clinical evaluation of superficial lesions should not be used as the sole form of measurement. However, when necessary, color photograph with metric caliber is acceptable.

For imaging of the chest, abdomen, and pelvis, use of CT is strongly encouraged. In cases where CT contrast is contraindicated, MRI may be utilized. When available, spiral CT acquisition should be done. Slice thickness should be adapted to the anatomical area and presumed size of the lesions. If limitations appear in volume acquisition, it is encouraged to choose a 1,5 pitch and thin slices, rather than a 1 pitch with thick slices. A centimeter scale should appear on films. Measurable disease as defined by RECIST requires the presence of at least one measurable target lesion at baseline. As stated in RECIST, the minimum size of the lesion should be no less than double the slice thickness of the CT reconstruction.

The determination of antitumor efficacy will be based on objective tumor assessments made according to the RECIST system of unidimensional evaluation (Appendix 3) and treatment decisions by the investigator will be based on these assessments. For the purpose of analysis, a CR or PR will be deemed a confirmed response if a subsequent assessment has been performed at least 4 weeks after the first assessment and the results confirm the initial finding. Of note, lesions in previously irradiated fields cannot be used for the determination of response but can be used for the determination of progression. Tumor markers will not be used in the assessment of response. For patients with previously documented positive bone marrow who achieve a complete response, please contact the sponsor with respect to the need for repeat aspiration.

All patients' files and radiological images must be available for source verification of patient data. Copies of all images of patients must be made available for independent review within 1 week of completion of imaging studies.

A charter for the independent review of imaging studies will describe the details of the independent review. The review will be blinded with respect to site, treatment assignment, and local interpretation of the imaging studies by independent radiologists.

7.3.1.1 *Summary of Response Evaluation Criteria in Solid Tumors (RECIST)*

Measurability of tumor lesions

At Screening, tumor lesions will be categorized by the investigator as measurable or non-measurable by RECIST as described below.

Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm with conventional CT. With spiral CT scan, lesion must be ≥ 10 mm in at least one dimension.

Non-measurable lesions - all other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan) and other non-measurable lesions. These include: bone lesions; leptomeningeal disease; ascites; pleural / pericardial effusion; inflammatory breast disease; lymphangitis cutis / pulmonis; abdominal masses that are not confirmed and followed by imaging techniques; and cystic lesions.

All measurements should be recorded in metric notation by use of a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

In the present study, lesions in previously irradiated fields cannot be used for the determination of response but can be used for the determination of progression.

Methods of measurements

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinically detected lesions will only be considered measurable when they are superficial (e.g. skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by color photography -including a ruler to estimate the size of the lesion- is recommended.

Lesions on chest X-ray are not acceptable as measurable target lesions. CT is required.

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.

Ultrasound (US) should not be used to measure tumor lesions that are clinically not easily accessible. It may be used as a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Tumor markers will not be used in the assessment of response.

Tumor response evaluation

Baseline documentation of “Target” and “Non-Target” lesions

All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required but the presence or absence of each should be noted throughout follow-up.

Response Criteria

Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions.

Partial Response (PR): At least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD.

Progression (PD): At least a 20% increase in the sum of LD of target lesions taking as references the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD since the treatment started.

Evaluation of non target lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Incomplete Response / Stable Disease: Persistence of one or more non-target lesion(s).

Progression (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. The overall assessment of response will involve all parameters as depicted in [Table 20](#).

Table 20 - Overall assessment of response

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response / SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

Frequency of tumor re-evaluation

In the present study, tumor will be re-evaluated every 6 weeks during treatment, and at least 4 weeks after the first observation of a complete or partial response. After discontinuation of protocol treatment, patients who have not progressed will still be re-evaluated every 6 weeks, unless they have started a new anti-cancer therapy.

Confirmatory measurements

Confirmation

The main goal of confirmation of objective response is to minimize the risk of overestimation of the response rate. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed. In the present study, responses always need to be confirmed.

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate. In the present study, any interval equal of longer than 4 weeks is appropriate, but it is recommended to use a 6 weeks interval.

In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval defined in the protocol. In the present study, this interval is 35 days.

7.3.2 Safety data

7.3.2.1 Adverse events

Safety profile based on incidence, severity (as graded by the NCI CTCAE, version 3.0), chronicity, and cumulative nature of treatment-emergent adverse events. Each patient will be assessed preferably by the same physician for potential adverse events according to the NCI CTC classification.

The NCI CTCAE will be provided in the Study Manual, or alternatively may be accessed through the NCI website at <http://ctep.info.nih.gov/reporting/ctc.html>.

7.3.2.2 Laboratory measurements

- Hematology (hemoglobin, WBC with differential and platelet count) will be performed by a local lab. Baseline results must be available for eligibility determination. At the start of each new treatment cycle, results must be available prior to treating the patient with study drug.
- Blood chemistry profile including sodium, potassium, calcium, phosphate, blood urea nitrogen (BUN), creatinine, albumin, total protein, AST, (SGOT), ALT (SGPT), total bilirubin, alkaline phosphatase, glucose will be performed by a local lab. Baseline results must be available for eligibility determination. At the start of each new treatment cycle, results must be available prior to treating the patient with study drug.
- Urinalysis including pH, glucose, and protein, will be performed (dipstick acceptable) when clinically indicated.
- Pregnancy test (serum or urine) for women of reproductive potential will be performed by the local lab within 7 days prior to randomization. Results must be available for eligibility determination.

7.3.2.3 Clinical examination

Physical examination: A physical examination including, but not limited to, general appearance, skin, neck, eyes, ears, nose, throat, breast, lungs, heart, abdomen, back, lymph nodes, extremities, and nervous system (both treatment arms)* will be performed. The physical examination will include examination of known and suspected sites of disease. Height will be recorded at baseline only. Body weight will also be recorded at the start of each treatment cycle.

* Neurological Examination will minimally include assessment of the following:

- History: paresthesia (numbness, tingling), dysesthesia, constipation, weakness, somnolence, confusion, disorientation, dizziness, memory loss, incoordination, hallucinations, seizure, visual disturbance, taste change, fainting.
- Exam: mental status, strength of extremities, gait, extra-ocular movements, tongue, sensory-touch including face, coin recognition, deep tendon reflexes, finger-nose test. More focused exam based on History as necessary.

Performance Status: The ECOG scale will be used (Appendix 2). Every attempt should be made to have the same individual perform the assessment throughout the study for any given patient for consistency of grading.

Vital signs: Measurements will be made of sitting pulse, temperature, and blood pressure after 5 minutes of rest.

ECG: A 12 lead (with a 10 second rhythm strip) will be used for all ECGs. It is preferable that the machine used has a capacity to calculate the standard intervals automatically.

7.3.3 Pharmacokinetic data

Not applicable for this study.

7.3.4 Pharmacodynamic data

Not applicable for this study.

7.3.5 Quality-of-life data

The QLQ-C30 profile questionnaire and QLQ-BR23 module specific to breast cancer are, respectively, 30 and 23 items in a questionnaire format. They will be self-administered by the patient (see Appendix 4 and 5) and should be completed within the 7 days prior to randomization, Day 1 every treatment cycle (except the first cycle), and at the End of Study/Withdrawal visit. For as long as the patient is being followed for other protocol measures, the QLQ-30-BR23 questionnaires should continue to be completed by the patient either in the clinic, if the patient is returning for reasons other than questionnaire completion, or by completion of the questionnaires at the patient's home and returned by mail every 6 weeks until progression, initiation of another anticancer therapy, or death.

On days in which treatment with study drug is scheduled, the patient should complete the questionnaire at the center just prior to treatment except for the first cycle.

It is recommended that a key person (eg, research nurse) at each center should be responsible for questionnaire data collection in order to optimize the compliance of the patient and to ensure the completeness of the data.

7.3.6 Health economic data

EQ-5D should be completed within the 7 days prior to randomization, Day 1 every odd treatment cycle (except the first cycle), and at the End of Study/Withdrawal visit. For as long as the patient is being followed for other protocol measures, the EQ-5D questionnaire should continue to be completed by the patient either in the clinic, if the patient is returning for reasons other than questionnaire completion, or by completion of the questionnaires at the patient's home and returned by mail every 6 weeks until progression, initiation of another anticancer therapy, or death.

Inpatient resource utilization data will be collected on Day 1 every odd treatment cycle (except the first cycle), and at the End of Study (Treatment)/Withdrawal visit.

7.4 GENERAL AND DIETARY RESTRICTIONS

None known.

8 ADVERSE EVENTS

8.1 DEFINITIONS

8.1.1 Adverse event

The term **adverse event** covers any unfavorable and unintended sign, symptom, syndrome, or illness that develops or worsens during the period of observation in the clinical study. Clinically relevant abnormal results of diagnostic procedures including abnormal laboratory findings (e.g., requiring unscheduled diagnostic procedures or treatment measures, or resulting in withdrawal from the study) are considered to be adverse events.

Worsening of a sign or symptom of the condition under treatment will normally be measured by efficacy parameters. However, if the outcome fulfils the definition of “serious adverse event”, it must be recorded as such (see Section 8.1.2).

The adverse event may be:

- A new illness
- Worsening of a concomitant illness
- An effect of the study medication, including comparator
- A combination of two or more of these factors

No causal relationship with the study medication or with the clinical study itself is implied by the use of the term “adverse event”.

Adverse events fall into the categories “non serious” and “serious” (see Section 8.1.2).

Surgical procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an adverse event, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not adverse events, if the condition(s) was (were) known before the start of study treatment. In the latter case the condition should be reported as medical history.

8.1.2 Serious adverse event

A serious adverse event is one that at any dose (including overdose):

- Results in death
- Is life-threatening¹
- Requires inpatient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability or incapacity²
- Is a congenital anomaly or birth defect
- Is an important medical event³

¹“Life-threatening” means that the patient was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

²“Persistent or significant disability or incapacity” means that there is a substantial disruption of a person’s ability to carry out normal life functions.

³Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A diagnosis of cancer during the course of a treatment should be considered as medically important. The List of Critical Terms (1998 adaptation of WHO Adverse Reaction Terminology Critical Terms List, provided in the “Instructions for completing the ‘Serious Adverse Event/Expedited Report from a Clinical Trial’ form”) should be used as guidance for adverse events that may be considered serious because they are medically important.

Clarification of the difference in meaning between “severe” and “serious”

The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as “serious”, which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.1.3 Alert terms and other reasons for expedited reporting to Pharmacovigilance

No special events are subject to reporting as alert terms in this study.

However, cases in which a “significant overdose” of RPR109881 was taken and a non-serious adverse event or no adverse event occurred are to be reported to the sponsor in an expedited manner on a “Serious Adverse Event/Expedited Report from a Clinical Trial” form.

For the purposes of this study, a significant overdose is defined as:

Single RPR109881 dose $\geq 105 \text{ mg/m}^2$.

In addition, any pregnancy diagnosed in a female patient or in the female partner of a male patient during treatment with RPR109881 or capecitabine must be reported to the sponsor immediately.

Information related to the pregnancy must be given on a “Drug Exposure Via Parent – Data Collection” form that will be provided by the sponsor.

8.2 PERIOD OF OBSERVATION

For the purposes of this study, the period of observation for collection of adverse events extends from the start of treatment with study drug (investigational agent or comparator) until 30 days after the final dose of study drug.

If the investigator detects a serious adverse event in a study patient after the end of the period of observation, and considers the event possibly related to prior study treatment, he or she should contact the sponsor to determine how the adverse event should be documented and reported.

8.3 DOCUMENTATION AND REPORTING OF ADVERSE EVENTS BY INVESTIGATOR

All adverse events that occur during the observation period set in this protocol (see Section 8.2) must be documented on the pages provided in the CRF in accordance with the instructions for the completion of adverse event reports in clinical studies. These instructions are provided in the investigator's study file and/or in the CRF itself.

The following approach will be taken for documentation:

- **All adverse events** (whether serious or non-serious, or considered as an alert term) must be documented on the “Adverse Event” page of the CRF.
- For the purposes of this study, blood abnormalities must be recorded on the AE CRF page if:
 - a. the laboratory abnormality is serious, or
 - b. the laboratory abnormality results in withdrawal from study, or
 - c. the laboratory abnormality results in dose reduction or treatment delay
- If the adverse event is serious (see Section 8.1.2), the investigator must complete, in addition to the “Adverse Event” page in the CRF, a “Serious Adverse Event/Expedited Report from a Clinical Trial” form at the time the serious adverse event is detected. This form must be sent to the study monitor who will forward it to the sponsor's Pharmacovigilance department. Complete contact information for the study monitor will be provided in the Investigator Study File.
- When a “significant overdose” of RPR109881 occurs without an adverse event, the investigator should only complete a “Serious Adverse Event/Expedited Report from a Clinical Trial” form. Instructions on where to send this form will be provided by the sponsor. In this case, there is no need to complete the “Adverse Event” page in the CRF.

Every attempt should be made to describe the adverse event in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be

reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

All patients who have adverse events, whether considered associated with the use of the investigational products or not, must be monitored to determine the outcome. The clinical course of the adverse event will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate follow-up. Should the adverse event result in death, a full pathologist's report should be supplied, if possible.

All questions on the completion and supply of adverse event report forms and any further forms issued to the investigator at a later date to clarify unresolved issues should be addressed to the sponsor.

8.4 IMMEDIATE REPORTING BY INVESTIGATOR TO SPONSOR

Serious adverse events and adverse events that fulfill a reason for expedited reporting to Pharmacovigilance ("significant overdose", as defined in Section 8.1.3) must be documented on a "Serious Adverse Event/Expedited Report from a Clinical Trial" form in accordance with the "Instructions for completing the 'Serious Adverse Event/Expedited Report from a Clinical Trial' form". This form must be completed and supplied to the sponsor within 24 hours, or at the latest on the following working day. The "Serious Adverse Event/Expedited Report from a Clinical Trial" form and the instructions are provided in the investigator's study file.

The investigator should also inform the study monitor in all cases by telephone and by faxing a copy of the SAE report. The sponsor will ensure that all legal reporting requirements are met. Complete contact information for the study monitor will be provided in the Investigator Study File.

The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the study drugs (investigational product or comparator).

Information not available at the time of the initial report (eg, an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up "Serious Adverse Event/Expedited Report from a Clinical Trial" form.

The "Instructions for completing the 'Serious Adverse Event/Expedited Report from a Clinical Trial' form" give more detailed guidance on the reporting of serious adverse events, adverse events that comply with alert terms, and adverse events initially reported as non-serious that become serious. In the latter situation, when a non-serious event becomes serious, details must be forwarded immediately to the sponsor on a "Serious Adverse Event/Expedited Report from a Clinical Trial" form.

9 WITHDRAWALS

9.1 WITHDRAWAL OF PATIENTS

Withdrawal from Study

Patients must be withdrawn from the study (ie, from any further study medication or study procedure) for the following reasons:

- At their own request or at the request of their legally authorized representative.*
- If, in the investigator's opinion, continuation in the study would be detrimental to the patient's well-being.
- At the specific request of the sponsor.
- Patient is lost to follow-up.

Withdrawal from Study Treatment

Patients must be withdrawn from study treatment (RPR109881 or capecitabine) under the following circumstances but will continue to be assessed and followed in the study unless any of the Withdrawal from Study criteria apply:

- At their own request or at the request of their legally authorized representative.*
- RECIST-defined disease progression, unless there is strong evidence of clinical benefit to justify continuation of dosing with study medication on protocol and this decision must be reviewed with the sponsor.
- Unacceptable toxicity.
- Need for other anticancer therapy not specified in the protocol or surgery or radiotherapy to the only site(s) of disease being evaluated in this protocol.
- Pregnancy

In all cases, the reason for and date of withdrawal must be recorded in the CRF and in the patient's medical records. The patient must be followed up to establish whether the reason was an adverse event, and, if so, this must be reported in accordance with the procedures in Section 8.

As far as possible, all examinations scheduled for the final study day (End of Study/Withdrawal visit) must be performed on all patients who receive study drug (investigational product or comparator) but do not complete the study according to protocol. Refer to Section 7.2.3.

The investigator must make every effort to contact patients lost to follow-up. Attempts to contact such patients must be documented in the patient's records (eg, times and dates and times of attempted telephone contact, receipt for sending a registered letter).

* “Legally authorized representative” means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient’s participation in the procedures involved in the research.

9.2 REPLACEMENT OF PATIENTS

There will be no replacement of patients randomized to treatment.

10 EMERGENCY PROCEDURES

10.1 EMERGENCY SPONSOR CONTACT

In emergency situations, the investigator should contact the sponsor by telephone at the number given on the title page of the protocol.

10.2 EMERGENCY IDENTIFICATION OF INVESTIGATIONAL PRODUCTS

This section is not applicable as this is an open-label study.

10.3 EMERGENCY TREATMENT

During and after a patient's participation in the trial, the investigator and/or institution should ensure that adequate medical care is provided to a patient for any adverse events, including clinically significant laboratory values, related to the trial. The investigator and/or institution should inform a patient when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

10.4 RPR109881 EXTRAVASATION PROCEDURES

Care should be taken to avoid extravasation of the drug outside of the vein when using RPR109881. If extravasation occurs or is suspected, the intravenous infusion should be stopped immediately. An attempt should be made to aspirate any extravasated drug through the needle in the vein. The needle should then be removed. Chemotherapy extravasation procedures utilized by the treating institution may be employed.

