HER2 Gene Amplification Testing by Fluorescence in situ Hybridization (FISH): Comparison of the American Society of Clinical Oncology (ASCO)-College of American Pathologists (CAP) Guidelines with FISH Scores used for enrollment in Breast Cancer International Research Group (BCIRG) Clinical Trials

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BREAST CANCER INTERNATIONAL RESEARCH GROUP
BCIRG

BCIRG 007

A MULTICENTER PHASE III RANDOMIZED TRIAL COMPARING DOCETAXEL (TAXOTERE®) AND TRASTUZUMAB (HERCEPTIN®) WITH DOCETAXEL (TAXOTERE®), CARBOPLATIN AND TRASTUZUMAB (HERCEPTIN®) AS FIRST LINE CHEMOTHERAPY FOR PATIENTS WITH METASTATIC BREAST CANCER CONTAINING THE HER2 GENE AMPLIFICATION

Project Number **BCIRG 007**
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I STUDY SUMMARY

TITLE

A MULTICENTER PHASE III RANDOMIZED TRIAL COMPARING DOCETAXEL (TAXOTERE®) AND TRASTUZUMAB (HERCEPTIN®) WITH DOCETAXEL (TAXOTERE®), CARBOPLATIN AND TRASTUZUMAB (HERCEPTIN®) AS FIRST LINE CHEMOTHERAPY FOR PATIENTS WITH METASTATIC BREAST CANCER CONTAINING THE HER2 GENE AMPLIFICATION.

OBJECTIVES

Primary Objective

To evaluate time to disease progression after treatment with either Herceptin® in combination with single-agent docetaxel (TH) or Herceptin® with Carboplatin and docetaxel (TCH) in metastatic breast cancer patients previously untreated with chemotherapy for advanced disease and whose cancer contains the HER2 gene amplification.

Secondary Objectives

To compare response rate, duration of overall response, overall survival.

To evaluate and compare the rate of clinical benefit, defined as CR, PR, or stable disease > 24 weeks.

To compare toxicity between the 2 arms.

To evaluate pathologic and molecular markers for predicting efficacy.

To correlate baseline peripheral levels of shed HER2 extracellular domain (ECD) with baseline FISH results and to determine whether peripheral levels of shed HER2 ECD constitute a prognostic and/or predictive factor vis-à-vis time to progression and survival.

To evaluate genetic and biochemical markers for predicting risk of developing cardiac dysfunction and later cardiac events in this patient population.

Study Design and Dosage Regimen

Multicenter prospective, non-blinded randomized Phase III trial. Two hundred and forty six (250) patients will be stratified at inclusion according to institution and prior adjuvant and/or neoadjuvant chemotherapy administration (none, chemotherapy with adjuvant and/or neoadjuvant taxane, chemotherapy without adjuvant and/or neoadjuvant taxane), and will be randomly assigned to received either docetaxel and Herceptin® (TH) or docetaxel, carboplatin and Herceptin® (TCH) until disease progression, second primary malignancy (except for curatively treated non-melanoma skin cancer or carcinoma in situ of the cervix), unacceptable toxicity or withdrawn consent.

TH:

A total of 8 cycles of docetaxel will be administered every 3 weeks. Herceptin® will be administered weekly during treatment with chemotherapy and then every 3 weeks during the follow-up period.

First cycle

Day 1: Herceptin® *4 mg/kg loading dose administered by IV infusion over 90 minutes.

Day 2: Docetaxel 100 mg/m² by IV infusion over 1 hour.

Day 8: Herceptin®* 2 mg/kg administered by IV infusion over 30 minutes.

Day 15: Herceptin® *2 mg/kg administered by IV infusion over 30 minutes.

***See Table 8 for Herceptin® infusion times and post-infusion observation periods**.*

Subsequent cycles (to start 3 weeks after Day 1 of 1st cycle)

Day 1: Docetaxel 100 mg/m² as 1 hour IV infusion given every 3 weeks, followed by Herceptin®* 2 mg/kg IV infusion over 30 minutes.

Day 8: Herceptin®* 2 mg/kg administered by IV infusion over 30 minutes.

Day 15: Herceptin® *2 mg/kg administered by IV infusion over 30 minutes.

***See Table 8 for Herceptin® infusion times and post-infusion observation periods**.*

Last cycle

Day 1: Docetaxel 100 mg/m² as 1 hour IV infusion followed by Herceptin® *2 mg/kg IV infusion over 30 minutes.

Day 8: Herceptin®* 2 mg/kg administered by IV infusion over 30 minutes.

Day 15: Herceptin® *2 mg/kg administered by IV infusion over 30 minutes.

Day 22: Herceptin®* 6 mg/kg administered by IV infusion over 30 minutes. (=EOC visit)

***See Table 8 for Herceptin® infusion times and post-infusion observation periods**.*

Herceptin® will then be administered at 6 mg/kg by IV infusion over 30 minutes every 3 weeks. Initiation of the q3weekly infusion of Herceptin® will correspond to the end of chemotherapy (EOC) visit.

Herceptin® will continue until disease progression, second primary malignancy (except for curatively treated non-melanoma skin cancer or carcinoma in situ of the cervix), unacceptable toxicity or withdrawn consent.

TCH:

A total of 8 cycles of docetaxel and carboplatin will be administered every 3 weeks. Herceptin® will be administered weekly during treatment with chemotherapy and then every three weeks during the follow-up period.

First cycle

Day 1: Herceptin®*4 mg/kg loading dose administered by IV infusion over 90 minutes.

Day 2: Docetaxel 75 mg/m^2 by IV infusion over 1 hour followed by carboplatin at target AUC = 6 mg/mL/min administered by IV infusion over 30 – 60 minutes minutes.

Day 8: Herceptin®* 2 mg/kg administered by IV infusion over 30 minutes.

Day 15: Herceptin®* 2 mg/kg administered by IV infusion over 30 minutes.

***See Table 8 for Herceptin® infusion times and post-infusion observation periods**.*

Subsequent cycles (to start 3 weeks after Day 1 of 1st cycle)

Day 1: Docetaxel 75 mg/m^2 by IV infusion over 1 hour followed by carboplatin at target AUC = 6 mg/mL/min administered by IV infusion 30 – 60 minutes every 3 weeks followed by Herceptin® *2 mg/kg administered by IV infusion over 30 minutes.

Day 8: Herceptin®* 2 mg/kg administered by IV infusion over 30 minutes.

Day 15: Herceptin®* 2 mg/kg administered by IV infusion over 30 minutes.