Drug handling precautions for cytotoxic agents should be followed. Avoid contact or inhalation. In case of skin contact, the affected area should be washed immediately and thoroughly with soap and water. In case of eye contact, rinse thoroughly with water. Seek medical advice as soon as possible.

10.5 OVERDOSE PROCEDURES

In the event of an overdose, the sponsor should be contacted to discuss the details of the overdose and formulate a clinical management plan.

11 STATISTICAL PROCEDURES

Complete details of the statistical analyses and methods, including data conventions, will be provided in a separate statistical analysis plan (SAP), which will be finalized before the first patient is randomized to the study.

11.1 ANALYSIS VARIABLES

11.1.1 General remark on efficacy data

- **Independent review**

The IRC (Independent Review Committee) will review the tumor assessments provided by investigators independently in a blinded fashion. The IRC will provide final assessment for responses (CR and PR), best response, date of first response, assessment of tumor progression, and the date of progression for each patient. The operational details of the review process will be provided in the IRC Charter.

The details of measurability of tumor lesions, tumor measurements, definitions / confirmation of tumor response and determination of overall response by RECIST are provided in Appendix 3 and will be summarized in the SAP.

- **Cut-off dates of the study**

There will be two cut-off dates for the study:

Cut-off date for the evaluation of PFS(see the definition in Section 11.1.2): The cut-off date for the PFS evaluation will be the date when the required 617 events for PFS analysis have been observed. No tumor assessments occurring after this cut-off date will be reviewed by the IRC. At the time of the PFS evaluation, analyses will also be performed for the safety and all other efficacy data relative to this cut-off date. It is anticipated that all efficacy data assessments except for OS are available and therefore will also be considered final at this time.

Cut-off date for the evaluation of OS (see the definition Section 11.1.3): The cut-off date for the OS evaluation will be the date when the required 618 deaths have been observed. At the time of OS evaluation, the safety data relative to this cut-off date will be analyzed.

The following table describes the plan of the futility and final analyses:

Table 21 - Futility and final analyses

Timing		200 patients	PFS Final	OS Final
Objective		Futility	PFS Evaluation	Final OS Evaluation
Data	PFS	-	Evaluated ($\alpha = 0.05$)	Done at PFS final
	OS	-	Evaluated (spending function based on $\alpha = 0.05$)	Evaluated (spending function based on $\alpha = 0.05$)
	RR	Evaluated (based on conditional power)	Evaluated	Done at PFS final
	Other Efficacy	-	Evaluated	Done at PFS final
	QoL	-	Evaluated	Done at PFS final
	Safety	Evaluated	Evaluated	Evaluated

11.1.2 Primary efficacy variable

The primary efficacy variable is Progression Free Survival (PFS) defined as the time from randomization to first documentation of RECIST-defined objective tumor progression or death due to any cause.

Tumor progressions and the date of the progressions will be determined by the IRC.

For the analysis purpose, whether a patient reaches the endpoint of PFS (died or reached the RECIST-defined objective tumor progression) or is censored with respect to PFS will be determined by the following algorithm:

- For those patients who did not die nor reached the RECIST-defined objective tumor progression before the cut-off date: These patients are censored and the censoring date will be determined by the following scenarios:
 - If the patient took any other anti-tumor therapy, then the censoring date is the date of the last valid tumor assessment before the patient took the anti-tumor therapy or the date of cut-off, whichever comes first;
 - If the patient did not take any other anti-tumor therapy then the censoring date is the date of the last valid tumor assessment or the date of cut-off, whichever comes first.

- For those patients who died or reached the RECIST-defined objective tumor progression before the cut-off date:
 - If a patient took any other anti-tumor therapy before she/he died or reached the RECIST-defined objective tumor progression, then the patient is censored and the censoring date is the date of the last valid tumor assessment before the patient took the anti-tumor therapy;
 - If a patient did not take any other anti-tumor therapy and died or progressed without confirmed tumor progression ≥ 12 weeks (≥ 84 days) after the date of the last valid tumor assessment, then the patient is censored on the date of the last valid tumor assessment;
 - The patient reaches the endpoint in any other cases.

The definition of further anti-tumor therapies will be provided in the SAP.

Best effort should be made to maintain the censored subjects due to inadequate follow-up as few as possible. Details of the censoring calculation and statistical methodology of censoring handling will be provided in the SAP.

11.1.3 Secondary efficacy variables

The secondary efficacy variables include:

- Overall Survival (OS) defined as the time from randomization to death.

The OS will be censored either at the last day that the survival status was available or the official cut-off day, whichever comes earlier.

However, best effort should be made to obtain the survival status of every subject even for those who withdrew their consent for treatment.

- Single Time Progression Rate (STPR) defined as the proportion of patients with objective disease progression defined by RECIST by Day 120 of treatment, or death, relative to the total number of patients in the analysis population.

In the definition, tumor progression and the date of the progressions are determined by the IRC.

Each subject in the ITT population can have 3 possible outcomes in terms of STPR: Event, No event and Non-evaluable:

- Event: the subject had a tumor progression or death prior to and including Day 130 assessment (Day 120 with an interval of 10 days). (Details will be provided in SAP).
- No event: the subject has had valid tumor assessments with no tumor progression or death before and including Day 130 assessment interval (Day 120 with an interval of 10 days).
- Non-evaluable: Any other cases.

The details of measurability of tumor lesions, tumor measurements, and definitions of tumor response are provided in Appendix 3.

- Response Rate (RR) defined as the proportion of patients with confirmed complete response (CR) or confirmed partial response (PR), defined by RECIST, relative to the total number of patients in the analysis population.

In the definition, both CR and PR and corresponding dates are determined by the IRC.

11.1.4 Other efficacy variables

The other efficacy variables include:

- Time to Tumor Response (TTR) defined as the time from randomization to the first documentation of objective tumor response defined by RECIST.

In the definition, both CR and PR and corresponding dates are determined by the IRC.

TTR is calculated and summarized only for those subjects who achieved a best overall response of CR or PR.

- Time to Treatment Failure (TTF) defined as the time from randomization to the first documentation of objective tumor progression defined by RECIST, or final discontinuation of all study treatment, or death, whichever comes first.

In the definition, tumor progression and the date of the progressions are determined by the IRC.

Censoring determination will follow the same principle as that for the primary efficacy variable. The details will be provided in the SAP.

- Duration of Response (DR) defined as the time from the first documentation of objective tumor response by defined RECIST to the first documentation of objective tumor progression defined RECIST or death.

In the definition, both CR and PR and corresponding dates are determined by the IRC.

Censoring determination will follow the same principle as that for the primary efficacy variable. The details will be provided in the SAP.

DR is calculated and summarized only for those subjects who achieved a best overall response of CR or PR.

11.1.5 Safety variables

The safety variables include:

- **AE**
 - On-treatment period: On-treatment period is the period from the first dose to 30 days after the last dose.

- **Treatment-emergent AEs (TEAEs):** A TEAE is defined as an AE that developed or worsened compared to baseline in severity during the on-treatment period defined above.
 - **Post-treatment AEs:** A “post-treatment AE” is defined as an AE that started after completion of the on-treatment period.
- **Special safety parameters**
 - Febrile neutropenia.
 - Infection with neutropenia.
 - Septic death.
 - Sensory neuropathy.
 - Diarrhea.
 - Hand-foot syndrome.
 - Fluid retention defined as one or more of the following symptoms related to study medication: edema, peripheral edema, lung edema, pleural effusion, ascites, pericardial effusion and weight gain.
 - **Discontinuation**
 - Treatment discontinuation and reasons.
 - Treatment discontinuation due to AEs.
 - **Major laboratory safety parameters**
 - **Hematology:** WBC, neutrophil, platelets, and hemoglobin.
 - **Selected Blood chemistry:** total bilirubin, alkaline phosphatase, SGOT (AST), and SGPT (ALT).

11.1.6 Quality of life and clinical benefit variables

- **Quality of life variables** as assessed by the EORTC QLQ-C30 questionnaire with the QLQ-BR23 breast cancer symptom module include:
 - Primary QoL endpoint: The Global health status/QoL score of the QLQ-C30.
 - The Breast/arm symptom scores of the QLQ-BR23.
- **Clinical benefit variables** include:
 - Change in body weight and performance status from baseline.

11.1.7 Health economic variables

For health economic evaluation, the following data will be collected:

- Resource Utilization
- EQ-5D

11.2 ANALYSIS POPULATIONS

Three analysis populations will be defined for this study:

- The intent-to-treat (ITT) population will consist of all randomized patients. The treatment code of each patient in the ITT population is determined by the treatment code originally assigned by randomization.

This population is the primary efficacy analysis population and will be used in the analyses of all primary and secondary efficacy variables.

- The As-Treated (AT) population will consist of all patients who receive at least 1 partial dose of study drug. The treatment code of each patient in the as-treated population is determined by the treatment the subject actually received.

This population will be evaluated for safety as well as for demographic and background information.

- The Evaluable Patient (EP) population will consist of all randomized patients who have measurable disease of breast cancer based on RECIST criteria, have baseline and at least one post-baseline valid tumor assessment (including symptomatic deterioration defined by RECIST), and also satisfy one of the following two conditions:
 - Received at least 2 cycles of treatment at the intended dose
 - Received less than 2 cycles of treatment at the intended dose but has evidence of disease progression or has withdrawn from study treatment due to unacceptable study drug-related toxicity.

The treatment code of each subject in the Evaluable population is determined by the treatment the subject actually received.

This population is the secondary efficacy analysis population and will be used in the analyses of the primary and selected secondary efficacy variables.

11.3 STATISTICAL METHODS

11.3.1 Demographic and baseline characteristics data

Demographic and other characteristics data at baseline that has potential influence on the primary outcome of the study will be examined by treatment group and compared using appropriate descriptive techniques.

Baseline variables of potential importance can include, for example, randomization stratification factors, age, baseline performance status, Her-2 receptor status, and estrogen receptor status/progesterone receptor status.

Summaries of demographic and baseline characteristics data will be provided for the ITT population. Summaries based on the “as treated” population will also be presented only if a major discrepancy with the ITT population is observed.

11.3.2 Extent of exposure

The extent of exposure will be assessed based on the following measurements:

- Number of cycles of study therapy.
- Cumulative dose.
- Dose intensity (mg/m²/week).
- Relative dose intensity (actual/planned).

Further details of the statistical evaluation of the extent of exposure data will be provided in the SAP.

11.3.3 Efficacy data

For all efficacy variables, the following null hypothesis and alternative will be tested:

H₀: No treatment difference,

H₁: RPR109881 is better than capecitabine.

All efficacy variables will be analyzed at an overall two-sided alpha level of 0.05.

11.3.3.1 Primary efficacy variable (PFS)

The primary analysis of PFS will be the comparison between the two treatment groups using a log rank test stratified by the randomization factors “treatment setting of prior taxanes administration” and “prior taxane responsiveness” as specified at the time of randomization.

The rates of PFS event will be estimated using the Kaplan-Meier method.

As a supportive analysis, the PFS will be also compared between the two treatment groups using a log rank test stratified by all 3 randomization factors.

All analyses will be performed on the ITT population and, as a secondary analysis, on the EP population.

11.3.3.2 Secondary efficacy variables

- Overall survival (OS): Time-to-death will be compared between the two treatments by the log-rank test procedure stratified by the randomization factors.

The survival curves will be estimated using Kaplan-Meier estimates.

Both analyses will be performed on the ITT population.

An interim analysis of OS is planned at the time when the targeted number events (PFS) are observed for the primary efficacy analysis. The nominal alpha values used for the interim analysis and final analysis will be determined by a Gamma(-7) function. Details are provided in the interim analysis section below.

- Single time progression rate (STPR): Comparison of single-time (Day120) progression rates between treatment groups will be performed using a Cochran-Mantel-Haenszel test, stratified by the randomization factors. This analysis will be performed in the ITT population.

A secondary analysis will also be performed using the Evaluable population.

The primary approach for handling a “Non-evaluable” outcome of STPR is to treat it as “no event”. The analyses based on the Evaluable population will support the robustness of the evaluation. The details will be in the SAP.

- Overall response rate (RR): Comparison of overall response rates between treatment groups will be performed using a Cochran-Mantel-Haenszel test, stratified by the randomization factors. This analysis will be performed in the ITT population.

A secondary analysis will also be performed using the Evaluable population

If a non-evaluable outcome of RR is observed, it will be treated as “non-response” in the analyses. The analyses based on evaluable population will support the robustness of the evaluation. The details will be in the SAP.

11.3.3.3 Other efficacy variables

- Time to tumor response (TTR): TTR will be summarized among responders in the ITT population by treatment group.
- Time to treatment failure (TTF): TTF will be analyzed in the ITT population using Kaplan-Meier estimates. The overall curves of the two treatment groups will be compared by the log-rank test procedure, stratified by the randomization factors.
- Duration of response (DR): DR will be summarized among responders in the ITT population by treatment group. The Kaplan-Meier curve will be provided by treatment group.

11.3.3.4 Additional analyses

In addition to the efficacy analyses described above, exploratory analyses will be performed to confirm the consistency of the results. The details will be provided in the SAP. These analyses will include:

- Consistency of the treatment effect: The consistency of the treatment effect will be evaluated for the PFS and OS with respect to the 3 stratification factors and other selected demographic / prognostic factors such as age (≤ 50 and > 50), performance status, Her-2 receptor status (+++ versus other), and estrogen receptor status/ progesterone receptor status using a Cox proportional model in the ITT population. The interaction of the treatment and the demographic / prognostic factors will be evaluated for the consistency of the treatment effect.

Summary statistics and corresponding 90% confidence intervals will be provided for each of the parameters specified above.

If necessary, similar analyses will be performed for other selected efficacy variables using appropriate statistical models.

- Baseline factor adjustment: The PFS and OS endpoints will be analyzed using a Cox proportional hazards model including treatment and selected prognostic factors such as age, performance status, Her-2 receptor status, and estrogen receptor status/ progesterone receptor status stratified by 3 stratification factors.
- More analyses are defined in the SAP

11.3.4 Safety data

The safety analyses will follow Aventis “Guideline for the Analysis and Reporting of Safety Data from Clinical Trials” (Document Number: GCLIN-BIO-GU-02-01). The details will be provided in the SAP. The safety summaries and analyses will be performed in the as-treated (AT) population.

11.3.4.1 TEAE

The primary and comprehensive analysis of safety will be based on the “treatment-emergent” principle. This analysis will comprise the basis upon which conclusions will be drawn regarding the safety profile.

TEAEs will be summarized with respect to the incidence, severity (as graded by the NCI CTCAE, version 3.0), possible related or not, chronicity, and cumulative nature. Frequency tables sorted by system organ class and sorted by frequency will be provided by treatment. A p-value using a Fisher’s Exact test between the treatment groups may be provided as a flag for review purpose for any coded term that occurs in 10% or more of patients in either treatment arm.

Details will be provided in the SAP.

11.3.4.2 Serious AE

Serious AEs will be summarized by system organ class. Details will be provided in the SAP.

11.3.4.3 Special safety parameters

The special safety parameters defined in Section 11.1.5 will be evaluated by treatment group. Frequency tables with 95% confidence intervals will be provided. Details will be provided in the SAP.

11.3.4.4 Discontinuation

- The frequencies of treatment discontinuations will be summarized by reason and treatment group.
- The frequencies of the treatment discontinuations due to AEs will be summarized by NCI-CTC grade and treatment group.

11.3.4.5 Major laboratory parameters

For the lab parameters defined in Section [11.1.5](#), the following analyses will be performed:

- Summary statistics (n and %) based on the worst NCI grade during the treatment period;
- A shift table for each of the parameters to assess the changes in the NCI grades from baseline to the worst grade during the treatment period.

11.3.5 Quality of life (QoL) data

For the QoL (Global health status/QoL score of the QLQ-C30, and the Breast/arm symptom scores of QLQ-BR23), a longitudinal analysis using a mixed model with change from baseline as the response will be performed to account for all the available assessments during the study, including follow-up visits. The longitudinal model will be constructed with treatment groups and covariates prospectively specified in the statistical analysis plan. All analyses will be conducted on the ITT population unless otherwise stated. Missing data will be addressed via an appropriate method, such as a pattern mixture model or a logistic regression model. For clinical benefit data, change from baseline on weight and performance status will also be assessed using a longitudinal analysis.

More details will be provided in the SAP.

11.3.6 Health economic data

- The utility provided by EQ5D will be used for health economics evaluation. The summary will be performed based on “EuroQoL EQ-5D User Guide” and EQ-5D Scoring Note” that is provided in the SAP.
- The “resource utilization” measurement will be summarized.

11.4 FUTILITY ANALYSIS

[Table 21](#) provides an outline of the futility analysis plan.

Independent Data Monitoring Committee (IDMC)

An IDMC will be selected to monitor the safety data and to perform the futility analysis as described below. These analyses will be performed in an unblinded fashion.

11.4.1 Futility analysis

11.4.1.1 Timing and objective

A futility analysis will be performed when the first 200 patients have had a minimum of two tumor assessments, died or progressed. The objective of this futility analysis is for consideration of early termination if lack of efficacy or unacceptable safety data are observed. Due to the nature of this futility analysis, no stopping boundary is to be specified. The futility data will be provided to the IDMC by the Sanofi-Aventis Biometrics department and Clinical Data Management department in a blinded fashion and the treatment code will be provided separately from the IVRS system. The IDMC will assess the unblinded futility data and provides its recommendation only to Sanofi-Aventis management. The operational details of the futility analysis will be provided in IDMC Charter.

11.4.1.2 Efficacy evaluation

The overall response rate (RR) will be evaluated based on a conditional power. The conditional power will be calculated by combining the rate observed at the time of the interim analysis and the assumed true response rates of 30% for RPR109881 and 20% for capecitabine. These assumed response rates are based on the observed rates in Study 204 for RPR109881 and available publications for capecitabine and give an 89% power at a 2-sided 5% alpha level with 400 subjects per arm. Termination of the trial will be considered if the conditional power is lower than 30%. This 30% level of conditional power was selected based on a worst-case scenario where a RR for RPR109881 is 10% and RR for capecitabine is 20% at the interim of 25% information time.

11.4.2 Interim evaluation of OS

11.4.2.1 Timing and objective

An interim analysis for OS will be performed by Aventis BDM at the time of the final analysis for PFS. The nature of this interim analysis is supportive. The other efficacy variables will also be evaluated at this time. The analyses for the other efficacy variables are considered as final.

11.4.2.2 Stopping boundary

Using a group sequential approach, a Gamma (-7) spending function will be used to determine the stopping boundary for the OS evaluation to reject the null hypothesis early. The reference for a Gamma type of spending function and a general theory of the “group sequential method” can be seen in [29,30].

11.4.2.3 OS evaluation

OS will be evaluated by a comparison of the time-to-death, as defined in Section 11.1.3, using a log-rank test stratified by the randomization factors “treatment setting of prior taxanes administration” and “prior taxane responsiveness” as specified at the time of randomization. The significance level used will be calculated using the “group sequential” approach with a Gamma(-7) spending function described above based on the proportion of the observed number of deaths at the interim time to the total planned number of deaths at the end of the study,

The death rates will be estimated with the Kaplan-Meier method.

11.4.2.4 Safety evaluation

Safety data including AE, SAE, vital sign, and major lab findings will also be evaluated at the time of the final PFS analysis.

11.4.3 Periodic safety review

The IDMC will perform data reviews periodically to monitor any potential safety issues. In order for the IDMC to make a meaningful assessment of the drug effect on safety, tumor assessment data will also be provided per IDMC’s request starting from the futility analysis and all safety reviews thereafter. Although the IDMC will have access to the unblinded efficacy data, the IDMC does not have intention to stop the trial at any interim look for any positive findings in drug efficacy. However, to protect the integrity of the study, a group sequential stopping boundary using a Gamma (-12) function is selected for the PFS endpoint to control the overall alpha level. From the date of the protocol amendment, it is predicted that there will be about 3 interim looks including the futility analysis before the final PFS analysis. The timing and other details will be provided in the IDMC Charter.

11.5 SAMPLE SIZE JUSTIFICATION

The sample size was calculated based on the following statistical hypotheses:

H_0 : Hazard Ratio = 1 (No treatment difference)

H_1 : Hazard Ratio < 1 (RPR109881 is better than capecitabine).

Approximately 800 patients, 400 patients randomized to the RPR109881 treatment arm and 400 patients to the capecitabine treatment arm, [REDACTED]

- [REDACTED]
- | [REDACTED]
- | [REDACTED]

The analysis of overall survival (OS) will be conducted when at least 618 deaths are observed, with a single interim analysis using an boundary determined by “group sequential” approach with a Gamma (-7) spending function to reject the null hypothesis, to be conducted at the time of the PFS assessment. This analysis will have 90% overall statistical power (two-sided alpha level of 0.05) to detect an OS hazard ratio of 0.77, assuming a median survival of capecitabine-treated patients of 15.2 months, corresponding to an improvement of approximate 30% in median survival.

The sample size calculation was performed using EAST 3 (Version 3.0.0, April 24th, 2003, Cytel Software Corporation).

12 ETHICAL AND LEGAL ASPECTS

12.1 GOOD CLINICAL PRACTICE

This study is to be conducted according to globally accepted standards of good clinical practice (as defined in the ICH E6 Guideline for Good Clinical Practice, 1 May 1996), in agreement with the Declaration of Helsinki and in keeping with local regulations.

12.2 DELEGATION OF INVESTIGATOR DUTIES

The investigator should ensure that all persons assisting with the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.

The investigator should maintain a list of subinvestigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

Should the investigator delegate the supervision of the investigational product administration to a designated person, this individual must have the appropriate medical qualifications to effectively conduct or supervise any potential resuscitation procedures.

12.3 PATIENT INFORMATION AND INFORMED CONSENT

Before being enrolled in the clinical study, patients must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to them.

An informed consent document that includes both information about the study and the consent form will be prepared and given to the patient. This document will contain all the elements required by the ICH E6 Guideline for Good Clinical Practice and any additional elements required by local regulations. The document must be in a language understandable to the patient and must specify who informed the patient. Where required by local law, the person who informs the patient must be a physician.

After reading the informed consent document, the patient must give consent in writing. The patient's consent must be confirmed at the time of consent by the personally dated signature of the patient and by the personally dated signature of the person conducting the informed consent discussions.

If the patient is unable to read, oral presentation and explanation of the written informed consent form and information to be supplied to patients must take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the personally dated signature of the patient or by a local legally recognized alternative (eg, the patient's thumbprint or

mark). The witness and the person conducting the informed consent discussions must also sign and personally date the consent document.

A copy of the signed consent document must be given to the patient. The original signed consent document will be retained by the investigator.

If a patient is not in a position to give informed consent because of his or her physical or mental condition, the consent of a legally authorized representative* must be sought. The consent must be confirmed at the time of consent by the personally dated signature of the representative and by the personally dated signature of the person conducting the informed consent discussions. A copy of the signed consent document must be given to the representative. The original signed consent document will be retained by the investigator. Local legal requirements must be observed and informed consent must be sought from the patient as soon as possible afterwards, if feasible. This procedure must have prior agreement from the independent ethics committee (IEC)/institutional review board (IRB).

* “Legally authorized representative” means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient’s participation in the procedure(s) involved in the research.

The investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

The investigator should inform the patient’s primary physician about the patient’s participation in the trial if the patient has a primary physician and if the patient agrees to the primary physician being informed.

12.4 CONFIDENTIALITY

Patient names will not be supplied to the sponsor. Only the patient number and patient initials will be recorded in the CRF, and if the patient name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The patients will be informed that representatives of the sponsor, independent ethics committee (IEC)/institutional review board (IRB), or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The investigator will maintain a personal patient identification list (patient numbers with the corresponding patient names) to enable records to be identified.

12.5 PROTOCOL AMENDMENTS

Neither the investigator nor the sponsor will alter this clinical study protocol without obtaining the written agreement of the other. Once the study has started, amendments should be made only in exceptional cases. The changes then become part of the clinical study protocol.

12.6 APPROVAL OF THE CLINICAL STUDY PROTOCOL AND AMENDMENTS

Before the start of the study, the clinical study protocol, informed consent document, and any other appropriate documents will be submitted to the IEC/IRB **with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought**. If applicable, the documents will also be submitted to the authorities, in accordance with local legal requirements.

Investigational products can only be supplied to the investigator after documentation on all ethical and legal requirements for starting the study has been received by the sponsor. This documentation must also include a list of the members of the IEC/IRB and their occupation and qualifications. If the IEC/IRB will not disclose the names of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. Formal approval by the IEC/IRB should preferably mention the study title, study code, study site (or region or area of jurisdiction, as applicable), amendment number where applicable, and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member.

Before the first patient is enrolled in the study, all ethical and legal requirements must be met.

The IEC/IRB and, if applicable, the authorities must be informed of all subsequent protocol amendments and administrative changes, in accordance with local legal requirements.

Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised.

The investigator must keep a record of all communication with the IEC/IRB and, if applicable, between a coordinating investigator and the IEC/IRB. This also applies to any communication between the investigator (or coordinating investigator, if applicable) and the authorities.

12.7 ONGOING INFORMATION FOR INDEPENDENT ETHICS COMMITTEE/ INSTITUTIONAL REVIEW BOARD

Unless otherwise instructed by the IEC/IRB, the investigator must submit to the IEC/IRB:

- Information on serious or unexpected adverse events from the investigator's site, as soon as possible
- Expedited safety reports from the sponsor, as soon as possible
- Periodic reports on the progress of the study

12.8 CLOSURE OF THE STUDY

The study must be closed at the site on completion. Furthermore, the sponsor or the investigator has the right to close this study site at any time. As far as possible, premature closure should occur after mutual consultation. Depending on local legislation, it may be necessary to inform IEC/IRB and the regulatory authorities when the study site is closed.

Study materials must be returned, disposed of, or retained as directed by the sponsor.

12.9 RECORD RETENTION

The investigator must obtain approval in writing from the sponsor before destruction of any records.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, because of international regulatory requirements, the sponsor may request retention for a longer period.

Essential documents include:

- Signed informed consent documents for all patients
- Patient identification code list*, screening log (if applicable) and enrollment log
- Record of all communications between the investigator and the IEC/IRB
- Composition of the IEC/IRB (or other applicable statement as described in Section 12.6)
- Record of all communications between the investigator and sponsor (or CRO)
- List of subinvestigators and other appropriately qualified persons to whom the investigator has delegated significant trial-related duties, together with their roles in the study and their signatures
- Copies of CRFs and of documentation of corrections for all patients
- Investigational product accountability records
- Record of any body fluids or tissue samples retained
- All other source documents (patient medical records, hospital records, laboratory records, etc.)
- All other documents as listed in section 8 of the ICH E6 Guideline for Good Clinical Practice (Essential Documents for the Conduct of a Clinical Trial)

Normally, these records will be held in the investigator's archives. If the investigator is unable to meet this obligation, he or she must ask the sponsor for permission to make alternative arrangements. Details of these arrangements should be documented.

*EU legislation requires this list to be maintained for a minimum of 15 years

12.10 LIABILITY AND INSURANCE

Liability and insurance provisions for this study are given in separate agreements.

12.11 FINANCIAL DISCLOSURE

Before the start of the study, the investigator will disclose to the sponsor any proprietary or financial interests he or she might hold in the investigational products or the sponsor company as outlined in the financial disclosure form provided by the sponsor. The investigator agrees to update this information in case of significant changes during the study or within one year of its completion. The investigator also agrees that, where required by law or regulation, the sponsor may submit this financial information to domestic or foreign regulatory authorities in applications for marketing authorizations.

Similar information will be provided by each subinvestigator to whom the investigator delegates significant study related responsibilities.

13 STUDY MONITORING AND AUDITING

Monitoring and auditing procedures developed or endorsed by the sponsor will be followed, in order to comply with GCP guidelines. Direct access to the on-site study documentation and medical records must be ensured.

13.1 STUDY MONITORING AND SOURCE DATA VERIFICATION

Monitoring will be done by personal visits from a representative of the sponsor (study monitor) who will check the CRFs for completeness and clarity, and crosscheck them with source documents. In addition to the monitoring visits, frequent communications (letter, telephone, and fax), by the study monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements.

Study close-out will be performed by the study monitor upon closure of the study.

13.2 ON-SITE AUDITS

Domestic and foreign regulatory authorities, the IEC/IRB, and an auditor authorized by the sponsor may request access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities. Medical records and other study documents may be copied during audit or inspection provided that patient names are obliterated on the copies to ensure confidentiality.

14 DOCUMENTATION AND USE OF STUDY FINDINGS

14.1 DOCUMENTATION OF STUDY FINDINGS

A CRF will be provided for each patient.

All protocol-required information collected during the study must be entered by the investigator, or designated representative, in the CRF. Details of CRF completion and correction will be explained to the investigator. If the investigator authorizes other persons to make entries in the CRF, the names, positions, signatures, and initials of these persons must be supplied to the sponsor.

The investigator, or designated representative, should complete the CRF pages as soon as possible after information is collected, preferably on the same day that a study patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

A source data location list will be prepared prior to study start. This list will be filed in both the trial master file and the investigator study file and updated as necessary.

The completed CRF must be reviewed and signed by the investigator named in the clinical study protocol or by a designated subinvestigator.

The sponsor will retain the originals of all CRFs. The investigator will retain a copy of all completed case report form CRF pages.

14.2 USE OF STUDY FINDINGS

All information concerning the product as well as any matter concerning the operation of the sponsor, such as clinical indications for the drug, its formula, methods of manufacture and other scientific data relating to it, that have been provided by the sponsor and are unpublished, are confidential and must remain the sole property of the sponsor. The investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the sponsor is obtained.

The sponsor has full ownership of the original CRFs completed as part of the study.

By signing the clinical study protocol, the investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. The authorities will be notified of the investigator's name, address, qualifications, and extent of involvement.

The sponsor will ensure that a final report on the study is prepared.

The investigator (or coordinating investigator) will be required to sign a statement that he or she confirms that, to the best of his or her knowledge, it accurately describes the conduct and results of the study.

All materials, documents and information supplied by the sponsor to the investigator, and all materials, documents and information prepared or developed in the course of the study to be performed under this protocol, shall be the sole and exclusive property of the sponsor. Subject to obligations of confidentiality, the investigator reserves the right to publish only the results of the work performed pursuant to this protocol, provided, however, that the investigator provides an authorized representative of the sponsor with a copy of any proposed publication for review and comment at least 45 days in advance of its submission for publication. In addition, if requested, the investigator will withhold publication an additional 90 days to allow for filing a patent application or taking such other measures as the sponsor deems appropriate to establish and preserve its proprietary rights.

It is agreed that, consistent with scientific standards, publication of the results of the study shall be made only as part of a publication of the results obtained by all sites performing the protocol. Authorship will be determined by the sponsor based on top participation in the trial according to patient accrual contributions, study design and analysis, and/or advisory capacity.

15 DECLARATIONS OF SPONSOR AND INVESTIGATOR

15.1 DECLARATION OF SPONSOR

This clinical study protocol was subject to critical review and has been approved by the Sponsor.
The information it contains is consistent with:

- The current risk-benefit evaluation of the investigational product
- The moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the principles of GCP as described in the Study Manual.

The investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

15.2 DECLARATION OF INVESTIGATOR

I confirm that I have read the above protocol. I understand it, and I will work according to the principles of GCP as described in 21 CFR parts 50, 54, 56, and 312 and according to applicable local requirements.

Investigator

Date: _____ Signature: _____

Name (block letters): _____

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APPENDICES

Appendix 1 TNM Tumor Staging

Appendix 2 ECOG Performance Status Scale

Appendix 3 Response Evaluation Criteria in Solid Tumors (RECIST)

Appendix 4 EORTC QLQ-30 Quality of Life Questionnaire

Appendix 5 EORTC QLQ-30/BR23 Breast Cancer Symptom Module

Appendix 6 EQ-5D Questionnaire

Appendix 7 Capecitabine Product Information

Appendix 8 Capecitabine Patient Information

APPENDIX 1: TNM TUMOR CLASSIFICATION

Table 22 - TNM staging system for breast cancer

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget)	Paget's disease of the nipple with no tumor
	Note: Paget's disease associated with a tumor is classified according to the size of the tumor.
T1	Tumor ≤ 2 cm in greatest dimension
T1mic	Microinvasion ≤ 0.1 cm in greatest dimension
T1a	Tumor > 0.1 cm but not > 0.5 cm in greatest dimension
T1b	Tumor > 0.5 cm but not > 1 cm in greatest dimension
T1c	Tumor > 1 cm but not > 2 cm in greatest dimension
T2	Tumor > 2 cm but not > 5 cm in greatest dimension
T3	Tumor > 5 cm in greatest dimension
T4	Tumor of any size with direct extension to
(a)	(a) chest wall or
(b)	(b) skin, only as described below
T4a	Extension to chest wall, not including pectoralis muscle
T4b	Edema (including peau d'orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed (eg, previously removed)
N0	No regional lymph node metastasis
N1	Metastasis in movable ipsilateral axillary lymph node(s)
N2	Metastases in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparent* ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastasis
N2a	Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastasis only in clinically apparent* ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastasis

N3	Metastasis in ipsilateral infraclavicular lymph node(s), or in clinically apparent* ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastasis in ipsilateral infraclavicular lymph node(s) and axillary lymph node(s)
N3b	Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastasis in ipsilateral supraclavicular lymph node(s)
Regional lymph nodes (pN) [†]	
pNX	Regional lymph nodes cannot be assessed (eg, previously removed or not removed for pathologic study)
pN0	No regional lymph node metastasis histologically, no additional examination for isolated tumor cells [‡]
pN0(i-)	No regional lymph node metastasis histologically, negative IHC
pN0(I+)	No regional lymph node metastasis histologically, positive IHC, no IHC cluster > 0.2 mm
pN0(mol-)	No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)
pN0(mol+)	No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)
pN1mi	Micrometastasis (> 0.2 mm, none > 2.0 mm)
pN1	Metastasis in one to three axillary lymph nodes and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent [§]
pN1a	Metastasis in one to three axillary lymph nodes
pN1b	Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent [§]
pN1c	Metastasis in one to three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent ^{§,¶}
pN2	Metastasis in four to nine axillary lymph nodes, or in clinically apparent* internal mammary lymph nodes in the absence of axillary lymph node metastasis
pN2a	Metastasis in four to nine axillary lymph nodes (at least one tumor deposit > 2.0 mm)
pN2b	Metastasis in clinically apparent* internal mammary lymph nodes in the absence of axillary lymph node metastasis
pN3	Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent* ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit > 2.0 mm), or metastasis to the infraclavicular lymph nodes

pN3b	Metastasis in clinically apparent* ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent§
pN3c	Metastasis in ipsilateral supraclavicular lymph nodes

Distant metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

NOTE. Adapted with permission of the American Joint Committee on Cancer (AJCC), Chicago, IL. The original source for this material is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-Verlag New York, www.springer-ny.com.