***See Table 8 for Herceptin® infusion times and post-infusion observation periods**.*

Last cycle

Day 1: Docetaxel 75 mg/m^2 by IV infusion over 1 hour followed by carboplatin at target AUC = 6 mg/mL/min administered by IV infusion 30 – 60 minutes followed by Herceptin® 2 mg/kg administered by IV infusion over 30 minutes.

Day 8: Herceptin® *2 mg/kg administered by IV infusion over 30 minutes.

Day 15: Herceptin®* 2 mg/kg administered by IV infusion over 30 minutes.

Day 22: Herceptin®* 6 mg/kg administered by IV infusion over 30 minutes. (=EOC visit)

***See Table 8 for Herceptin® infusion times and post-infusion observation periods**.*

Herceptin® will then be administered at 6 mg/kg by IV infusion over 30 minutes every 3 weeks. Initiation of the q3weekly infusion of Herceptin® will correspond to the end of chemotherapy (EOC) visit.

Herceptin® will continue until disease progression, second primary malignancy (except for curatively treated non-melanoma skin cancer or carcinoma in situ of the cervix), unacceptable toxicity or withdrawn consent.

Dose reduction and/or treatment delay and treatment discontinuation are planned for severe hematological and/or non-hematological toxicities.

Shed HER2 extracellular domain (ECD)

Serum samples are to be collected at the same time as the tumor evaluation on i. e: at baseline, at the end of cycles 3 and 6, at end of chemotherapy and then every 2 months during the first 2 years of follow-up, until disease progression, second primary malignancy (except curatively treated non melanoma skin cancer or carcinoma in situ of the cervix), or death whichever occurs first.

Cardiac genetic and biochemical markers

Blood samples are to be collected at baseline for cardiac genetic markers.

Plasma samples are to be collected at the same time as LVEF one, at baseline, at the end of cycles 3 and 6, at end of chemotherapy and then every 4 months during the first 2 years of follow-up and at any time of clinical evidence of cardiac failure.

Prophylactic Premedication Regimen

Patients will receive the following prophylactic steroid regimen for docetaxel-related fluid retention and hypersensitivity:

Dexamethasone 8 mg orally for 6 doses

1. night before chemotherapy
2. morning of chemotherapy
3. 1 hour before docetaxel infusion (may be given orally or by intravenous)
4. night of chemotherapy
5. morning the day after chemotherapy
6. evening the day after chemotherapy

Alternatives to Dexamethasone 8 mg oral may be:
Methylprednisolone 40 mg or Prednisone 50 mg or Prednisolone 50 mg.

Antiemetic Prophylaxis

Antiemetic prophylaxis is mandatory for all patients. Selection of antiemetics is at the discretion of the investigator.

Selection of Patients

INCLUSION CRITERIA

1. Written informed consent prior to beginning specific protocol procedures including expected cooperation of the patients for the treatment and follow-up must be obtained and documented according to the local regulatory requirements.

2. Histologically or cytologically proven breast adenocarcinoma at first diagnosis.

3. Metastatic breast cancer.

4. Patients must have either measurable or nonmeasurable lesions according to the RECIST criteria.
   Patients having truly nonmeasurable lesions (see exclusion criteria # 4) as their only site of disease will not be eligible, with the following exception: osteolytic bone lesions as the only manifestation of the disease having at least two lytic sites present and confirmed by bone X-ray, MRI or CT scan.

5. Primary tumor or metastatic tumor must show the presence of the HER2 gene amplification by Fluorescence In-Situ Hybridization (FISH analysis) by a designated central laboratory (see Appendix 3A for complete details).

6. Age $\geq$ 18 years and age $\leq$ 75 years. The upper age limit is not meant to be exclusionary but rather is based on the lack of safety data for the TCH regimen in women >75 years of age

7. Karnofsky Performance status index $\geq$ 60%.

8. Previous Therapy

   a. Hormonal therapy

   Patients may have had previous hormonal therapy as adjuvant treatment and/or as treatment for metastatic disease provided that the patient has progressive disease at study entry and the hormonal agent has been stopped at the time of randomization.

   b. Chemotherapy

   Patients may have had adjuvant and/or neoadjuvant chemotherapy.
   Patients having received a taxane as prior adjuvant and/or neoadjuvant therapy are eligible providing the relapse occurred at least 6 months following discontinuation of the taxane.

   Patients having received a taxane and Herceptin® combination as prior adjuvant and/or neoadjuvant therapy are eligible providing the relapse occurred at least 12 months after the last administration of Herceptin®.

   Patients having received an anthracycline or anthracenedione containing regimen as prior adjuvant and/or neoadjuvant therapy for any past or current neoplasm are eligible provided the total cumulative dose received is as follows: doxorubicin $\leq$ 360 mg/m^2 or epirubicin $\leq$ 720 mg/m^2 or mitoxantrone $\leq$ 72 mg/m^2 and treatment stopped at least 4 weeks prior to study registration.

   Patients CANNOT have had chemotherapy for locally advanced or metastatic breast cancer i.e. the treatment allocated in this study should be first line chemotherapy for metastatic disease.

   c. Herceptin®

   Patients having received a Herceptin®-containing regimen (except Herceptin® and taxane combination) as prior adjuvant and/or neoadjuvant therapy are eligible providing the relapse occurred at least 6 months following discontinuation of Herceptin®.

   Patients CANNOT have had Herceptin® for locally advanced or metastatic breast cancer.

   d. Radiotherapy

   Previous radiation therapy may have been given providing at least 4 weeks has elapsed from the end of radiotherapy and study registration unless radiotherapy involved only one single field to treat one single

metastatic bone lesion. For evaluation of any previously irradiated lesion in the study, clear progression must have been shown at study entry.

9. Patients must have fully recovered from toxic effects of previous antitumor therapy, excluding alopecia.

10. Normal cardiac function must be confirmed by LVEF (MUGA scan or echocardiography) and ECG within 1 month prior to registration. Result for the LVEF must be above or equal to the lower limit of normal for the institution.

11. Laboratory requirements: (within 7 days prior to registration)

    a. Hematology:
    Neutrophils $\geq 1.5 \times 10^9$/L
    Platelets $\geq 100 \times 10^9$/L
    Hemoglobin ≥ 10 g/dL

    b. Hepatic function:
    Total bilirubin $\leq$ 1 UNL
    ASAT (SGOT) and ALAT (SGPT) $\leq$ 5 UNL
    Alkaline phosphatase $\leq$ 5 UNL; except in presence of bone metastases or any non-malignant bone disease and in absence of any liver disorders.
    Patients with ASAT and/or ALAT > 1.5 x UNL **associated** with alkaline phosphatase > 2.5 x UNL are not eligible for the study.
    Patients with prior history of viral hepatitis (B, C) (serology performed) with transaminases (ASATand ALAT) and Alkaline Phosphatase and Total bilirubin > 1 UNL are not eligible for the study.

    c. Renal function:
    Creatinine $\leq$ 175 µmol/L (2 mg/dL)

    If creatinine is between 140 – 175 µmol/L (1.6-2.0 mg/dL), the creatinine clearance (calculated or measured) must be $\geq$ 60 mL/min.