Abbreviations: IHC, immunohistochemistry; RT-PCR, reverse transcriptase polymerase chain reaction.

*“Clinically apparent” is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

† Classification is based on axillary lymph node dissection with or without sentinel lymph node dissection. Classification based solely on sentinel lymph node dissection without subsequent axillary lymph node dissection is designated (sn) for “sentinel node” (eg, pN0(i+)(sn)).

‡ Isolated tumor cells are defined as single tumor cells or small cell clusters not greater than 0.2 mm, usually detected only by immunohistochemical or molecular methods but which may be verified on hematoxylin and eosin stains. Isolated tumor cells do not usually show evidence of metastatic activity (eg, proliferation or stromal reaction).

§ “Not clinically apparent” is defined as not detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

¶ If associated with more than three positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden.

Revision of the American Joint Committee on Cancer Staging System for Breast Cancer, *Journal of Clinical Oncology*, Vol 20, No 17 (September 1), 2002: pp 3628-3636

APPENDIX 2: ECOG PERFORMANCE STATUS SCALE

Table 23 - ECOG performance status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. cannot carry on any self-care. Totally confined to bed or chair
5	Dead

As published in *Am. J. Clin. Oncol.* (CCT) 1982; 5:649-655.

APPENDIX 3: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST)

SPECIAL ARTICLE

New Guidelines to Evaluate the Response to Treatment in Solid Tumors

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Anticancer cytotoxic agents go through a process by which their antitumor activity—on the basis of the amount of tumor shrinkage they could generate—has been investigated. In the late 1970s, the International Union Against Cancer and the World Health Organization introduced specific criteria for the codification of tumor response evaluation. In 1994, several organizations involved in clinical research combined forces to tackle the review of these criteria on the basis of the experience and knowledge acquired since then. After several years of intensive discussions, a new set of guidelines is ready that will supersede the former criteria. In parallel to this initiative, one of the participating groups developed a model by which response rates could be derived from unidimensional measurement of tumor lesions instead of the usual bidimensional approach. This new concept has been largely validated by the Response Evaluation Criteria in Solid Tumors Group and integrated into the present guidelines. This special article also provides some philosophic background to clarify the various purposes of response evaluation. It proposes a model by which a combined assessment of all existing lesions, characterized by target lesions (to be measured) and nontarget lesions, is used to extrapolate an overall response to treatment. Methods of assessing tumor lesions are better codified, briefly within the guidelines and in more detail in Appendix I. All other aspects of response evaluation have been discussed, reviewed, and amended whenever appropriate. [J Natl Cancer Inst 2000; 92:205–16]

A. PREAMBLE

Early attempts to define the objective response of a tumor to an anticancer agent were made in the early 1960s (1,2). In the mid- to late 1970s, the definitions of objective tumor response were widely disseminated and adopted when it became apparent that a common language would be necessary to report the results of cancer treatment in a consistent manner.

The World Health Organization (WHO) definitions published in the 1979 WHO Handbook (3) and by Miller et al. (4) in 1981 have been the criteria most commonly used by investigators around the globe. However, some problems have developed with the use of WHO criteria: 1) The methods for integrating into response assessments the change in size of measurable and “evaluable” lesions as defined by WHO vary among research groups, 2) the minimum lesion size and number of lesions to be

recorded also vary, 3) the definitions of progressive disease are related to change in a single lesion by some and to a change in the overall tumor load (sum of the measurements of all lesions) by others, and 4) the arrival of new technologies (computed tomography [CT] and magnetic resonance imaging [MRI]) has led to some confusion about how to integrate three-dimensional measures into response assessment.

These issues and others have led to a number of different modifications or clarifications to the WHO criteria, resulting in a situation where response criteria are no longer comparable among research organizations—the very circumstance that the WHO publication had set out to avoid. This situation led to an initiative undertaken by representatives of several research groups to review the response definitions in use and to create a revision of the WHO criteria that, as far as possible, addressed areas of conflict and inconsistency.

In so doing, a number of principles were identified:

- 1) Despite the fact that “novel” therapies are being developed that may work by mechanisms unlikely to cause tumor regression, there remains an important need to continue to describe objective change in tumor size in solid tumors for the foreseeable future. Thus, the four categories of complete response, partial response, stable disease, and progressive disease, as originally categorized in the *WHO Handbook* (3), should be retained in any new revision.
- 2) Because of the need to retain some ability to compare favorable results of future therapies with those currently available, it was agreed that no major discrepancy in the meaning and the concept of partial response should exist between the old and the new guidelines, although measurement criteria would be different.
- 3) In some institutions, the technology now exists to determine

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See “Note” following “References.”

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changes in tumor volume or changes in tumor metabolism that may herald shrinkage. However, these techniques are not yet widely available, and many have not been validated. Furthermore, it was recognized that the utility of response criteria to date had not been related to precision of measurement. The definition of a partial response, in particular, is an arbitrary convention—there is no inherent meaning for an individual patient of a 50% decrease in overall tumor load. It was not thought that increased precision of measurement of tumor volume was an important goal for its own sake. Rather, standardization and simplification of methodology were desirable. Nevertheless, the guidelines proposed in this document are not meant to discourage the development of new tools that may provide more reliable surrogate end points than objective tumor response for predicting a potential therapeutic benefit for cancer patients.

- 4) Concerns regarding the ease with which a patient may be considered mistakenly to have disease progression by the current WHO criteria (primarily because of measurement error) have already led some groups such as the Southwest Oncology Group to adopt criteria that require a greater increase in size of the tumor to consider a patient to have progressive disease (5). These concerns have led to a similar change within these revised WHO criteria (see Appendix II).
- 5) These criteria have not addressed several other areas of recent concern, but it is anticipated that this process will continue and the following will be considered in the future:
 - Measures of antitumor activity, other than tumor shrinkage, that may appropriately allow investigation of cytostatic agents in phase II trials;
 - Definitions of serum marker response and recommended methodology for their validation; and
 - Specific tumors or anatomic sites presenting unique complexities.

B. BACKGROUND

These guidelines are the result of a large, international collaboration. In 1994, the European Organization for Research and Treatment of Cancer (EORTC), the National Cancer Institute (NCI) of the United States, and the National Cancer Institute of Canada Clinical Trials Group set up a task force (see Appendix III) with the main objective of reviewing the existing sets of criteria used to evaluate response to treatment in solid tumors. After 3 years of regular meetings and exchange of ideas within the task force, a draft revised version of the WHO criteria was produced and widely circulated (see Appendix IV). Comments received (response rate, 95%) were compiled and discussed within the task force before a second version of the document integrating relevant comments was issued. This second version of the document was again circulated to external reviewers who were also invited to participate in a consensus meeting (on behalf of the organization that they represented) to discuss and finalize unresolved problems (October 1998). The list of participants to this consensus meeting is shown in Appendix IV and included representatives from academia, industry, and regulatory authorities. Following the recommendations discussed during the consensus meeting, a third version of the document was produced, presented publicly to the scientific community (American Society for Clinical Oncology, 1999), and submitted to the *Journal of the National Cancer Institute* in June 1999 for official publication.

Data from collaborative studies, including more than 4000 patients assessed for tumor response, support the simplification of response evaluation through the use of unidimensional measurements and the sum of the longest diameters instead of the conventional method using two measurements and the sum of the products. The results of the different retrospective analyses (comparing both approaches) performed by use of these different databases are described in Appendix V. This new approach, which has been implemented in the following guidelines, is based on the model proposed by James et al. (6).

C. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES

1. Introduction

The introduction explores the definitions, assumptions, and purposes of tumor response criteria. Below, guidelines that are offered may lead to more uniform reporting of outcomes of clinical trials. Note that, although single investigational agents are discussed, the principles are the same for drug combinations, noninvestigational agents, or approaches that do not involve drugs.

Tumor response associated with the administration of anticancer agents can be evaluated for at least three important purposes that are conceptually distinct:

- Tumor response as a prospective end point in early clinical trials. In this situation, objective tumor response is employed to determine whether the agent/regimen demonstrates sufficiently encouraging results to warrant further testing. These trials are typically phase II trials of investigational agents/regimens (see section 1.2), and it is for use in this precise context that these guidelines have been developed.
- Tumor response as a prospective end point in more definitive clinical trials designed to provide an estimate of benefit for a specific cohort of patients. These trials are often randomized comparative trials or single-arm comparisons of combinations of agents with historical control subjects. In this setting, objective tumor response is used as a surrogate end point for other measures of clinical benefit, including time to event (death or disease progression) and symptom control (see section 1.3).
- Tumor response as a guide for the clinician and patient or study subject in decisions about continuation of current therapy. This purpose is applicable both to clinical trials and to routine practice (see section 1.1), but use in the context of decisions regarding continuation of therapy is not the primary focus of this document.

However, in day-to-day usage, the distinction among these uses of the term "tumor response" can easily be missed, unless an effort is made to be explicit. When these differences are ignored, inappropriate methodology may be used and incorrect conclusions may result.

1.1. Response Outcomes in Daily Clinical Practice of Oncology

The evaluation of tumor response in the daily clinical practice of oncology may not be performed according to predefined criteria. It may, rather, be based on a subjective medical judgment that results from clinical and laboratory data that are used to assess the treatment benefit for the patient. The defined criteria

developed further in this document are not necessarily applicable or complete in such a context. It might be appropriate to make a distinction between "clinical improvement" and "objective tumor response" in routine patient management outside the context of a clinical trial.

1.2. Response Outcomes in Uncontrolled Trials as a Guide to Further Testing of a New Therapy

"Observed response rate" is often employed in single-arm studies as a "screen" for new anticancer agents that warrant further testing. Related outcomes, such as response duration or proportion of patients with complete responses, are sometimes employed in a similar fashion. The utilization of a response rate in this way is not encumbered by an implied assumption about the therapeutic benefit of such responses but rather implies some degree of biologic antitumor activity of the investigated agent.

For certain types of agents (i.e., cytotoxic drugs and hormones), experience has demonstrated that objective antitumor responses observed at a rate higher than would have been expected to occur spontaneously can be useful in selecting anticancer agents for further study. Some agents selected in this way have eventually proven to be clinically useful. Furthermore, criteria for "screening" new agents in this way can be modified by accumulated experience and eventually validated in terms of the efficiency by which agents so screened are shown to be of clinical value by later, more definitive, trials.

In most circumstances, however, a new agent achieving a response rate determined *a priori* to be sufficiently interesting to warrant further testing may not prove to be an effective treatment for the studied disease in subsequent randomized phase III trials. Random variables and selection biases, both known and unknown, can have an overwhelming effect in small, uncontrolled trials. These trials are an efficient and economic step for initial evaluation of the activity of a new agent or combination in a given disease setting. However, many such trials are performed, and the proportion that will provide false-positive results is necessarily substantial. In many circumstances, it would be appropriate to perform a second small confirmatory trial before initiating large resource-intensive phase III trials.

Sometimes, several new therapeutic approaches are studied in a randomized phase II trial. The purpose of randomization in this setting, as in phase III studies, is to minimize the impact of random imbalances in prognostic variables. However, randomized phase II studies are, by definition, not intended to provide an adequately powered comparison between arms (regimens). Rather, the goal is simply to identify one or more arms for further testing, and the sample size is chosen so to provide reasonable confidence that a truly inferior arm is not likely to be selected. Therefore, reporting the results of such randomized phase II trials should not imply statistical comparisons between treatment arms.

1.3. Response Outcomes in Clinical Trials as a Surrogate for Palliative Effect

1.3.1. Use in nonrandomized clinical trials. The only circumstance in which objective responses in a nonrandomized trial can permit a tentative assumption of a palliative effect (i.e., beyond a purely clinical measure of benefit) is when there is an actual or implied comparison with historical series of similar patients. This assumption is strongest when the prospectively

determined statistical analysis plan provides for matching of relevant prognostic variables between case subjects and a defined series of control subjects. Otherwise, there must be, at the very least, prospectively determined statistical criteria that provide a very strong justification for assumptions about the response rate that would have been expected in the appropriate "control" population (untreated or treated with conventional therapy, as fits the clinical setting). However, even under these circumstances, a high rate of observed objective response does not constitute proof or confirmation of clinical therapeutic benefit. Because of unavoidable and nonquantifiable biases inherent in nonrandomized trials, proof of benefit still requires eventual confirmation in a prospectively randomized, controlled trial of adequate size. The appropriate end points of therapeutic benefit for such a trial are survival, progression-free survival, or symptom control (including quality of life).

1.3.2. Use in randomized trials. Even in the context of prospectively randomized phase III comparative trials, "observed response rate" should not be the sole, or major, end point. The trial should be large enough that differences in response rate can be validated by association with more definitive end points reflecting therapeutic benefit, such as survival, progression-free survival, reduction in symptoms, or improvement (or maintenance) of quality of life.

2. Measurability of Tumor Lesions at Baseline

2.1. Definitions

At baseline, tumor lesions will be categorized as follows: measurable (lesions that can be accurately measured in at least one dimension [longest diameter to be recorded] as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan [see section 2.2]) or nonmeasurable (all other lesions, including small lesions [longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan] and truly nonmeasurable lesions).

The term "evaluable" in reference to measurability is not recommended and will not be used because it does not provide additional meaning or accuracy.

All measurements should be recorded in metric notation by use of a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of treatment.

Lesions considered to be truly nonmeasurable include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

(Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable, and the conditions under which such lesions should be considered must be defined in the protocol when appropriate.)

2.2. Specifications by Methods of Measurements

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

2.2.1. Clinical examination. Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography—including a ruler to estimate the size of the lesion—is recommended.

2.2.2. Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable. More details concerning the use of this method of assessment for objective tumor response evaluation are provided in Appendix I.

2.2.3. CT and MRI. CT and MRI are the best currently available and most reproducible methods for measuring target lesions selected for response assessment. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed by use of a 5-mm contiguous reconstruction algorithm; this specification applies to the tumors of the chest, abdomen, and pelvis, while head and neck tumors and those of the extremities usually require specific protocols. More details concerning the use of these methods of assessment for objective tumor response evaluation are provided in Appendix I.

2.2.4. Ultrasound. When the primary end point of the study is objective response evaluation, ultrasound should not be used to measure tumor lesions that are clinically not easily accessible. It may be used as a possible alternative to clinical measurements for superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination. Justifications for not using ultrasound to measure tumor lesions for objective response evaluation are provided in Appendix I.

2.2.5. Endoscopy and laparoscopy. The utilization of these techniques for objective tumor evaluation has not yet been fully or widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may be available only in some centers. Therefore, utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete histopathologic response when biopsy specimens are obtained.

2.2.6. Tumor markers. Tumor markers alone cannot be used to assess response. However, if markers are initially above the upper normal limit, they must return to normal levels for a patient to be considered in complete clinical response when all tumor lesions have disappeared. Specific additional criteria for standardized usage of prostate-specific antigen and CA (cancer antigen) 125 response in support of clinical trials are being validated.

2.2.7. Cytology and histology. Cytologic and histologic techniques can be used to differentiate between partial response and complete response in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). New techniques to better establish objective tumor

response will be integrated into these criteria when they are fully validated to be used in the context of tumor response evaluation.

3. Tumor Response Evaluation

3.1. Baseline Evaluation

3.1.1. Assessment of overall tumor burden and measurable disease. To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary end point. Measurable disease is defined by the presence of at least one measurable lesion (as defined in section 2.1). If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

3.1.2. Baseline documentation of "target" and "nontarget" lesions. All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter. The baseline sum longest diameter will be used as the reference by which to characterize the objective tumor response.

All other lesions (or sites of disease) should be identified as nontarget lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

3.2. Response Criteria

3.2.1. Evaluation of target lesions. This section provides the definitions of the criteria used to determine objective tumor response for target lesions. The criteria have been adapted from the original *WHO Handbook* (3), taking into account the measurement of the longest diameter only for all target lesions: complete response—the disappearance of all target lesions; partial response—at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter; progressive disease—at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions; stable disease—neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

3.2.2. Evaluation of nontarget lesions. This section provides the definitions of the criteria used to determine the objective tumor response for nontarget lesions: complete response—the disappearance of all nontarget lesions and normalization of tumor marker level; incomplete response/stable disease—the persistence of one or more nontarget lesion(s) and/or the maintenance of tumor marker level above the normal limits; and progressive disease—the appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions (1).

(Note: Although a clear progression of "nontarget" lesions only is exceptional, in such circumstances, the opinion of the

treating physician should prevail and the progression status should be confirmed later by the review panel [or study chair].

3.2.3. Evaluation of best overall response. The best overall response is the best response recorded from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see section 3.3.1). Table 1 provides overall responses for all possible combinations of tumor responses in target and nontarget lesions with or without the appearance of new lesions.