12. Complete radiology and tumor measurement work up within 4 weeks prior to registration.

    a. Chest (AP and Lateral)
    Chest X-ray and/or chest CT scan and/or MRI.

    b. Abdomen
    Abdominal CT scan and/or MRI and/or ultrasound. If abdominal ultrasound is positive, abdominal CT scan and/or MRI must be performed and will be used to follow the patient throught the entire duration of the trial.

    c. Bone
    Bone Scintigraphy. If bone scintigraphy is positive, bone X-ray and/or CT scan and/or MRI must be performed and will be used to follow the patient throughout the entire duration of the trial.

13. Negative pregnancy test (urine or serum) within 7 days prior to registration for all women of childbearing potential. Patients of childbearing potential must implement adequate non-hormonal contraceptive measures during study treatment.

14. Patients must be accessible for treatment and follow-up. Patients registered in this trial must be treated and followed in a participating center.

EXCLUSION CRITERIA

1 Prior chemotherapy for locally advanced (stage IIIB) disease, local recurrence or metastatic disease.

2 Pregnant or lactating patients.

3 Prior treatment with Herceptin® for advanced breast cancer.

4 Prior Platinum salt containing regimen as adjuvant and/or neoadjuvant therapy for any past or current neoplasm.

5 One lytic bone metastasis, blastic bone metastases, mixed bone metastases, lymphangitic carcinomatosis, ascites, pleural/pericardial effusion, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses that are not confirmed and followed by imaging techniques, cystic lesions and/or irradiated not progressive lesions as only manifestation of metastatic disease.

6 Prior history or known clinical manifestation of brain or leptomeningeal involvement.

7 Non-metastatic disease as evidenced by local recurrent lesion within partially resected breast.

8 Concurrent treatment with any other anti-cancer therapy.

9 Pre-existing neuropathy-motor or sensory of a severity ≥ grade 2 by NCI CTC criteria, version 2.0.

10 Other serious illness or medical condition:

a. previous history of myocardial infarction within 1 year from registration;
b. unstable angina pectoris;
c. any history of documented congestive heart failure;
d. concomitant grade 3 or grade 4 cardiovascular arrhythmia (NCI CTC, version 2.0);
e. patients with poorly controlled hypertension i.e diastolic greater than 100 mm/Hg;
f. history of significant neurologic or psychiatric disorders including psychotic disorders, dementia or seizures that would prohibit the understanding and giving of informed consent;
g. active uncontrolled infection;
h. active peptic ulcer, unstable diabetes mellitus;
i. patients with severe dyspnoea due to complications of advanced malignancy or respiratory insufficiency requiring supplemental O_2.

11 Past or current history of neoplasm other than breast carcinoma, except for:

a. Curatively treated non-melanoma skin cancer;
b. Carcinoma in situ of the cervix;
c. Other cancer curatively treated and with no evidence of disease for at least 10 years.

12. Chronic treatment with corticosteroids **unless** initiated > 6 months prior to study entry **and** at low dose (≤ 20 mg methylprednisolone or equivalent).

13. Concomitant therapy with any hormonal agent such as raloxifene, tamoxifen, or other selective estrogen receptor modulators (SERMs), given for breast cancer prevention or for osteoporosis. Patients must have discontinued these agents prior to registration.

14. Patients receiving concurrent bisphosphonates are not eligible if osteolytic bone metastases are the only evaluable site of disease, unless bisphosphonate treatment is discontinued before randomization. Concomitant treatment with bisphosphonates may be used in patients with tumor lesions other than only bone metastases or for non-oncologic indications provided treatment in both cases has been started at least 3 months prior to study entry.

15. Definite contraindications for the use of corticosteroids.

16. Concurrent treatment with other experimental drugs. Participation in another clinical trial with any investigational not marketed drug within 30 days prior to study entry.

17. Known allergy reactions to any of the drugs used in the study.

18. Male patients, as no clinical efficacy or safety data are available from phase I-II studies.

NUMBER OF PATIENTS / ENROLLMENT & FOLLOW-UP PERIOD

Sample Size:	250 patients will be randomized (125 patients per treatment arm)
Enrollment Start:	December 2001
Enrollment Stop:	March 2004

EFFICACY EVALUATION

Assessment and reporting of tumor response will be done in accordance with the model established by the Response Evaluation Criteria in Solid Tumors (RECIST) group [99].

An intent-to-treat (ITT) analysis will be conducted for all randomized patients.

Time to Progression is the primary efficacy endpoint. It will be calculated from the date of randomization to the date of first documented disease progression or 2nd primary malignancy (with the exception of curatively treated non-melanoma skin cancer or carcinoma in situ of the cervix- see Exclusion Criteria 10a, 10b), or death except if the cause of death is definitely unrelated to malignant disease, whichever comes first.

Response rate (RR) will be defined as the percentage of patients in the group who achieve a complete or partial response.

Duration of overall response (CR+PR) will be 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.

Clinical benefit will consist of complete response, partial responses and stable disease lasting ≥ to 24 weeks.

Survival will be measured from the date of randomization to the date of death.

STATISTICAL CONSIDERATIONS

The primary objective of this trial is to show that TCH differs from TH in terms of time to progression (TTP). The following assumptions are made:

- the median TTP of HER2 FISH positive metastatic patients receiving TH will be around 7 months
- there will be a 50% improvement in median TTP for patients receiving TCH
- the error rate for a false positive outcome (α) is set to 5%, using two- sided significance tests
- the error rate for a false negative outcome (β) is set to 20%, i.e. the power of the trial is set to 80% for the difference of clinical interest

A sample of 238 eligible patients is required under these assumptions. Assuming that 5% of the patients will be found ineligible after randomization, the total sample size needed in the trial is 250 (125 patients per treatment arm).

The analysis of tumor response, TTP and OS will be performed on an intent-to-treat basis. The intent-to-treat population consists of all patients who are randomized in the study.

The Kaplan-Meier product limit method will be used to estimate the TTP and the OS. The logrank test, stratified for prior adjuvant and/ or neoadjuvant chemotherapy (none, chemotherapy with adjuvant and/or neoadjuvant taxane, chemotherapy without adjuvant and/or neoadjuvant taxane), will be used to compare the two treatment arms with respect to TTP and OS.

Cox's proportional hazards regression analysis will be performed for TTP and OS in order to adjust the treatment comparison for the major prognostic factors. These factors include clinical baseline parameters, pathological markers and molecular markers. Such adjusted analyses will be considered secondary to the main analysis. Any subset analyses will be reported with appropriate caveats.

Logistic regression analysis will be performed for objective response rate in order to adjust the treatment comparison for the major prognostic factors. These factors include clinical baseline parameters, pathological markers and molecular markers. Such adjusted analyses will be considered secondary to the main analysis. Any subset analyses will be reported with appropriate caveats.

All tests of hypotheses will be two-sided. Confidence intervals of the median survival will be calculated using the method of Brookmeyer and Crowley [115].

II INTRODUCTION AND BACKGROUND

2.1 Introduction

Breast cancer is a leading cancer site in women around the world. More than 796,000 new cases (21% of all cancer sites) were diagnosed in 1999 with 314,000 reported deaths in women (14.1%). In the United States, 182,800 new cases (30.4% of all cancers in US women) and 40,800 deaths (15.2% of all cancer deaths) are estimated to occur in the year 2000 [1]. In Canada, an estimated 31,000 new cases of breast cancer will be diagnosed (30.7% of all cancer) with an estimated 8,200 deaths from breast cancer (18.8% of all cancer) for the year 2000 [2]. In the European community, an estimated 135,000 new cases per year (24% of all cancer cases) and 58,000-recorded deaths per year (18% of all cancer deaths) are reported [3].

Surgery is the main modality of treatment in patients with breast cancer. Surgery and/or radiotherapy can control local-regional disease in the majority of patients. However, more than 60% will ultimately die due to widespread disease [4].

In the past 10 years, adjuvant hormonal or cytostatic treatment has been increasingly used [5]. Ongoing studies show that adjuvant treatment can prolong time to recurrence and probably survival in some subsets of patients [6-7].

2.2 Drug Treatment of Metastatic Breast Cancer

Few adult solid tumours are as sensitive to as wide a variety of pharmaceutical interventions as is breast carcinoma. Patients whose cancers express steroid hormone receptors can often be successfully treated with endocrine-based therapies. Initial endocrine responses are typically durable for approximately one year, but some patients will enjoy very prolonged remissions. Patients, who achieve an excellent initial response, will often re-respond to salvage hormone therapies. For patients whose cancers do not express hormone receptors or which relapse following, or fail to respond to endocrine therapy, cytotoxic chemotherapy is generally indicated.

Breast cancer is a partially chemotherapy-sensitive neoplasm. Patients with overt metastases, while generally incurable, nevertheless benefit from cytotoxic treatment with an improvement in their quality of life and with prolonged survival [8]. Adjuvant chemotherapy may contribute to the cure of earlier stage disease [9].

The anthracyclines, antimetabolites, vinca alkaloids and alkylating agents all have meaningful activity and long-established roles in the routine therapy of this disease. Until the mid 1990s, doxorubicin was generally regarded as being the most active drug in metastatic breast cancer. As a single agent, it produced response rates of 40-70%. Of the older drugs, it can be argued that cisplatin was in fact the second most active agent after doxorubicin (see below). Modern combination regimens will produce objective responses in the majority of patients with locally advanced or metastatic disease. Some patients, who are close to death with impending failure of crucial organ systems, will be restored to reasonably good health, and some of these will go on to live for periods of time which range from months to years. Most of these responses are partial however, and in all but exceptional cases, are temporary. Durable complete remission is rare [10].

Among the novel chemotherapeutic drugs introduced in the 1990's (taxanes, vinorelbine, gemcitabine, 5-fluorouracil prodrugs), the taxanes have emerged as very effective compounds and the available results suggest that they will be remembered in the future as the breast cancer chemotherapy of the 1990's. However, the impact of the taxanes on the natural history of breast cancer is yet to be defined, despite the trend of results suggesting that these agents could have the potential for significant advancement in the management of breast cancer.

Trastuzumab (Herceptin®), the humanized monoclonal antibody that selectively targets the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2) is emerging as a biological modifer. Considering the importance of HER2 as a prognostic and predictive factor in breast cancer and the recent development of trastuzumab (Herceptin®), new studies both in early and metastatic stage are ongoing or planned for patients who overexpress or amplify HER2.

2.3 Rationale for the use of Herceptin®

2.3.1 Human Epidermal Growth Factor Receptor 2 (HER2)

Growth factors and their receptors are known to play critical roles in development, cell growth, and differentiation. In almost all human tissues a number of these receptors possess intrinsic tyrosine kinase activity that is activated upon interaction of the receptor with its cognate ligand. Abnormal expression of human epidermal growth factor receptor 2 (HER2) is frequently observed in a number of primary human tumors, suggesting that the overexpression of this growth factor receptor may contribute to transformation and tumorigenesis. In most of these cases, pathologic HER2 protein overexpression is thought to result from gene amplification and has been correlated with poor clinical outcome in patients with both breast and ovarian cancers. Approximately 25% to 30% of patients with breast and 8-11% of ovarian cancers overexpress HER2. [11-13] Similar correlations may exist for gastric cancers, non-small cell lung cancers, and adenocarcinoma of the salivary gland and endometrium [14].

2.3.1.1 Antibodies Against HER2

Murine monoclonal antibodies (muMAbs) against HER2 were produced to study the basic biology of this protein. Those antibodies directed against the extra cellular domain of the HER2 receptor were shown to inhibit the proliferation of human tumor cells over expressing pl85HER2. [15] The most encouraging results were obtained with muMAb *4D5,* which produced significant anti proliferative effects *in vitro* against mammalian cancer cells including human breast cell lines that over express the HER2 receptor [14]. muMAb 4D5 has no effect on cell lines that do not over express the receptor [16-20].

Pre clinical *in vivo* studies with muMAb 4D5 were conducted using both human breast and ovarian cancer hetero transplants from surgically excised human tumor specimens. [20,21] The tumors were characterized to determine which had amplification and over expression of the HER2 gene. Results of these studies again established a clear antiproliferative effect against those human tumors characterized by over expression of the HER2 receptor. No effect was seen on tumor xenografts that did not over express the receptor.

Herceptin®, the humanized version of muMAb 4D5, was engineered by inserting the complementarity determining regions (CDRs) of muMAb 4D5 into the framework of a consensus human IgG [17]. Herceptin® binds the extra cellular domain of the HER2 receptor with 3 times greater affinity than does muMAb *4D5.* Herceptin® is comparable to muMAb 4D5 in blocking cell proliferation; however, unlike muMAb 4D5, it induces antibody dependent cellular cytotoxicity (ADCC) against tumor cell lines in the presence of human peripheral blood mononuclear cells (PBMCs).