(Notes:

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective disease progression, even after discontinuation of treatment.
- Conditions that may define early progression, early death, and inevaluability are study specific and should be clearly defined in each protocol (depending on treatment duration and treatment periodicity).
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine-needle aspiration/biopsy) before confirming the complete response status.)

3.2.4. Frequency of tumor re-evaluation. Frequency of tumor re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up of every other cycle (i.e., 6–8 weeks) seems a reasonable norm. Smaller or greater time intervals than these could be justified in specific regimens or circumstances.

After the end of the treatment, the need for repetitive tumor evaluations depends on whether the phase II trial has, as a goal, the response rate or the time to an event (disease progression/death). If time to an event is the main end point of the study, then routine re-evaluation is warranted of those patients who went off the study for reasons other than the expected event at frequencies to be determined by the protocol. Intervals between evaluations twice as long as on study are often used, but no strict rule can be made.

Table 1. Overall responses for all possible combinations of tumor responses in target and nontarget lesions with or without the appearance of new lesions*

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

*CR = complete response; PR = partial response; SD = stable disease; and PD = progressive disease. See text for more details.

3.3. Confirmatory Measurement/Duration of Response

3.3.1. Confirmation. The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. This aspect of response evaluation is particularly important in nonrandomized trials where response is the primary end point. In this setting, to be assigned a status of partial response or complete response, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

In the case of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval (in general, not less than 6–8 weeks) that is defined in the study protocol (see section 3.3.3).

(Note: Repeat studies to confirm changes in tumor size may not always be feasible or may not be part of the standard practice in protocols where progression-free survival and overall survival are the key end points. In such cases, patients will not have "confirmed response." This distinction should be made clear when reporting the outcome of such studies.)

3.3.2. Duration of overall response. The duration of overall response is measured from the time that measurement criteria are met for complete response or partial response (whichever status is recorded first) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The duration of overall complete response is measured from the time measurement criteria are first met for complete response until the first date that recurrent disease is objectively documented.

3.3.3. Duration of stable disease. Stable disease is measured from the start of the treatment until the criteria for disease progression is met (taking as reference the smallest measurements recorded since the treatment started). The clinical relevance of the duration of stable disease varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of stable disease. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

(Note: The duration of response or stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency that should take into account many parameters, including disease types and stages, treatment periodicity, and standard practice. However, these limitations to the precision of the measured end point should be taken into account if comparisons among trials are to be made.)

3.4. Progression-Free Survival/Time to Progression

This document focuses primarily on the use of objective response end points. In some circumstances (e.g., brain tumors or investigation of noncytoreductive anticancer agents), response evaluation may not be the optimal method to assess the potential anticancer activity of new agents/regimens. In such cases, progression-free survival/time to progression can be considered valuable alternatives to provide an initial estimate of biologic effect of new agents that may work by a noncytotoxic mecha-

nism. It is clear though that, in an uncontrolled trial proposing to utilize progression-free survival/time to progression, it will be necessary to document with care the basis for estimating what magnitude of progression-free survival/time to progression would be expected in the absence of a treatment effect. It is also recommended that the analysis be quite conservative in recognition of the likelihood of confounding biases, e.g., with regard to selection and ascertainment. Uncontrolled trials using progression-free survival or time to progression as a primary end point should be considered on a case-by-case basis, and the methodology to be applied should be thoroughly described in the protocol.

4. Response Review

For trials where the response rate is the primary end point, it is strongly recommended that all responses be reviewed by an expert or experts independent of the study at the study's completion. Simultaneous review of the patients' files and radiologic images is the best approach.

(Note: When a review of the radiologic images is to take place, it is also recommended that images be free of marks that might obscure the lesions or bias the evaluation of the reviewer[s].)

5. Reporting of Results

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). (Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.)

All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4–9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4–9 will be protocol specific.

All conclusions should be based on all eligible patients.

Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should be provided.

6. Response Evaluation in Randomized Phase III Trials

Response evaluation in phase III trials may be an indicator of the relative antitumor activity of the treatments evaluated but may usually not solely predict the real therapeutic benefit for the population studied. If objective response is selected as a primary end point for a phase III study (only in circumstances where a direct relationship between objective tumor response and a real therapeutic benefit can be unambiguously demonstrated for the population studied), the same criteria as those applicable to phase II trials (RECIST guidelines) should be used.

On the other hand, some of the guidelines presented in this special article might not be required in trials, such as phase III trials, in which objective response is *not* the primary end point. For example, in such trials, it might not be necessary to measure as many as 10 target lesions or to confirm response with a follow-up assessment after 4 weeks or more. Protocols should be written clearly with respect to planned response evaluation and whether confirmation is required so as to avoid *post-hoc* decisions affecting patient evaluability.

APPENDIX I. SPECIFICATIONS FOR RADIOLOGIC IMAGING

These notes are recommendations for use in clinical studies and, as such, these protocols for computed tomography (CT) and magnetic resonance imaging (MRI) scanning may differ from those employed in clinical practice at various institutions. The use of standardized protocols allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

Specific Notes

- For chest x-ray, not only should the film be performed in full inspiration in the posteroanterior projection, but also the film to tube distance should remain constant between examinations. However, patients in trials with advanced disease may not be well enough to fulfill these criteria, and such situations should be reported together with the measurements.

Lesions bordering the thoracic wall are not suitable for measurements by chest x-ray, since a slight change in position of the patients can cause considerable differences in the plane in which the lesion is projected and may appear to cause a change that is actually an artifact. These lesions should be followed by a CT or an MRI. Similarly, lesions bordering or involving the mediastinum should be documented on CT or MRI.

- CT scans of the thorax, abdomen, and pelvis should be contiguous throughout the anatomic region of interest. As a rule of thumb, the minimum size of the lesion should be no less than double the slice thickness. Lesions smaller than this are subject to substantial "partial volume" effects (i.e., size is underestimated because of the distance of the cut from the longest diameter; such a lesion may appear to have responded or progressed on subsequent examinations, when, in fact, they remain the same size [Fig. 1]). This minimum lesion size for a given slice thickness at baseline ensures that any lesion appearing smaller on subsequent examinations will truly be decreasing in size. The longest diameter of each target lesion should be selected in the axial plane only.

The type of CT scanner is important regarding the slice thickness and minimum-sized lesion. For spiral (helical) CT scanners, the minimum size of any given lesion at baseline may be 10 mm, provided the images are reconstructed contiguously at 5-mm intervals. For conventional CT scanners, the minimum-sized lesion should be 20 mm by use of a contiguous slice thickness of 10 mm.

The fundamental difference between spiral and conventional CT is that conventional CT acquires the information only for the particular slice thickness scanned, which is then expressed as a two-dimensional representation of that thickness or volume as a gray scale image. The next slice thickness needs to be scanned before it can be imaged and so on. Spiral CT acquires the data for the whole volume imaged, typically the whole of the thorax or upper abdomen in a single breath hold of about 20–30 seconds. To view the images, a suitable reconstruction algorithm is selected, by the machine, so the data are appropriately imaged. As suggested above, for spiral CT, 5-mm reconstructions can be made, thereby allowing a minimum-sized lesion of 10 mm.

Spiral CT is now the standard in most hospitals involved in cancer

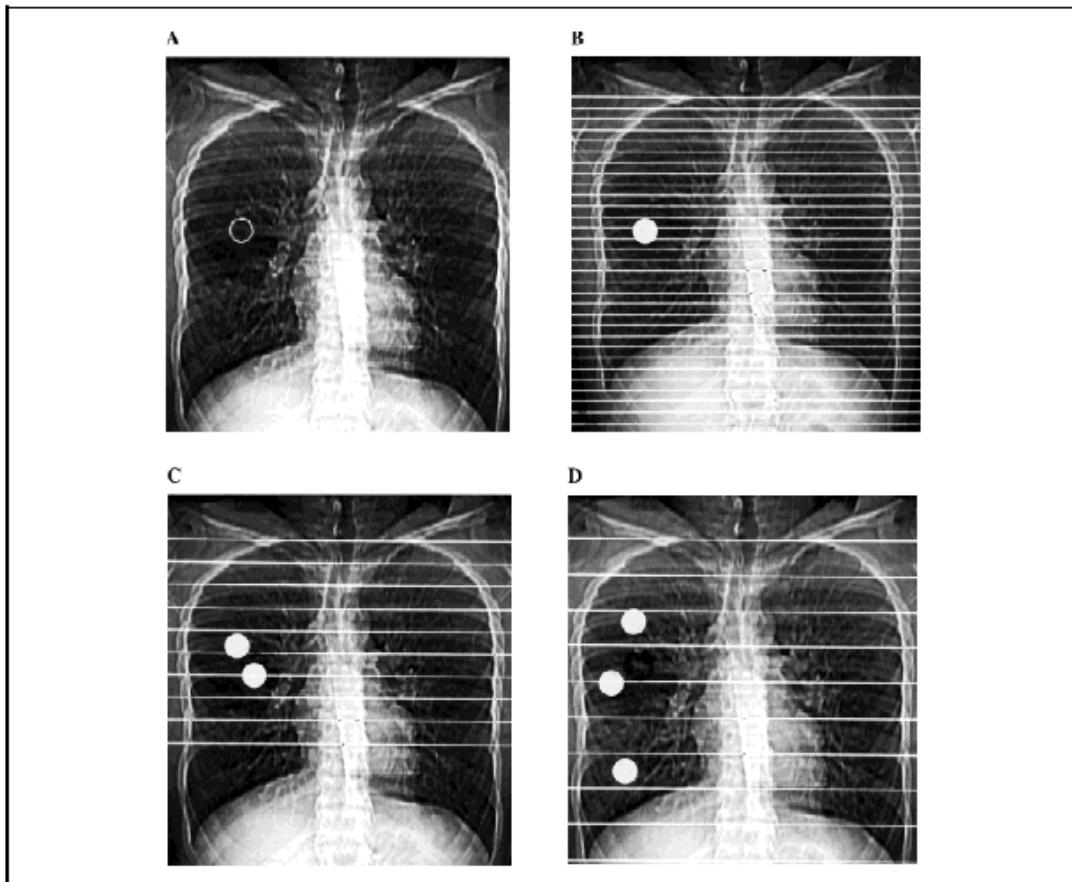


Fig 1. A) Computed tomography (CT) "scannogram" of the thorax with a simulated 20-mm lesion in the right mid-zone. B) CT "scannogram" of the thorax with contiguous slices of 10-mm thickness. Each volume within the slice thickness is scanned, and the average attenuation coefficient (i.e., density of multiple small cubes [voxels]) is represented spatially in two dimensions (pixels) as a cross-sectional image on a gray scale. It is important to note each line on the figure is a spatial representation of the average density for the structures that pass through that slice thickness, and the line does not represent a thin "cut" through it at that level. Therefore, a lesion of at least 20 mm will appear about its true diameter on at least one image because sufficient volume of the lesion is present

so as not to average it down substantially. C) CT scannogram performed at 15-mm intervals. Depending on how much of the tumor is within the slice thickness, the average density may be substantially underestimated, as in the upper of the two lesions, or it may approximate the true tumor diameter, lower lesion. This is an oversimplification of the process but illustrates the point without going into the physics of CT reconstruction. D) CT scannogram performed at 24-mm intervals and of 10-mm thickness. The lesion may be imaged through its diameter, it may be partially imaged, or it may not be imaged at all. This is the equivalent of imaging a very small lesion and trying to determine whether its true diameter has changed from one examination to the next.

management in the United States, Europe, and Japan, so the above comments related to spiral CT are pertinent. However, some institutions involved in clinical trials will have conventional CT, but the number of these scanners will decline as they are replaced by spiral CT.

Other body parts, where CT scans are of different slice thickness (such as the neck, which is typically 5-mm thickness), or in the young pediatric population, where the slice thickness may be different, the minimum-sized lesion allowable for measurability of the lesion may be different. However, it should be double the slice thickness. The slice thickness and the minimum-sized lesion should be specified in the study protocol.

In patients in whom the abdomen and pelvis have been imaged, oral contrast agents should be given to accentuate the bowel against other

soft-tissue masses. This procedure is almost universally undertaken on a routine basis.

Intravenous contrast agents should also be given, unless contraindicated for medical reasons such as allergy. This is to accentuate vascular structures from adjacent lymph node masses and to help enhance liver and other visceral metastases. Although, in clinical practice, its use may add little, in the context of a clinical study where objective response rate based on measurable disease is the end point, unless an intravenous contrast agent is given, a substantial number of otherwise measurable lesions will not be measurable. The use of intravenous contrast agents may sometimes seem unnecessary to monitor the evolution of specific disease sites (e.g., in patients in whom the disease is apparently restricted to the periphery of the lungs). However, the aim of a clinical

study is to ensure that lesions are truly resolving, and there is no evidence of new disease at other sites scanned (e.g., small metastases in the liver) that may be more easily demonstrated with the use of intravenous contrast agent that should, therefore, also be considered in this context.

The method of administration of intravenous contrast agents is variable. Rather than try to institute rigid rules regarding methods for administering contrast agents and the volume injected, it is appropriate to suggest that an adequate volume of a suitable contrast agent should be

given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient.

All images from each examination should be included and not "selected" images of the apparent lesion. This distinction is intended to ensure that, if a review is undertaken, the reviewer can satisfy himself/herself that no other abnormalities coexist. All window settings should be included, particularly in the thorax, where the lung and soft-tissue windows should be considered.

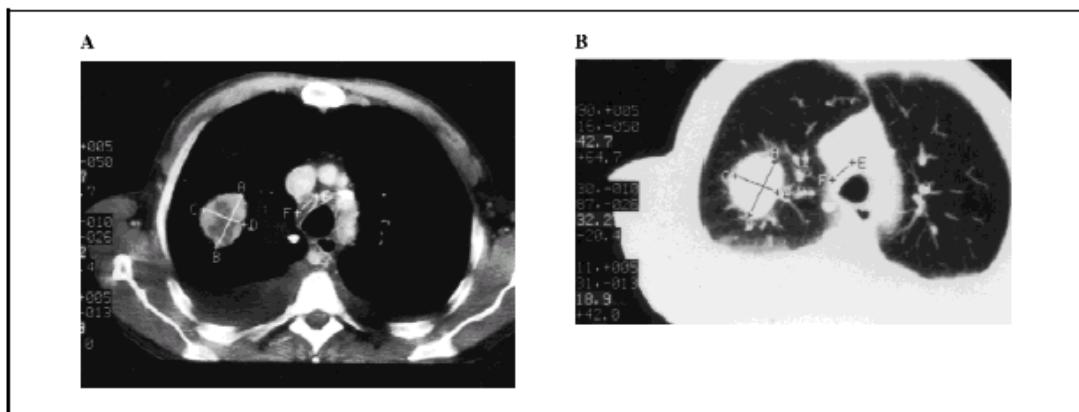


Fig 2. A) Computed tomography (CT) scan of the thorax at the level of the carina on "soft-tissue" windows. Two lesions have been measured with calipers. The intraparenchymal lesion has been measured bidimensionally, using the greatest diameter and the greatest perpendicular distance. Unidimensional measurements require only the greatest diameter to be measured. The anterior-carinal lymph node has been measured using unidimensional criteria. B) The same image as

above imaged on "lung" windows, with the calipers remaining as they were for the soft-tissue measurements. The size of the lung lesion appears different. The anterior-carinal lymph node cannot be measured on these windows. The same windows should be used on subsequent examinations to measure any lesions. Some favor soft-tissue windows, so paratracheal, anterior, and subcarinal lesions may be followed on the same settings as intraparenchymal lesions.

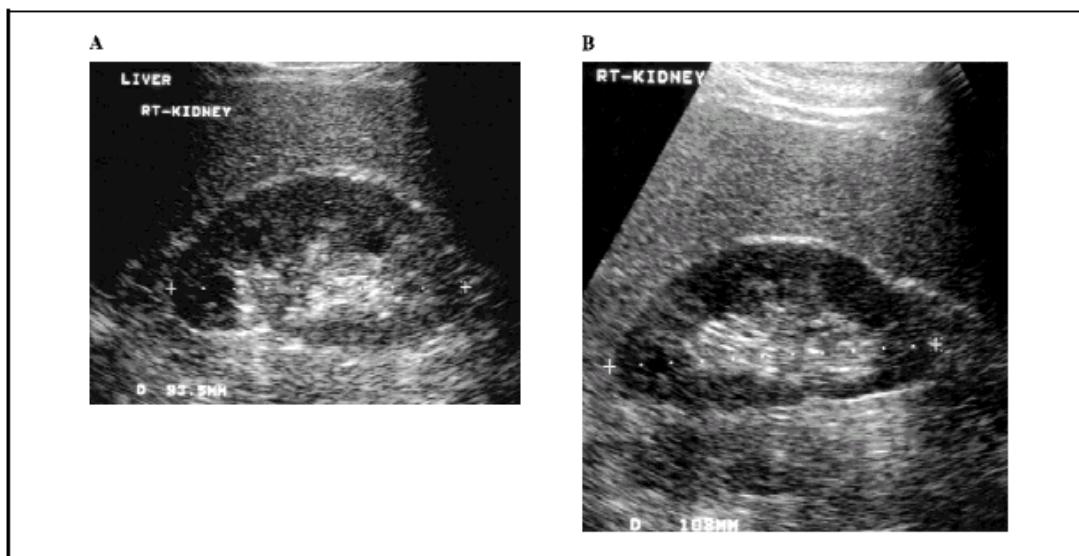


Fig 3. A) Ultrasound scan of a normal structure, the right kidney, which has been measured as 93 mm with the use of callipers. B) Ultrasound scan of the same kidney taken a few minutes later when it measures 108 mm. It appears to have increased in size by 16%. The difference is due to foreshortening of the kidney

in panel A. The lack of anatomic landmarks makes accurate measurement in the same plane on subsequent examinations difficult. One has to hope that the measurements given on the hard copy film are a true and accurate reflection of events.

Lesions should be measured on the same window setting on each examination. It is not acceptable to measure a lesion on lung windows on one examination and on soft-tissue settings on the next (Fig. 2). In the lung, it does not really matter whether lung or soft-tissue windows are used for intraparenchymal lesions, provided a thorough assessment of nodal and parenchymal disease has been undertaken and the target lesions are measured as appropriate by use of the same window settings for repeated examinations throughout the study.

• Use of MRI is a complex issue. MRI is entirely acceptable and capable of providing images in different anatomic planes. It is, therefore, important that, when MRI is used, lesions must be measured in the same anatomic plane by use of the same imaging sequences on subsequent examinations. MRI scanners vary in the images produced. Some of the factors involved include the magnet strength (high-field magnets require shorter scan times, typically 2–5 minutes), the coil design, and patient cooperation. Wherever possible, the same scanner should be used. For instance, the images provided by a 1.5-Tesla scanner will differ from those provided by a 0.5-Tesla scanner. Although comparisons can be made between images from different scanners, such comparisons are not ideal. Moreover, many patients with advanced malignancy are in pain, so their ability to remain still for the duration of a scan sequence—on the order of 2–5 minutes—is limited. Any movement during the scan time leads to motion artifacts and degradation of image quality, so that the examination will probably be useless. For these reasons, CT is, at this point in time, the imaging modality of choice.

• Ultrasound examinations should not be used in clinical trials to measure tumor regression or progression of lesions that are not superficial because the examination is necessarily subjective. Entire examinations cannot be reproduced for independent review at a later date, and it must be assumed, whether or not it is the case, that the hard-copy films available represent a true and accurate reflection of events (Fig. 3). Furthermore, if, for example, the only measurable lesion is in the para-aortic region of the abdomen and if gas in the bowel overlies the lesion, the lesion will not be detected because the ultrasound beam cannot penetrate the gas. Accordingly, the disease staging (or restaging for treatment evaluation) for this patient will not be accurate.

The same imaging modality must be used throughout the study to measure disease. Different imaging techniques have differing sensitivities, so any given lesion may have different dimensions at any given time if measured with different modalities. It is, therefore, not acceptable to interchange different modalities throughout a trial and use these measurements. It must be the same technique throughout.

It is desirable to try to standardize the imaging modalities without adding undue constraints so that patients are not unnecessarily excluded from clinical trials.

APPENDIX II. RELATIONSHIP BETWEEN CHANGE IN DIAMETER, PRODUCT, AND VOLUME

Appendix II, Table 2. Relationship between change in diameter, product, and volume*

	Diameter, $2r$	Product, $(2r)^2$	Volume, $4/3\pi r^3$
Response	Decrease	Decrease	Decrease
	30%	50%	65%
Disease progression	50%	75%	87%
	Increase	Increase	Increase
	12%	25%	40%
	20%	44%	73%
	25%	56%	95%
	30%	69%	120%

*Shaded areas represent the response evaluation criteria in solid tumors (diameter) and World Health Organization (product) criteria for change in tumor size to meet response and disease progression definitions.

APPENDIX III. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) WORKING GROUP AND SPECIAL ACKNOWLEDGMENTS

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APPENDIX IV. PARTICIPANTS IN THE OCTOBER 1998 WORKSHOP TO DEVELOP THE FINAL RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) DOCUMENT AND FURTHER ACKNOWLEDGMENTS

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APPENDIX V. RETROSPECTIVE COMPARISON OF RESPONSE/DISEASE PROGRESSION RATES OBTAINED WITH THE WORLD HEALTH ORGANIZATION (WHO)/SOUTHWEST ONCOLOGY GROUP CRITERIA AND THE NEW RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) CRITERIA

To evaluate the hypothesis by which unidimensional measurement of tumor lesions may substitute for the usual bidimensional approach, a number of retrospective analyses have been undertaken. The results of these analysis are given below in this section.

1. Comparison of Response and Disease Progression Rates by Use of WHO (or Modified WHO) or RECIST Methods

1.1. Trials Evaluated

No specific selection criteria were employed except that trial data had to include serial (repeated) records of tumor measurements. Several

groups evaluated their own data on one or more such studies (National Institute of Canada Clinical Trials Group, Kingston, ON; U.S. National Cancer Institute, Bethesda, MD; and Rhone-Poulenc Rorer Pharmaceuticals Inc., Paris, France) or made data available for evaluation to the U.S. National Cancer Institute (Southwest Oncology Group and Bristol-Myers Squibb, Wallingford, CT)

1.2. Response Criteria Evaluated

Not all databases were assessed for all response outcomes. At the outset of this process, the most interest was in the assessment of complete plus partial response rate comparisons by both the WHO and new RECIST criteria. Once these data suggested no impact of using the new criteria on the response rate, several more databases were analyzed for the impact of the use of the new criteria not only on complete response plus partial response but also on stable disease and progressive disease rates (see Appendix V, Table 4) and on time to disease progression (see Appendix V, Table 5).

1.3. Methods of Comparison

For each patient in each study, baseline sums were calculated (sum of products of the two longest diameters in perpendicular dimensions for WHO and sum of longest diameters for RECIST). After each assessment, when new tumor measures were available, the sums were recalculated. Patients were assigned complete response, partial response, stable disease, and progressive disease as their "best" response on the basis of achieving the measurement criteria as indicated in Appendix V, Table 3. For both WHO and RECIST, a minimum interval of 4 weeks was required to consider complete response and partial response confirmed. Each patient could, therefore, be assigned a best response according to each of the two criteria. The overall response and disease progression rates could be calculated for the population studied for each trial or dataset examined.

(Note: For WHO progressive disease, as is the convention in most groups, an increase in sums of products was required, not an increase in only one lesion.)

1.4. Results

2. Evaluation of Time to Disease Progression

Time to disease progression was evaluated, comparing WHO criteria with RECIST in a dataset provided by the Southwest Oncology Group

Appendix V, Table 3. Definition of best response according to WHO or RECIST criteria*

Best response	WHO change in sum of products	RECIST change in sums longest diameters
CR	Disappearance; confirmed at 4 wks†	Disappearance; confirmed at 4 wks†
PR	50% decrease; confirmed at 4 wks†	30% decrease; confirmed at 4 wks†
SD	Neither PR nor PD criteria met	Neither PR nor PD criteria met
PD	25% increase; no CR, PR, or SD documented before increased disease	20% increase; no CR, PR, or SD documented before increased disease

*WHO = World Health Organization; RECIST = Response Evaluation Criteria in Solid Tumors; CR = complete response, PR = partial response, SD = stable disease, and PD = progressive disease.

†For the Bristol-Myers Squibb (Wallingford, CT) dataset, only unconfirmed CR and PR have been used to compare best response measured in one dimension (RECIST criteria) versus best response measured in two dimensions (WHO criteria). The computer flag identifying confirmed response in this dataset could not be used in the comparison for technical reasons.

Appendix V, Table 4. Comparison of RECIST (unidimensional) and WHO (bidimensional) criteria in the same patients recruited in 14 different trials*

Tumor site/type	Criteria	No. of patients evaluated	Best response					RR	PD rate
			CR	PR	SD	PD			
Breast†	WHO	48	4	22				54%	
	RECIST	48	4	22				54%	
Breast‡	WHO	172	4	36				23%	
	RECIST	172	4	40				26%	
Brain†	WHO	31	12	10				71%	
	RECIST	31	12	10				71%	
Melanoma†	WHO	190	9	37				24%	
	RECIST	190	9	34				23%	
Breast§	WHO	531	50	102				29%	
	RECIST	531	50	108				30%	
Colon§	WHO	1096	12	137				14%	
	RECIST	1096	12	133				13%	
Lung§	WHO	1197	60	317				32%	
	RECIST	1197	60	318				32%	
Ovary§	WHO	554	24	108				24%	
	RECIST	554	24	105				23%	
Lung†	WHO	24	0	4	16	4	17%	17%	
	RECIST	24	0	4	19	1	17%	4%	
Colon†	WHO	31	1	6	15	9	23%	29%	
	RECIST	31	1	5	16	9	21%	29%	
Sarcoma†	WHO	28	1	4	13	10	18%	36%	
	RECIST	28	1	5	17	5	21%	18%	
Ovary†	WHO	45	0	7	19	19	16%	42%	
	RECIST	45	0	6	21	18	13%	40%	
Breast	WHO	306	18	114	117	57	43%	19%	
	RECIST	306	18	108	124	56	41%	18%	
Breast	WHO	360	10	73	135	142	23%	39%	
	RECIST	361	10	70	139	142	22%	39%	
Total (all studies where tumor response was evaluated)	WHO	4613	205	977			25.6%		
	RECIST	4614	205	968			25.4%		
Total (all studies where PD as well as CR + PR were evaluated)	WHO	794			315	241		30.3%	
	RECIST	795			336	231		29%	

*WHO = World Health Organization (3); RECIST = Response Evaluation Criteria in Solid Tumors; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; and RR = response rate.

†Data from the National Cancer Institute of Canada Clinical Trials Group phase II and III trials.

‡Data from the National Cancer Institute, United States phase III trial.

§Data from Bristol-Myers Squibb (Wallingford, CT) phase II and III trials.

||Data from Rhone-Poulenc Rorer Pharmaceuticals Inc., (Paris, France) phase III trials (note: one patient in this database had unidimensional measured lesions only and could not be evaluated with the WHO criteria).

Appendix V, Table 5. Proportions of patients with disease progression by different assessment methods*

	No. of patients	%
Total No. of progressors	234	100
Progress by appearance of new lesions†	118	50
Progress by increase in pre-existing measurable disease	116	50
Same date of disease progression by WHO and RECIST criteria	215	91.9
Different date of disease progression	19	8.1
Earlier PD with WHO criterion	17	7.3
Earlier PD with unidimensional criterion	2	0.9

*PD = progressive disease; WHO = World Health Organization; and RECIST = Response Evaluation Criteria in Solid Tumors.

†Also includes a few patients with PD because of marked increase of nonmeasurable disease.

Appendix V, Table 6. Magnitude of time to disease progression disagreements when differences existed*

	No. of patients	% (of 234, see above)
No. of progressors with differing progression dates	19	8.1
8–9 wks' difference	3	1.3
12 wks' difference	1	0.4
24–31 wks' difference†	2	0.9
Difference uncertain due to censoring of either WHO or RECIST progression time‡	13	5.6

*WHO = World Health Organization; RECIST = Response Evaluation Criteria in Solid Tumors.

†For one patient, progression by RECIST (one-dimension) criteria preceded that by WHO criteria by 24 weeks due primarily to one-dimensional growth. For a second patient, with a colon tumor that increased in cross-section by 25%, then regressed completely, and then recurred, progression by WHO criteria preceded that by RECIST criteria by 31 weeks.

‡As indicated in Appendix V, Table 6, 13 of the 19 patients had uncertain disease progression time differences when comparing RECIST and WHO criteria. In these patients, the RECIST progression criteria were not met by the time that disease progression by Southwest Oncology Group (SWOG) criteria (5) had occurred (50% increase or a 10 cm² increase in tumor cross-section). Notably, six of these patients had the same disease progression dates determined by use of WHO (25% bidimensional increase) and SWOG (50% bidimensional increase) criteria. Since 20% unidimensional increase (RECIST) is equivalent to approximately 44% bidimensional increase, it is likely, although not certain, that disease progression by RECIST unidimensional criteria would have occurred soon after disease progression by SWOG and WHO criteria. For three patients, the difference between the WHO and SWOG 50% bidimensional increase was 10–12 weeks. Again, it is likely, although it cannot be proven, that RECIST criteria would have been met soon after. The remaining four of the 13 patients where difference between WHO and RECIST progression times are uncertain were categorized as progressive disease following SWOG's criteria (5) because of an increase of the tumor surface of greater than or equal to 10 cm². For these patients, the magnitude of the difference is entirely uncertain.

(SWOG). Since SWOG criteria (5) for disease progression is a 50% increase in the sum of the products, or new disease, or an absolute increase of 10 cm² in the sum of the products, this dataset provided the means of assessing the impact of time to disease progression differences between a 25% increase in the sum of the products and a 20% increase in the sum of the longest diameters (equivalent to approximately a 44% increase in the product sum).

2.1. Dataset Evaluated

The dataset includes 234 patients with progressive disease as defined by the SWOG (5). All patients had baseline measurable disease followed by the same technique(s) until disease progression. The tumor types included were melanoma and colorectal, lung, and breast cancers.

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NOTE

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APPENDIX 4: EORTC QLQ-30 QUESTIONNAIRE

EO RTC Q LQ -C30 (version 3)				
We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.				
Please fill in your initials: Your birthdate (Day, Month, Year): Today's date (Day, Month, Year):				
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	Not at all	A little	Quite a bit	Very much
2. Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3. Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week:				
6. Were you limited in doing either your work or other daily activities?	Not at All	A little	Quite a bit	Very much
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at all	A little	Quite a bit	Very much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 Very poor	2	3	4	5	6	7 Excellent
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30. How would you rate your overall quality of life during the past week?

1 Very poor	2	3	4	5	6	7 Excellent
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APPENDIX 5: EORTC QLQ-BR23 QUESTIONNAIRE

EORTC QLQ-BR23				
Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week:				
During the past week:	Not at all	A little	Quite a bit	Very much
1. Did you have a dry mouth?	1	2	3	4
2. Did food and drink taste different than usual?	1	2	3	4
3. Were your eyes painful, irritated or watery?	1	2	3	4
4. Have you lost any hair?	1	2	3	4
5. Answer this question only if you had any hair loss: Were you upset by the loss of hair?	1	2	3	4
6. Did you feel ill or unwell?	1	2	3	4
7. Did you have hot flushes?	1	2	3	4
8. Did you have headaches?	1	2	3	4
9. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
10. Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
11. Did you find it difficult to look at yourself naked?	1	2	3	4
12. Have you been dissatisfied with your body?	1	2	3	4
13. Were you worried about your health in the future?	1	2	3	4
During the past four weeks:	Not at all	A little	Quite a bit	Very much
14. To what extent were you interested in sex?	1	2	3	4
15. To what extent were you sexually active? (with or without intercourse)	1	2	3	4
16. Answer this question only if you have been sexually active. To what extent was sex enjoyable for you?	1	2	3	4

Please go on to the next page

During the past week:	Not at all	A little	Quite a bit	Very much
17. Did you have any pain in your arm or shoulder?	1	2	3	4
18. Did you have a swollen arm or hand?	1	2	3	4
19. Was it difficult to raise your arm or to move it sideways?	1	2	3	4
20. Have you had any pain in the area of your affected breast?	1	2	3	4
21. Was the area of your affected breast swollen?	1	2	3	4
22. Was the area of your affected breast oversensitive?	1	2	3	4
23. Have you had skin problems on or in the area of your affected breast (e.g. itchy, dry, flaky)?	1	2	3	4

SPECIMEN

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APPENDIX 6: EQ-5D QUESTIONNAIRE

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

Self-Care

- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

Usual Activities (e.g. work, study, housework, family or leisure activities)

- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

Pain/Discomfort

- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

Anxiety/Depression

- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own
health state
today

Best
imaginable
health state



Worst
imaginable
health state

APPENDIX 7: CAPECITABINE PRODUCT INFORMATION



XELODA® (capecitabine) TABLETS

DESCRIPTION: XELODA (capecitabine) is a fluoropyrimidine carbamate with antineoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is converted to 5-fluorouracil. The chemical name for capecitabine is 5'-deoxy-5-fluoro-N-[(pentoxycarbonyl)-cytidine and has a molecular weight of 359.35. Capecitabine has the following structural formula:



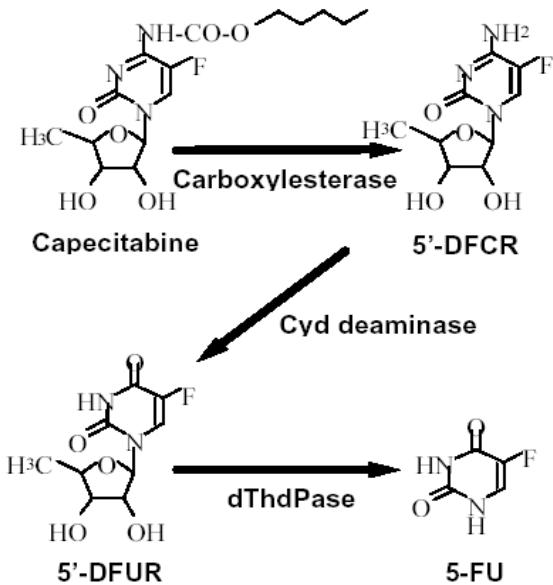
Capecitabine is a white to off-white crystalline powder with an aqueous solubility of 26 mg/mL at 20°C.