Toxicology studies were conducted in mice and rhesus monkeys (monkeys were chosen as the primary species for toxicology trials because Herceptin® binds to the rhesus monkey HER2 receptor). No drug-related effects were observed.

2.3.1.2 Methods to Detect HER2 Overexpression

Pathologic HER2 Overexpression in human breast cancers is almost invariably due to amplification of the HER2 gene [22,23]. Less than 5% of breast cancers show overexpression without gene amplification. Currently, the most frequently performed assay for assessment of HER2 status is immunohistochemistry. However, HER2 immunohistochemistry, especially as performed with FDA-approved assays, is known to have a high rate of both false-positive and false-negative results, which are at least in part dependent on the subjective interpretation of the assay in different laboratories. More over, recent data have shown that patients amplifying the oncogene HER2 (FISH positive) were the only ones likely to benefit from Herceptin® based therapy [24]. The relationship between HER2 overexpression and c-erbB2 amplification as measured by FISH was analysed using 623 clinical specimens with a forced 1:1 ratio of positive (2+/3+) to negative (0/1+) results by the Clinical Trials Assay (CTA), 317 CTA+ and 306 CTA- [24]. These specimens were then analyzed by FISH. The amplification rates by CTA score were 3+, 89.3%; 2+, 23.9%; 1+, 6.7%; 0, 4.2%. The overall 2x2 concordance between the CTA and FISH was 81.3%. The relationship between c-erbB2 amplification status and Herceptin® clinical benefit was then evaluated in 3 pivotal trials. In study H0648g (see also paragraph 2.3.2), the addition of Herceptin® to chemotherapy (AC or paclitaxel) resulted in a response rate of 54% versus 31% with chemotherapy alone and a 30% increase in median survival (26 months versus 20 months) for the FISH positive subgroup. The FISH negative subgroup showed no improvement in response rate (38% versus 38%) and no improvement in survival. In H0649g, response rate in the FISH positive subgroup was 19%. No responses were seen in the FISH negative subgroup including 17 patients demonstrating a 3+ CTA score. In H0650g, the FISH positive subgroup showed a 34% response rate while the FISH negative subgroup demonstrated a 7% response rate (2 patients) [25,26]. Based on these data, we require that a tumor sample be forwarded to one of the designated central laboratories for FISH determination prior to randomization.

Serum assays for detecting levels of shed extracellular domain (ECD) of HER2 in peripheral blood for comparison with the FISH analysis as a predictive factor in determining a patient's outcome with Herceptin®-containing regimens are currently being investigated [27,28] although results are preliminary at this time. This may also prove to be an efficient means of testing for HER2 and thereby targeting those patients who will benefit most from Herceptin®. We have thus decided to study this and collect serum samples within the context of the study, as well.

2.3.2 Clinical Studies of Herceptin®

Various phase I-II studies with Herceptin®, whether as monotherapy or in combination with cytotoxic agents have been conducted [29-32]. The data shows that Herceptin® is an active agent in HER2+ metastatic breast cancer patients. The evidence of the added value of Herceptin® in the treatment of HER2+ breast cancer patients comes from a large phase III trial, which lead to the registration of Herceptin®, [25, 33, 34].

In this study, 469 patients with HER2 -overexpressing (IHC $2^+/3^+$) metastatic breast cancer not previously treated with chemotherapy for metastatic disease were entered. The first and larger group consisted of patients with metastatic disease who had received no prior anthracycline therapy in the adjuvant setting. Randomization was to treatment with anthracycline and cyclophosphamide (AC) in standard doses either alone or in combination with Herceptin®. The second group consisted of patients with metastatic disease who had received anthracycline therapy in the adjuvant setting. Randomization in this group was to treatment with Taxol® alone or with Herceptin®. The Taxol® subgroups (n=188) had worse prognostic factors (ie a higher proportion of premenopausal patients, tumors negative for hormonal receptors, positive lymph nodes at time of initial surgery), had more prior therapy (adjuvant chemotherapy, myeloblative chemotherapy, radiotherapy) and a shorter disease-free interval from surgery for primary diagnosis to metastatic disease than did the AC subgroups (n=281). Results are seen in Table 1. A statistically significant improvement in time to disease progression, response rate and overall survival at 2 years was seen with the combination of Herceptin® and chemotherapy in both groups of patients. Similar results are seen in the FISH positive subgroups in time to disease progression, response rate and overall survival statistically significant either for the combined groups or subgroups. Patients treated with concurrent administration of Herceptin® and AC, however, had an increased risk of Class III/IV cardiac dysfunction (16%) compared to patients treated with doxorubicin and cyclophosphamide alone (3%). This cardiac risk appears to limit the use of combination of Herceptin® and doxorubicin in first line metastatic and adjuvant strategies for breast cancer. Further information suggests that cardiac dysfunction is also seen with Herceptin® in association with Taxol® (2%) versus Taxol® alone (1%).

Table 1 Phase III Multicenter Results H0648g

	Combined Results		Paclitaxel Subgroups		AC Subgroups	
	H+Chemo	Chemo Alone	H+P	P alone	H+AC	AC
	(n=235)	(n=234)	(n=92)	(n=96)	(n=143)	(n=138)
Time to Progression						
Median (Months)	7.4	4.6	6.9	2.8	7.8	6.1
p-value	< 0.0001		< 0.0001		< 0.002	
95% CI	(7.0-9.0)	(4.4-5.4)	(5.3-9.9)	(2.0-4.3)	(7.3-9.4)	(4.9-7.1)
Overall Response Rate (%)	50	32	41	17	56	42
95% CI	(44 - 57)	(26 - 38)	(31 – 51)	(9 – 24)	(48 – 64)	(34 – 50)
p-value (χ^2-test)	< 0.0001		< 0.0002		0.02	
Duration of Response						
Median (months)	9.1	6.1	10.5	4.5	9.1	6.7
p-value	< 0.001		< 0.01		0.005	
Survival Time						
Median (Months)	25.1	20.3	22.1	18.4	26.8	21.4
p-value (log rank)	0.046		0.17		0.16	
95% CI	(22.2-29.5)	(16.8-24.2)	(16.9-28.6)	(12.7-24.4)	(23.3-32.9)	(18.3-26.6)

Although trastuzumab (Herceptin®) has been administered weekly in the pivotal studies, 2 studies are now available looking at the safety, tolerability and pharmacokinetics of Herceptin® when administered every 3 weeks in women with HER2 positive (IHC 2+, 3+) metastatic breast cancer. The first study looked at Herceptin® q3weekly in combination with paclitaxel [35], the second is a monotherapy q3weekly study of Herceptin® (unpublished data). Initial results from the former study, with Herceptin® and paclitaxel being administered every 3 weeks, were presented at ASCO 2001. Thirty-two patients received Herceptin® and paclitaxel administered every 3 weeks. Herceptin® dose consisted of an 8 mg/kg load by IV infusion over 90 minutes followed 6 mg/kg IV infusions over 90 minutes every 3 weeks. Eight cycles of paclitaxel at 175 mg/m^2 by IV every 3 weeks was planned. Baseline characteristics were median age of 53 years, 63% with prior adjuvant chemotherapy, 63% with prior metatstatic therapy, and 70% with prior anthracycline exposure. Tumor sites at baseline were as follows: 50% of patients had lung involvement, 47% had liver, 66% had bone and 38% had regional involvement, respectively. An average of 6 cycles of paclitaxel and 7 cycles of Herceptin® were administered, respectively. Toxicities seen with the q3weekly regimen were not markedly different from the previous study (H0648g) with Herceptin® given in a q1weekly dosing schedule. Three patients discontinued treatment due to toxicity. Four patients developed an infusion reaction with each subsequently continuing on treatment. Twelve patients developed myalgia. Two patients had decreases in LVEF of >15%, one of which developed grade 3 cardiac failure.
At the time of this report, 17 patients continued with therapy. Of 32 patients having received the q3weekly combination of Herceptin® and paclitaxel, 9.4% had a complete response, 43.8% had a partial response (overall response rate of 53%) and 25% had stable disease. Duration of response was 6.3 months and time to progression was 10. 9 months.

Preliminary results from the monotherapy program looking at q3weekly administration of Herceptin® have recently been reported (unpublished data). Eighty patients with HER2 overexpressing metastatic breast cancer are expected to be enrolled, with 50 patients
having been recruited to date. Patients who were 3+ by immunohistochemistry or positive by FISH analysis were entered. Prior adjuvant therapy is allowed, but patients may not have had prior chemotherapy for metastatic disease. Patients are to receive a loading dose of 8 mg/kg of Herceptin® by IV infusion over 90 minutes, followed by q3weekly IV infusions of 6 mg/kg. At the time of this report, the median number of cycles of treatment received was 3. Number of cycles of treatment reported at this time is as follows:

Cycle Number	1	2	3	4	5	6	7	8	9
Patients treated	50	43	29	18	14	12	4	1	1

Eleven patients have withdrawn from the study. Reasons include one patient having a cerebrovascular accident resulting in death and the remaining patients withdrawing because of insufficient response. Four serious adverse events have been reported. One patient dying from the cerebrovascular accident was mentioned above. One patient was diagnosed with a benign endometrial polyp for which a dilatation and curettage was required. The third patient was hospitalized for severe pain at the site of her disease (sternum and left supraclavicular fossa). The event resolved and patient continued to receive Herceptin. The last case was that of a patient who developed an episode of shortness of breath following her loading dose of Herceptin®. This patient had a history of malignant pleural effusion. The event resolved and Herceptin® was discontinued.

Hematological toxicity seen with the q3weekly regimen was minimal and mild with the most severe anemia and neutropenia reported as grade 2, respectively, and grade 1 for thrombocytopenia. Of 15 patients who have had 2 measurements of LVEF performed at baseline and at cycle 4, 1 patient had a decrease of LVEF of 24% with a concomitant mild dyspnea. Infusion reactions were mild to moderate and consisted of fatigue, headache, pyrexia, rigors and shivering. Other nonehematologic toxicities reported were mild and moderate. No response data is available from the monotherapy q3weekly study.

2.3.3 Clinical pharmacology of Herceptin®

The pharmacokinetics of Herceptin® have been studied in breast cancer patients with metastatic disease.
In early pharmacokinetic analysis from pivotal studies using a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg, a mean half-life of 5.8 days (range of 1 to 32 days) was observed. However, reanalysis of pharmacokinetic data as previously outlined reveals now half-life of trastuzumab of approximately 28.5 days (95% confidence interval, 25.5 – 32.8 days). Thus, Herceptin® may persist in the circulation for up to 24 weeks (range 18-24) after stopping Herceptin® treatment. It is already known that, when used in combination, Herceptin® and anthracyclines are associated with an increased risk of cardiotoxicity. In addition, the use of anthracyclines after stopping Herceptin® may possibly be at increased risk of cardiotoxicity. If possible, physicians should avoid anthracycline base therapy for up to 24 weeks after stopping Herceptin® therapy. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

Further comparions between the q3weekly and weekly regimens showed that peak serum concentrations and average concentrations (AUC/dosing interval) were higher with the q3weekly regimen than seen with weekly administration. Peak Herceptin® serum concentrations for the q3weekly regimen were 164 μg /mL as compared to 100 μg /mL for the weekly regimen. Average concentrations were 81 μg /mL in the q3weekly regimen versus 53 μg /mL in the qweekly regimen. Pre-dose concentrations (at week 3) were lower than seen in the weekly study (39 versus 53.4 μg /mL, respectively).
A series of simulations were done based on the pharmacokinetic parameters estimated previously for Herceptin® using a population PK approach on the published data from several studies (Roche internal data). The simulations were done for the weekly (4+2 mg/kg) and the 3 weekly (8+6 mg/kg) dosing regimens assuming that no dose was missed and then for a range of time delays in the scheduled doses.

It was assumed that if dosing is re-started after a delay, the trough concentrations at steady-state should stay within 20% of the original levels. In the simulations, if re-start of the maintenance dose was associated with a long and gradual come back to the steady-state, a loading dose was added as if we wanted to start the treatment for a new patient.

The results show that if a patient misses a dose by less than a week, continuing with the usual maintenance dose (2mg/kg for the weekly schedule, 6mg/kg for the 3 weekly schedule) would not cause a long lack of exposure and, therefore, there is no need for re-loading the patients. If a patient misses a dose by more than a week, the continuation of the maintenance dose will not bring the levels back quickly to within the 20% of the original steady-state levels. Without a loading dose it takes a long time (6-8 weeks at least) to get back to within this range. Hence, a delay more than 1 week in dose warrants re-loading the patients.

It has been noticed in simulations where dosing was re-started after one week delay with a loading dose for both weekly and 3 weekly schedule that the C_{max} after re-loading will be about 20-30% higher than C_{max} levels prior to the dose delay. However, the benefit of regaining the steady state levels in a short time against a potential risk of a 20-30% increase in C_{max} may be justified. Therefore, the recommendation for re-loading following missed or delayed doses of Herceptin is maintained.