XELODA is supplied as biconvex, oblong film-coated tablets for oral administration. Each light peach-colored tablet contains 150 mg capecitabine and each peach-colored tablet contains 500 mg capecitabine. The inactive ingredients in XELODA include: anhydrous lactose, croscarmellose sodium, hydroxypropyl methylcellulose, microcrystalline cellulose, magnesium stearate and purified water. The peach or light peach film coating contains hydroxypropyl methylcellulose, talc, titanium dioxide, and synthetic yellow and red iron oxides.

CLINICAL PHARMACOLOGY: Capecitabine is relatively non-cytotoxic in vitro. This drug is enzymatically converted to 5-fluorouracil (5-FU) in vivo.

Bioactivation: Capecitabine is readily absorbed from the gastrointestinal tract. In the liver, a 60 kDa carboxyesterase hydrolyzes much of the compound to 5'-deoxy-5-fluorocytidine (5'-DFCR). Cytidine deaminase, an enzyme found in most tissues, including tumors, subsequently converts 5'-DFCR to 5'-deoxy-5-fluorouridine (5'-DFUR). The enzyme, thymidine phosphorylase (dTThdPase), then hydrolyzes 5'-DFUR to the active drug 5-FU. Many tissues throughout the body express thymidine phosphorylase. Some human carcinomas express this enzyme in higher concentrations than surrounding normal tissues.

Metabolic Pathway of capecitabine to 5-FU



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XELODA® (capecitabine)

Mechanism of Action: Both normal and tumor cells metabolize 5-FU to 5-fluoro-2-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). These metabolites cause cell injury by two different mechanisms. First, FdUMP and the folate cofactor, N5,10-methylenetetrahydrofolate, bind to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate from

uracil. Thymidylate is the necessary precursor of thymidine triphosphate, which is essential for the synthesis of DNA, so that a deficiency of this compound can inhibit cell division. Second, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA processing and protein synthesis.

Pharmacokinetics in Colorectal Tumors and Adjacent Healthy Tissue: Following oral administration of capecitabine 7 days before surgery in patients with colorectal cancer, the median ratio of 5-FU concentration in colorectal tumors to adjacent tissues was 2.9 (range from 0.9 to 8.0). These ratios have not been evaluated in breast cancer patients or compared to 5-FU infusion.

Human Pharmacokinetics: The pharmacokinetics of XELODA and its metabolites have been evaluated in about 200 cancer patients over a dosage range of 500 to 3500 mg/m²/day. Over this range, the pharmacokinetics of capecitabine and its metabolite, 5'-DFCR were dose proportional and did not change over time. The increases in the AUCs of 5'-DFUR and 5-FU, however, were greater than proportional to the increase in dose and the AUC of 5-FU was 34% higher on day 14 than on day 1. The elimination half-life of both parent capecitabine and 5-FU was about ½ of an hour. The inter-patient variability in the C_{max} and AUC of 5-FU was greater than 85%.

Absorption, Distribution, Metabolism and Excretion: Capecitabine reaches peak blood levels in about 1.5 hours (T_{max}) with peak 5-FU levels occurring slightly later, at 2 hours. Food reduced both the rate and extent of absorption of capecitabine with mean C_{max} and $AUC_{0-\infty}$ decreased by 60% and 35%, respectively. The C_{max} and $AUC_{0-\infty}$ of 5-FU were also reduced by food by 43% and 21%, respectively. Food delayed T_{max} of both parent and 5-FU by 1.5 hours (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Plasma protein binding of capecitabine and its metabolites is less than 60% and is not concentration-dependent. Capecitabine was primarily bound to human albumin (approximately 35%).

Capecitabine is extensively metabolized enzymatically to 5-FU. The enzyme dihydropyrimidine dehydrogenase hydrolyzes 5-FU, the product of capecitabine metabolism, to the much less toxic 5-fluoro-5,6-dihydro-fluorouracil (FUH₂). Dihydropyrimidinase cleaves the pyrimidine ring to yield 5-fluoro-ureido-propionic acid (FUPA). Finally, β-ureido-propionase cleaves FUPA to α-fluoro-β-alanine (FBAL) which is cleared in the urine.

Capecitabine and its metabolites are predominantly excreted in urine; 95.5% of administered capecitabine dose is recovered in urine. Fecal excretion is minimal (2.6%). The major metabolite excreted in urine is FBAL which represents 57% of the administered dose. About 3% of the administered dose is excreted in urine as unchanged drug.

Special Populations:

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

Hepatic Insufficiency: XELODA has been evaluated in 13 patients with mild to moderate hepatic dysfunction due to liver metastases defined by composite score including bilirubin, AST/ALT and alkaline phosphatase following a single 1255 mg/m² dose of capecitabine. Both $AUC_{0-\infty}$ and C_{max} of capecitabine increased by 60% in patients with hepatic dysfunction compared to patients with normal hepatic function (n=14). The $AUC_{0-\infty}$ and C_{max} of 5-FU was not affected. In patients with mild to moderate hepatic dysfunction due to liver metastases, caution should be exercised when XELODA is administered. The effect of severe hepatic dysfunction on XELODA is not known (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Insufficiency: No formal pharmacokinetic study was conducted in patients with renal impairment (see PRECAUTIONS).

Drug-Drug Interactions:

Drugs Metabolized by Cytochrome P450 Enzymes: In vitro enzymatic studies with human liver microsomes indicated that capecitabine and 5'-DFUR had no inhibitory effects on substrates of cytochrome P450 for the major isoenzymes such as 1A2, 2A6, 3A4, 2C9, 2C19, 2D6, and 2E1, suggesting a low likelihood of interactions with drugs metabolized by cytochrome P450 enzymes.

Antacid: When Maalox® (20 mL), an aluminum hydroxide- and magnesium hydroxide-containing antacid, was administered immediately after capecitabine (1250 mg/m², n=12 cancer patients), AUC and C_{max} increased by 16% and 35%, respectively, for capecitabine and by 18% and 22%, respectively, for 5'-DFCR. No effect was observed on the other three major metabolites (5'-DFUR, 5-FU, FBAL) of capecitabine.

XELODA has a low potential for pharmacokinetic interactions related to plasma protein binding.

CLINICAL STUDIES: In a phase I study with XELODA in patients with solid tumors, the maximum tolerated dose as a single agent was 3000 mg/m² when administered daily for 2 weeks, followed by a 1-week rest period. The dose-limiting toxicities were diarrhea and leukopenia.

Breast Carcinoma: The antitumor activity of XELODA was evaluated in an open-label single-arm trial conducted in 24 centers in the US and Canada. A total of 162 patients with stage IV breast cancer were enrolled. The primary endpoint was tumor response rate in patients with measurable disease, with response defined as a ≥50% decrease in sum of the products of the perpendicular diameters of bidimensionally measurable disease for at least 1 month. XELODA was administered at a daily dose of 2510 mg/m² for 2 weeks followed by a 1-week rest period and given as 3-week cycles. The baseline demographics and clinical characteristics for all patients (n=162) and those with measurable disease (n=135) are shown in the table below. Resistance was defined as progressive disease while on treatment, with or without an initial response, or relapse within 6 months of completing treatment with an anthracycline-containing adjuvant chemotherapy regimen.

Table 1. Baseline Demographics and Clinical Characteristics

	Patients With Measurable Disease (n=135)	All Patients (n=162)
Age (median, years)	55	56
Karnofsky PS	90	90
No. Disease Sites		
1-2	43 (32%)	60 (37%)
3-4	63 (46%)	69 (43%)
>5	29 (22%)	34 (21%)
Dominant Site of Disease		

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EFC6089 [XRP9881B/3001] - Larotaxel

21-Sep-2006
Final

Visceral ¹	101 (75%)	110 (68%)
Soft Tissue	30 (22%)	35 (22%)
Bone	4 (3%)	17 (10%)
Prior Chemotherapy		
Paclitaxel	135 (100%)	162 (100%)
Anthracycline ²	122 (90%)	147 (91%)
5-FU	110 (81%)	133 (82%)
Resistance to Paclitaxel	103 (76%)	124 (77%)
Resistance to an Anthracycline ²	55 (41%)	67 (41%)
Resistance to both Paclitaxel and an Anthracycline ²	43 (32%)	51 (31%)

¹Lung, pleura, liver, peritoneum

²Includes 2 patients treated with an anthracenedione

Antitumor responses for patients with disease resistant to both paclitaxel and an anthracycline are shown in the table below.

Table 2. Response Rates in Doubly-Resistant Patients

	Resistance to Both Paclitaxel and an Anthracycline (n=43)
CR	0
PR ¹	11
CR + PR ¹	11
Response Rate ¹ (95% C.I.)	25.6% (13.5, 41.2)
Duration of Response, ¹ Median in days ² (Range)	154 (63 to 233)

¹Includes 2 patients treated with an anthracenedione

²From date of first response

For the subgroup of 43 patients who were doubly resistant, the median time to progression was 102 days and the median survival was 255 days. The objective response rate in this population was supported by a response rate of 18.5% (1 CR, 24 PRs) in the overall population of 135 patients with measurable disease, who were less resistant to chemotherapy (see Table 1). The median time to progression was 90 days and the median survival was 306 days.

INDICATIONS AND USAGE: XELODA is indicated 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 is not indicated, eg, patients who have received cumulative doses of 400 mg/m² 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 completing treatment with an anthracycline-containing adjuvant regimen.

This indication is based on demonstration of a response rate. No results are available from controlled trials that demonstrate a clinical benefit resulting from treatment, such as improvement in disease-related symptoms, disease progression, or survival.

CONTRAINDICATIONS: XELODA is contraindicated in patients who have a known hypersensitivity to 5-fluorouracil.

WARNINGS: *Coagulopathy:* Altered coagulation parameters and/or bleeding have been reported in patients taking XELODA concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These events occurred within several days and up to several months after initiating XELODA therapy and, in a few cases, within one month after stopping XELODA. These events occurred in patients with and without liver metastases. Patients taking coumarin-derivative anticoagulants concomitantly with XELODA should be monitored regularly for alterations in their coagulation parameters (PT or INR) (see PRECAUTIONS: Drug-Drug Interactions).

Diarrhea: XELODA can induce diarrhea, sometimes severe. Patients with severe diarrhea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. The median time to first occurrence of grade 2-4 diarrhea was 31 days (range from 1 to 322 days). National Cancer Institute of Canada (NCIC) grade 2 diarrhea is defined as an increase of 4 to 6 stools/day or nocturnal stools, grade 3 diarrhea as an increase of 7 to 9 stools/day or incontinence and malabsorption, and grade 4 diarrhea as an increase of ≥10 stools/day or grossly bloody diarrhea or the need for parenteral support. If grade 2, 3 or 4 diarrhea occurs, administration of XELODA should be immediately interrupted until the diarrhea resolves or decreases in intensity to grade 1. Following grade 3 or 4 diarrhea, subsequent doses of XELODA should be decreased (see DOSAGE AND ADMINISTRATION). Standard antidiarrheal treatments (eg, loperamide) are recommended.

Necrotizing enterocolitis (typhlitis) has been reported.

Geriatric Patients (gastrointestinal toxicity): Patients ≥80 years old may experience a greater incidence of gastrointestinal grade 3 or 4 adverse events (see PRECAUTIONS: Geriatric Use). Among the 14 patients 80 years of age and greater treated with capecitabine, three (21.4%), three (21.4%) and one (7.1%) patients experienced reversible grade 3 or 4 diarrhea, nausea and vomiting, respectively.

Among the 313 patients age 60 to 79 years old, the incidence of gastrointestinal toxicity was similar to that in the overall population.

Pregnancy: XELODA may cause fetal harm when given to a pregnant woman. Capecitabine at doses of 198 mg/kg/day during organogenesis caused teratogenic malformations and embryo death in mice. In separate pharmacokinetic studies, this dose in mice produced 5'-DFUR AUC values about 0.2 times the corresponding values in patients administered the recommended daily dose. Teratogenic malformations in mice included cleft palate, anophthalmia, microphthalmia, oligodactyly, polydactyly, syndactyly, kinky tail and dilation of cerebral ventricles. At doses of 90 mg/kg/day, capecitabine given to pregnant monkeys during organogenesis caused fetal death. This dose produced 5'-DFUR AUC values about 0.6 times the corresponding values in patients administered the recommended daily dose. There are no adequate and well-controlled studies in pregnant women using XELODA. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with XELODA.

PRECAUTIONS: General: Patients receiving therapy with XELODA should be monitored by a physician experienced in the use of cancer chemotherapeutic agents. Most adverse events are reversible and do not need to result in discontinuation, although doses may need to be withheld or reduced (see DOSAGE AND ADMINISTRATION).

Hand-and-Foot Syndrome: Hand-and-foot syndrome (palmar-planter erythrodysthesia or chemotherapy induced acral erythema) is characterized by the following: numbness, dyesthesia/paresthesia, tingling, painless or painful swelling, erythema, desquamation, blistering and severe pain. Grade 2 hand-and-foot syndrome is defined as painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities of daily living. Grade 3 hand-and-foot syndrome is defined as moist desquamation, ulceration, blistering and severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living. If grade 2 or 3 hand-and-foot syndrome occurs, administration of XELODA should be interrupted until the event resolves or decreases in intensity to grade 1. Following grade 3 hand-and-foot syndrome, subsequent doses of XELODA should be decreased (see DOSAGE AND ADMINISTRATION).

Cardiac: There has been cardiotoxicity associated with fluorinated pyrimidine therapy, including myocardial infarction, angina, dysrhythmias, cardiogenic shock, sudden death and electrocardiograph changes. These adverse events may be more common in patients with a prior history of coronary artery disease.

Hepatic Insufficiency: Patients with mild to moderate hepatic dysfunction due to liver metastases should be carefully monitored when XELODA is administered. The effect of severe hepatic dysfunction on the disposition of XELODA is not known (see CLINICAL PHARMACOLOGY AND DOSAGE AND ADMINISTRATION).

Hyperbilirubinemia: Grade 3 or 4 hyperbilirubinemia occurred in 17% (n=97) of 570 patients with either metastatic breast or colorectal cancer who received a dose of 2510 mg/m² daily for 2 weeks followed by a 1-week rest period. Of 339 patients who had hepatic metastases at baseline and 231 patients without hepatic metastases at baseline, grade 3 or 4 hyperbilirubinemia occurred in 21.2% and 10.4%, respectively. Seventy-four (76%) of the 97 patients with grade 3 or 4 hyperbilirubinemia also had concurrent elevations in alkaline phosphatase and/or hepatic transaminases; 6% of these were grade 3 or 4. Only 4 patients (4%) had elevated hepatic transaminases without a concurrent elevation in alkaline phosphatase. If drug related grade 2-4 elevations in bilirubin occur, administration of XELODA should be immediately interrupted until the hyperbilirubinemia resolves or decreases in intensity to grade 1. NCIC grade 2 hyperbilirubinemia is defined as 1.5 x normal, grade 3 hyperbilirubinemia as 1.5-3 x normal and grade 4 hyperbilirubinemia as >3 x normal. (See recommended dose modifications under DOSAGE AND ADMINISTRATION.)

Renal Insufficiency: There is little experience inpatients with renal impairment. Physicians should exercise caution when XELODA is administered (see DOSAGE AND ADMINISTRATION).

Hematologic: In 570 patients with either metastatic breast or colorectal cancer who received a dose of 2510 mg/m² administered daily for 2 weeks followed by a 1-week rest period, 4%, 2%, and 3% of patients had grade 3 or 4 neutropenia, thrombocytopenia and decreases in hemoglobin, respectively.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies in animals to evaluate the carcinogenic potential of capecitabine have not been conducted. Capecitabine was not mutagenic in vitro to bacteria (Ames test) or mammalian cells (Chinese hamster V79/Hprt gene mutation assay). Capecitabine was clastogenic in vitro to human peripheral blood lymphocytes but not clastogenic in vivo to mouse bone marrow (micronucleus test). Fluorouracil causes mutations in bacteria and yeast. Fluorouracil also causes chromosomal abnormalities in the mouse micronucleus test in vivo.

Impairment of Fertility: In studies of fertility and general reproductive performance in mice, oral capecitabine doses of 760 mg/kg/day disturbed estrus and consequently caused a decrease in fertility. In mice that became pregnant, no fetuses survived this dose. The disturbance in estrus was reversible. In males, this dose caused degenerative changes in the testes, including decreases in the number of spermatocytes and spermatids. In separate pharmacokinetic studies, this dose in mice produced 5'-DFUR AUC values about 0.7 times the corresponding values in patients administered the recommended daily dose.

Information for Patients (see Patient Package Insert): Patients and patients' caregivers should be informed of the expected adverse effects of XELODA, particularly nausea, vomiting, diarrhea, and hand-and-foot syndrome, and should be made aware that patient-specific dose adaptations during therapy are expected and necessary (see DOSAGE AND ADMINISTRATION). Patients should be encouraged to recognize the common grade 2 toxicities associated with XELODA treatment.

Diarrhea: Patients experiencing grade 2 diarrhea (an increase of 4 to 6 stools/day or nocturnal stools) or greater should be instructed to stop taking XELODA immediately. Standard antidiarrheal treatments (eg, loperamide) are recommended.

Nausea: Patients experiencing grade 2 nausea (food intake significantly decreased but able to eat intermittently) or greater should be instructed to stop taking XELODA immediately. Initiation of symptomatic treatment is recommended.