2.3.4 Synergism between Herceptin® and chemotherapeutic agents

Studies in preclinical models used combination therapy for breast cancer cells that overexpress HER2, and the use of agents that interfere with HER2 function in combination with paclitaxel resulted in significant antitumor effects [19, 20, 37, 38, 40]. The most compelling preclinical rationale, however, for the combination of carboplatin/Herceptin® is derived from studies designed to determine the effects of combined chemotherapy / Herceptin® in *vitro* and *in vivo* breast cancer models. These studies demonstrate that there are additive and/or synergistic therapeutic effects between a number of chemotherapeutic agents and Herceptin® [20]. The most significant therapeutic interaction is the synergistic effect seen with cisplatin or carboplatin and Herceptin® [19, 20]. This synergistic effect results in a two-log increase in cytotoxic killing of HER2 positive cells exposed to the combination. The effect is not seen in cells in which HER2 overexpression does not exist. Antibodies to Herceptin® were detected in a single patient in the above clinical trials, however the patient did not demonstrate an adverse clinical event [33, 34, 39]. In addition to this synergistic effect with platinum analogues, the preclinical studies demonstrate also synergistic effects with docetaxel [20] while additive effects have been noted with other drugs including Paclitaxel [39]

Hancock et al demonstrated that a combination of cisplatin and the TAb 250 monoclonal antibody, which is specific to an extracellular epitope of the c-erbB-2 protein (gp 185), significantly enhanced the cytotoxic effect of cisplatin in human breast tumor cell lines and in mice with human tumor xenografts that overexpress c-erbB-2. This synergistic cytotoxicity was apparent over a wide range of antibody concentrations, including concentrations that showed no inhibitory effect alone [37]. Pietras et al also demonstrated this phenomenon in a drug-resistant ovarian cancer cell line with overexpression of p185HER2 [19]. The increase in cytotoxicity may be a result of inhibition of repair of cisplatin induced DNA damage by the antibody, [19, 37, 40].

2.4 Rationale for the use of Herceptin® with docetaxel and platinum based chemotherapies

2.4.1 Docetaxel monochemotherapy

The great majority of phase II studies were performed using docetaxel at a dose of 100 mg/m^2 given over 1 hour every 3 weeks [41-62]. The 1-hour schedule and the relatively small difference in doses used in phase II studies probably account for the consistency of results observed throughout the various studies. With respect to docetaxel, 4 phase III monochemotherapy trials are published or reported to date [59-62]. In the first trial, docetaxel 100 mg/m^2 was compared to doxorubicin 75 mg/m^2 in first line metastatic after failure of alkylating agents [59]. Docetaxel induced more responses than doxorubicin (48% vs 33%, p=0.008), while median time to progression was longer with docetaxel (26 weeks vs 21 weeks, p=ns) although overall survival was identical in both treatment arms. The risk-benefit ratio appeared to favor docetaxel in this trial, suggesting that docetaxel may be more powerful than doxorubicin in first-line therapy of advanced breast cancer. Moreover, the results from a study of 331 metatstatic breast cancer patients randomized to receive either paclitaxel 200 mg/m^2 or doxorubicin 75 mg/m^2 strongly favor doxorubicin with a response rate of 41% versus 25% (p=0.003) and with a significantly longer time to progression (7.5 months versus 4.2 months, p=0.001). There was no survival difference between the two arms, which may be related to the prospective crossover built into the study. Paclitaxel was thus inferior to doxorubicin in terms of RR and TTP [63].

The 3 other phase III trials were performed in patients with metastatic breast cancer after failure of anthracyclines, comparing docetaxel 100 mg/m^2 given over 1 hour to various salvage regimens [60-62]. The largest study (392 patients) randomized patients between docetaxel and mitomycin-C (12 mg/m^2 q6 weeks) plus vinblastine (6 mg/m^2 q3weeks) [60]. Efficacy was significantly better for docetaxel with higher overall response rate (30% vs 12%, p=0.001), longer time to treatment failure (19 weeks vs 11 weeks, p=0.001) and most importantly longer overall survival (11.4 months vs 8.7 months, p=0.0097). The next study (283 patients) was performed by the Scandinavian group and compared docetaxel to methotrexate plus 5-fluorouracil (5-FU), respectively 200 mg/m^2 and 600 mg/m^2 day 1 and 8 q3weeks [61]. Again and confirming the previous trial, efficacy was significantly in favor of docetaxel with better response rates (42% vs 21%, p=0.0001) and longer time to progression (27 weeks vs 13 weeks, p=0.0001). Survival was similar in both arm, possibly related to the built-in crossover. Finally, the last trial studied, in 172 patients, docetaxel vs NAF (vinorelbine 25 mg/m^2 day 1 and 5 q3weeks plus continuous infusion 5-FU 750 mg/m^2 over days 1 through 5 q3weeks). Response rates were 43% for docetaxel and 39% for NAF (p=ns). Time to progression and overall survival was longer with docetaxel (respectively 28 weeks vs 22 weeks and 19.1 months vs 13.9 months), but did not reach statistical significance [62].

All these phase III data suggest that docetaxel represents potentially the single most active chemotherapeutic agent for the treatment of breast cancer.

2.4.2 Platinum Based Chemotherapies

The platinum co-ordination complexes are broadly active in human cancers. They are a crucial component of therapy for germ-cell tumours, lung and ovarian cancers. They also have substantial activity in metastatic breast cancer, but are seldom used in routine clinical practice. When used as first-line chemotherapy for metastases, objective response rates in two phase II trials of cisplatin were 52% and 47% [65]. Platinum compounds however are much less active in the salvage setting [64-66].

Carboplatin is a platinum co-ordination complex with a similar spectrum of activity, but with a different toxicity profile from the parent compound cisplatin. At routine doses carboplatin produces substantially less nephrotoxicity, neurotoxicity and nausea than does cisplatin. Myelotoxicity, and especially thrombocytopenia, are more prominent with carboplatin than with cisplatin. Carboplatin is active in metastatic breast cancer. In an early study, Kolaric et al reported a 20% rate of objective response among 20 previously untreated patients [65]. Martino et al treated 34 patients without prior chemotherapy for metastases and reported a 35% rate of response [64]. O'Brien and colleagues performed a phase II evaluation in which patients with metastatic disease were treated with a dose of carboplatin which was predicted to achieve an area under the time-versus-concentration curve of 7 mg/min/mL. In this study, objective responses were achieved by 33% of 27 previously untreated patients, and by 8% of 13 patients with prior chemotherapy for metastases [66].