Vomiting: Patients experiencing grade 2 vomiting (2 to 5 episodes in a 24-hour period) or greater should be instructed to stop taking XELODA immediately. Initiation of symptomatic treatment is recommended.

Hand-and-Foot Syndrome: Patients experiencing grade 2 hand-and-foot syndrome (painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patients' activities of daily living) or greater should be instructed to stop taking XELODA immediately.

Stomatitis: Patients experiencing grade 2 stomatitis (painful erythema, edema or ulcers of the mouth or tongue, but able to eat) or greater should be instructed to stop taking XELODA immediately. Initiation of symptomatic treatment is recommended (see DOSAGE AND ADMINISTRATION).

Fever and Neutropenia: Patients who develop a fever of 100.5°F or greater or other evidence of potential infection should be instructed to call their physician.

Drug-Food Interaction: In all clinical trials, patients were instructed to administer XELODA within 30 minutes after a meal. Since current safety and efficacy data are based upon administration with food, it is recommended that XELODA be administered with food (see DOSAGE AND ADMINISTRATION).

Drug-Drug Interactions:

Antacid: The effect of an aluminum hydroxide- and magnesium hydroxide-containing antacid (Maalox)* on the pharmacokinetics of capecitabine was investigated in 12 cancer patients. There was a small increase in plasma concentrations of capecitabine and one

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metabolite (5'-DFUR); there was no effect on the 3 major metabolites (5'-DFUR, 5-FU and FBAL).

Coumarin Anticoagulants: Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. Patients taking coumarin-derivative anticoagulants concomitantly with capecitabine should be monitored regularly for alterations in their coagulation parameters (PT or INR) (see WARNINGS: *Coagulopathy*).

Phenytoin: Postmarketing reports indicate that some patients receiving capecitabine and phenytoin had toxicity associated with elevated phenytoin levels. The level of phenytoin should be carefully monitored in patients taking XELODA and phenytoin doses may need to be reduced (see DOSAGE AND ADMINISTRATION: *Dose Modification Guidelines*).

Leucovorin: The concentration of 5-fluorouracil is increased and its toxicity may be enhanced by leucovorin. Deaths from severe enterocolitis, diarrhea, and dehydration have been reported in elderly patients receiving weekly leucovorin and fluorouracil.

Pregnancy: Teratogenic Effects: Category D (see WARNINGS). Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with XELODA.

Nursing Women: It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving XELODA therapy.

Pediatric Use: The safety and effectiveness of XELODA in persons <18 years of age have not been established.

Geriatric Use: No separate studies have been conducted to examine the effect of age on the pharmacokinetics of capecitabine and its metabolites. Patients ≥80 years old may experience a greater incidence of gastrointestinal grade 3 or 4 adverse events (see WARNINGS). Among the 14 patients 80 years of age and greater treated with capecitabine, 21.4%, 21.4% and 7.1% experienced grade 3 or 4 diarrhea, nausea and vomiting, respectively. Among the 313 patients 60 to 79 years old, the incidence was similar to the overall population.

The elderly may be pharmacodynamically more sensitive to the toxic effects of 5-FU. Physicians should pay particular attention to monitoring the adverse effects of XELODA in the elderly.

ADVERSE REACTIONS:

The following table shows the adverse events occurring in ≥5% of patients reported as at least remotely related to the administration of XELODA. Rates are rounded to the nearest whole number. The data are shown both for the study in stage IV breast cancer and for a group of 570 patients with breast and colorectal cancer who received a dose of 2510 mg/m² administered daily for 2 weeks followed by a 1-week rest period. The 570 patients were enrolled in 6 clinical trials (162 from the breast cancer trial described under CLINICAL STUDIES, 83 other patients with breast cancer and 325 patients with colorectal cancer). The mean duration of treatment was 121 days. A total of 71 patients (13%) discontinued treatment because of adverse events/intercurrent illness.

Thrombocytopenia	24	3	1	21	1	1
Anemia	72	3	1	74	2	1
Lymphopenia	94	44	15	94	36	10
Hepatobiliary						
Hyperbilirubinemia	22	9	2	34	14	3

-Not observed or applicable.

Shown below by body system are the adverse events in <5% of patients reported as related to the administration of XELODA and that were clinically at least remotely relevant. In parentheses the incidence of grade 3 or 4 occurrences of each adverse event.

Gastrointestinal: intestinal obstruction (1.1), rectal bleeding (0.4), GI hemorrhage (0.2), esophagitis (0.4), gastritis, colitis, duodenitis, haematemesis, necrotizing enterocolitis

Skin: increased sweating (0.2), photosensitivity (0.2), radiation recall syndrome (0.2)

General: chest pain (0.2)

Neurological: ataxia (0.4), encephalopathy (0.2), depressed level of consciousness (0.2), loss of consciousness (0.2)

Metabolism: cachexia (0.4), hypertriglyceridemia (0.2)

Respiratory: dyspnea (0.5), epistaxis (0.2), bronchospasm (0.2), respiratory distress (0.2)

Infections: oral candidiasis (0.2), upper respiratory tract infection (0.2), urinary tract infection (0.2), bronchitis (0.2), pneumonia (0.2), sepsis (0.4), bronchopneumonia (0.2), gastroenteritis (0.2), gastrointestinal candidiasis (0.2), laryngitis (0.2), esophageal candidiasis (0.2)

Musculoskeletal: bone pain (0.2), joint stiffness (0.2)

Cardiac: angina pectoris (0.2), cardiomyopathy

Vascular: hypotension (0.2), hypertension (0.2), venous phlebitis and thrombophlebitis (0.2), deep venous thrombosis (0.7), lymphoedema (0.2), pulmonary embolism (0.4), cerebrovascular accident (0.2)

Blood: coagulation disorder (0.2), idiopathic thrombocytopenic purpura (0.2), pancytopenia (0.2)

Psychiatric: confusion (0.2)

Renal and Urinary: nocturia (0.2)

Hepatobiliary: hepatic fibrosis (0.2), cholestatic hepatitis (0.2), hepatitis (0.2)

Immune System: drug hypersensitivity (0.2)

OVERDOSAGE: Acute: Based on experience in animals and in humans treated up to doses of 3514 mg/m²/day, the anticipated manifestations of acute overdose would be nausea, vomiting, diarrhea, gastrointestinal irritation and bleeding, and bone marrow depression. Medical management of overdose should include customary supportive medical interventions aimed at correcting the presenting clinical manifestations. Although no clinical experience has been reported, dialysis may be of benefit in reducing circulating concentrations of 5'-DFUR, a low-molecular weight metabolite of the parent compound.

Single doses of XELODA were not lethal to mice, rats, and monkeys at doses up to 2000 mg/kg (2.4, 4.8, and 9.6 times the recommended human daily dose on a mg/m² basis).

DOSAGE AND ADMINISTRATION: The recommended dose of XELODA is 2500 mg/m² administered orally daily with food 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) at the end of a meal. XELODA tablets should be swallowed with water. The following table displays the total daily dose by body surface area and the number of tablets to be taken at each dose.

Table 4. XELODA Dose Calculation According to Body Surface Area

Dose level 2500 mg/m ² /day		Number of tablets to be taken at each Dose (morning and evening)	
Surface Area (m ²)	Total Daily* Dose (mg)	150 mg	500 mg
≤1.24	3000	0	3
1.25-1.36	3300	1	3
1.37-1.51	3600	2	3
1.52-1.64	4000	0	4
1.65-1.76	4300	1	4
1.77-1.91	4600	2	4
1.92-2.04	5000	0	5
2.05-2.17	5300	1	5
≥2.18	5600	2	5

*Total Daily Dose divided by 2 to allow equal morning and evening doses.

Dose Modification Guidelines: Patients should be carefully monitored for toxicity. Toxicity due to XELODA administration may be managed by symptomatic treatment, dose interruptions and adjustment of XELODA dose. Once the dose has been reduced it should not be increased at a later time.

The phenytoin dose may need to be reduced when phenytoin is concomitantly administered with XELODA (see PRECAUTIONS: *Drug-Drug Interactions*).

Table 5. Recommended Dose Modifications

Toxicity NCIC Grades*	During a Course of Therapy	Dose Adjustment For Next Cycle (% of starting dose)
• Grade 1	Maintain dose level	Maintain dose level
• Grade 2		
-1 st appearance	Interrupt until resolved to grade 0-1	100%
-2 nd appearance	Interrupt until resolved to grade 0-1	75%
-3 rd appearance	Interrupt until resolved to grade 0-1	50%
-4 th appearance	Discontinue treatment permanently	
• Grade 3		
-1 st appearance	Interrupt until resolved to grade 0-1	75%
-2 nd appearance	Interrupt until	50%

Table 3. Percent Incidence Of Adverse Events Considered Remotely, Possibly or Probably Related to Treatment in 5% of Patients

Adverse Event	Phase 2 Trial in Stage IV Breast Cancer (n=162)			Overall Safety Database (n=570)		
	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
GI						
Diarrhea	57	12	3	50	11	2
Nausea	53	4	-	44	4	-
Vomiting	37	4	-	26	3	-
Stomatitis	24	7	-	23	4	-
Abdominal pain	20	4	-	9	1	-
Constipation	15	1	-	9	1	-
Dyspepsia	8	-	-	6	-	-
Skin and Subcutaneous						
Hand-and-Foot Syndrome	57	11	-	45	13	-
Dermatitis	37	1	-	31	1	-
Nail disorder	7	-	-	4	-	-
General						
Fatigue	41	8	-	34	5	-
Pyrexia	12	1	-	10	-	-
Pain in limb	6	1	-	4	-	-
Neurological						
Paraesthesia	21	1	-	12	-	-
Headache	9	1	-	7	1	-
Dizziness	8	-	-	3	-	-
Insomnia	8	-	-	3	-	-
Metabolism						
Anorexia	23	3	-	20	2	-
Dehydration	7	4	1	5	2	1
Eye						
Eye irritation	15	-	-	10	-	-
Musculoskeletal						
Myalgia	9	-	-	4	-	-
Cardiac						
Edema	9	1	-	6	-	-
Blood						
Neutropenia	26	2	2	22	3	2

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-3 rd appearance	resolved to grade 0-1 Discontinue treatment permanently	
• Grade 4		
-1 st appearance	Discontinue permanently <i>or</i> If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	50%

*National Cancer Institute of Canada Common Toxicity Criteria were used except for the Hand and-Foot Syndrome (see PRECAUTIONS).

Dosage modifications are not recommended for grade 1 events. Therapy with XELODA should be interrupted upon the occurrence of a grade 2 or 3 adverse experience. Once the adverse event has resolved or decreased in intensity to grade 1, then XELODA therapy may be restarted at full dose or as adjusted according to the above table. If a grade 4 experience occurs, therapy should be discontinued or interrupted until resolved or decreased to grade 1, and therapy should be restarted at 50% of the original dose. Doses of capecitabine omitted for toxicity are not replaced or restored; instead the patient should resume the planned treatment cycles.

Adjustment of Starting Dose in Special Populations:

Hepatic Impairment: In patients with mild to moderate hepatic dysfunction due to liver metastases, no starting dose adjustment is necessary; however, patients should be carefully monitored. Patients with severe hepatic dysfunction have not been studied.

Renal Impairment: Insufficient data are available in patients with renal impairment to provide a dosage recommendation.

Geriatrics: The elderly may be pharmacodynamically more sensitive to the toxic effects of 5-FU and therefore, physicians should exercise caution in monitoring the effects of XELODA in the elderly. Insufficient data are available to provide a dosage recommendation.

HOW SUPPLIED: XELODA is supplied as biconvex, oblong film-coated tablets, available in bottles as follows:

150 mg

color: light peach

engraving: XELODA on one side, 150 on the other

150 mg tablets packaged in bottles of 120 (NDC 0004-1100-51)

500 mg

color: peach
engraving: XELODA on one side, 500 on the other
500 mg tablets packaged in bottles of 240 (NDC 0004-1101-16)
Storage Conditions: Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).
keep tightly closed. [See USP Controlled Room Temperature]

*Maalox is a registered trademark of Novartis.



Pharmaceuticals

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APPENDIX 8: CAPECITABINE PATIENT INFORMATION

XELODA® (capecitabine)

PATIENT PACKAGE INSERT (text only):

Patient Information About XELODA® (capecitabine) Tablets

This information will help you learn more about XELODA® (capecitabine) Tablets. It cannot, however, cover all possible precautions or side effects associated with XELODA nor does it list all the benefits and risks of XELODA. Your doctor should always be your first choice for detailed information about your medical condition and your treatment. Be sure to ask your doctor about any questions you may have.

What is XELODA?

- XELODA [zeh-LOE-duh] is an oral medication for the treatment of advanced breast cancer resistant to treatment with paclitaxel [pak-ihh-TAK-sil] and an anthracycline [an-thruh-SYEkleen]-containing chemotherapy regimen. Paclitaxel is also known as Taxol®*. Anthracyclines include Adriamycin®† or doxorubicin.
- XELODA tablets come in two strengths: 150 mg (light peach) and 500 mg (peach).

How does XELODA work?

XELODA is converted in the body to the substance 5-fluorouracil. In some patients, this substance kills cancer cells and decreases the size of the tumor.

Who should not take XELODA?

- Patients allergic to 5-fluorouracil.
- Studies in animals suggest that XELODA may cause serious harm to an unborn child. No studies have been done with pregnant women. If you are pregnant, be sure to discuss with your doctor whether XELODA is right for you. Also, tell your doctor if you are nursing.

How should I take XELODA?

Your doctor will prescribe a dose and treatment regimen that is right for *you*. Your doctor may want you to take a combination of 150 mg and 500 mg tablets for each dose. If a combination of tablets is prescribed, it is very important that you correctly identify the tablets. Taking the wrong tablets could result in an overdose (too much medication) or underdose (too little medication). The 150 mg tablets are light peach in color and have 150 engraved on one side. The 500 mg tablets are peach in color and have 500 engraved on one side.

- Take the tablets in the combination prescribed by your doctor for your **morning and evening doses**.
- Take the tablets within **30 minutes after the end of a meal** (breakfast and dinner).
- XELODA tablets should be **swallowed with water**.
- It is important that you take all your medication as prescribed by your doctor.
- If you are taking the vitamin folic acid, please inform your doctor.
- If you are taking phenytoin (also known as Dilantin®‡), please inform your doctor. Your doctor may need to more frequently test the levels of phenytoin in your blood and/or change the dose of phenytoin that you are taking.
- If you are taking warfarin (also known as Coumadin®§), please inform your doctor. Your doctor may need to more frequently check how quickly your blood is clotting.

How long will I have to take XELODA?

It is recommended that XELODA be taken for 14 days followed by a 7-day rest period (no drug) given as a 21-day cycle. Your doctor will determine how many cycles of treatment you will need.

What if I miss a dose?

If you miss a dose of XELODA, do not take the missed dose at all and do not double the next one. Instead, continue your regular dosing schedule and check with your doctor.

What are the most common side effects of XELODA?

The most common side effects of XELODA are:

- diarrhea, nausea, vomiting, stomatitis (sores in mouth and throat), abdominal pain, constipation, loss of appetite or decreased appetite, and dehydration (excessive water loss from the body).
- hand-and-foot syndrome (palms of the hands or soles of the feet tingle, become numb, painful, swollen or red), rash, dry or itchy skin.
- tiredness, weakness, dizziness, headache, and fever.

When should I call my doctor?

It is important that you **CONTACT YOUR DOCTOR IMMEDIATELY** if you experience the following side effects. This will help reduce the likelihood that the side effect will continue or become serious. Your doctor may instruct you to decrease the dose and/or temporarily discontinue treatment with XELODA.

STOP taking XELODA immediately and contact your doctor if any of these symptoms occur:

- **Diarrhea:** if you have more than 4 bowel movements each day or any diarrhea at night.
- **Vomiting:** if you vomit more than once in a 24-hour time period.
- **Nausea:** if you lose your appetite, and the amount of food you eat each day is much less than usual.
- **Stomatitis:** if you have pain, redness, swelling, or sores in your mouth.
- **Hand-and-foot syndrome:** if you have pain, swelling or redness of hands and/or feet.
- **Fever or Infection:** if you have a temperature of 100.5°F or greater, or other evidence of infection.

XELODA® (capecitabine)

If caught early, most of these side effects usually improve within 2 to 3 days after you stop taking XELODA. If they don't improve within 2 to 3 days, call your doctor again. After side effects have improved, your doctor will tell you whether to start taking XELODA again or what dose to use.

How should I store and use XELODA?

- Never share XELODA with anyone.
- XELODA should be stored at normal room temperature (about 65° to 85°F).
- Keep this and all other medications out of the reach of children.
- In case of accidental ingestion or if you suspect that more than the prescribed dose of this medication has been taken, contact your doctor or local poison control center or emergency room IMMEDIATELY.
- Medicines are sometimes prescribed for uses other than those listed in this leaflet. If you have any questions or concerns, or want more information about XELODA, contact your doctor or pharmacist.

* Taxol is a registered trademark of Bristol-Myers Squibb Company.

† Adriamycin is a registered trademark of Pharmacia & Upjohn Company.

‡ Dilantin is a registered trademark of Parke-Davis.

§ Coumadin is a registered trademark of DuPont Pharma.