Platinum-based combination regimens in breast cancer: Cisplatin and etoposide produced response rates of 0%- 50% [67-69]. Other doublet regimens which have been studied include cisplatin/cytosar (7% response rate) and cisplatin / 5-FU [70-72]. Vinorelbine has emerged as a highly active drug in the treatment of metastatic breast cancer. The combination of vinorelbine and cisplatin was reported by Shamseddine et al to produce a very impressive 61% rate of response in 25 pre-treated patients [73]. Similarly Ray-Coquand et al reported a 41% response rate in pre-treated patients [74]. The MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) regimen produced responses in 57-80% of patients [75-78].

The combination of carboplatin and etoposide has been subjected to several evaluations. In three of these studies, carboplatin/etoposide was used as first chemotherapy for metastases. Van der Gast and colleagues reported a 27% rate of objective response in 34 patients [79], Crown et al 42% response in 19 previously untreated patients [80], and Deltetto 50% in 12 patients [81]. There has been a wide range of reported response rates (0-50%) for this combination in pre-treated patients [82-85].

Smith and colleagues at the Royal Marsden have conducted a series of innovative trials using long–term continuous infusion 5-fluorouracil together with three-weekly administrations of lower dose cisplatin and epirubicin. In an early study involving patients with locally advanced disease, a response rate of 98% was reported, among forty-nine patients, including 66% clinical complete remissions. In a subsequent study, carboplatin was substituted for cisplatin. Fifty-two patients with metastatic (36) or locally advanced (16) breast cancer were treated. The response rate was 81% with a complete response rate of 17% in patients with metastatic disease and 56% in patients with locally advanced cancer [86].

2.4.3 Docetaxel-based combinations

Developing combination chemotherapy in metastatic setting has been a necessary step before proceeding to the adjuvant setting. Given the high individual activity of docetaxel and doxorubicin as single agents in breast cancer, and their potential limited cross-resistance, evidenced by the confirmed activity of docetaxel in patients resistant to anthracyclines, the rationale for the development of combinations or sequence based upon these two agents was compelling. Furthermore, the extrahematological toxicity profile of the 2 agents, with limitation of overlapping toxicities, suggested the potentiality for exploitation of the maximum benefit from each agent, in particular in terms of cardiac toxicity.

Nabholtz and colleagues showed that the combination of docetaxel and doxorubicin was superior to doxorubicin and cyclophosphamide in patients with previously untreated MBC. This phase III trial comparing AC (60/600 mg/m2) or AT (50 mg/m2 doxorubicin and 75 mg/m2 docetaxel), maximum 8 cycles as first-line treatment for patients with metastatic breast cancer were recently presented. A total of 429 patients without prior anthracycline exposure were randomized to a maximum of eight cycles of AC (n=215) or AT (n=214). The overall response rate was statistically significantly higher than patients treated with AC (60% for AT and 47% for AC, p=0.012). Patients treated with AT also experienced a significantly longer time to disease progression (p=0.01) and time to treatment failure (p=0.02) than those treated with AC [87]. These results also confirm the findings from phase II trials confirming the lack of influence of docetaxel on doxorubicin-induced cardiomyopathy. Moreover, a large study that compared AC to AT (Taxol) as first-line metastatic treatment in 275 women, no advantage in terms of response rate and progression free survival was shown with AT over AC at a median follow-up of 19 months [88].

Concerning **Platinum-Taxane Combinations,** docetaxel and cisplatin share different mechanisms of actions and resistance, no overlapping toxicities, and both have shown to have activity in advanced breast cancer. In phase I studies, the feasibility of

administering docetaxel in combination with the platinums has been demonstrated in patients with lung and breast cancer. Phase I combination studies suggest that without growth factor support, 75 mg/m^2 of docetaxel followed immediately by 75 mg/m^2 of cisplatin, is a manageable regimen [89]. The dose limiting toxicities were hematologic. Approximately half of the cycles were followed by Grade 4 (< 0.5 x 10^9 cells/L) neutropenia, which was of brief duration, non-cumulative, and rarely complicated by concomitant fever (febrile neutropenia). The most frequent non-hematologic toxicities were nausea/vomiting and diarrhea. Pharmacokinetics (PK) of docetaxel and cisplatin were performed during the first cycle of administration of this combination and were consistent with the published results from single-agent studies suggesting no major pharmacokinetic interaction. Cisplatin is known to cause a dose-dependent peripheral neuropathy. Single agent docetaxel has been reported to cause a mild neuropathy in Phase I and II. The combination of docetaxel and cisplatin induces a dose-dependent predominately sensory neuropathy. All patients enrolled into one Phase I study of locally advanced solid tumors had detailed neurological examinations. At cumulative doses of both cisplatin and docetaxel above 200 mg/m^2, 26 of 35 (74%) patients developed a neuropathy, which was mild in 15, moderate in 10 and severe in one patient [90].

The cisplatin/docetaxel doublet is highly active in MBC. Investigators in Dublin and France conducted a phase I-II evaluation of these drugs in patients with MBC and no prior chemotherapy for metastases. These patients had extensive exposure to adjuvant chemotherapy. Four dose levels were used: 75/75; 85/75 85/100 100/100 mg/m^2, of docetaxel and cisplatin respectively. Of the 38 patients treated, 69% had prior adjuvant chemotherapy, including anthracyclines in more than 40%. An overall response rate of 60% was reported, and among chemotherapy naïve patients, the response rate was approximately 80%. Doses of 75 mg/m^2 of each drug were well tolerated, with dose-limiting gastro-intestinal toxicity occurring at higher doses. Bernard et al [91] treated 32 patients with prior anthracycline exposure with 100 mg/m2 docetaxel followed by cisplatin 100 mg/m^2, repeated every 3 weeks for a maximum of 8 cycles. The most common toxicity was grade 3-4 neutropenia, which occurred in 17 patients (55%): 23 out of 32 patients required GCSF. Cutaneous and neurologic toxicities were frequent (78% and 75% of patients, respectively), but were moderate. 16 patients (50%) exhibited fluid retention (severe, 3 patients). No toxic death was noted. Twenty-one patients (65%) required a dose reduction. With a median follow-up of 10 months (1-14+), fifteen out of 30 evaluable patients (50%) had an objective response (2 CRs). The liver response was 50% and 9 of 17 anthracycline-resistant patients responded.

In a phase II study looking at anthracycline-pretreated metastatic breast cancer patients, Antoine et al [92] enrolled 20 patients to receive 100 mg/m^2 of docetaxel followed by 100 mg/m^2 of cisplatin every 3 weeks for 8 cycles. The most common toxicity seen was grade 4 neutropenia in 14 patients (70%) and 50% of cycles. Grade 3-4 thrombocytopenia was noted in 5 patients. Other toxicities were mild and of low grade. These included 5 patients with Grade 1-2 neurotoxicity, 7 patients with grade 1-2 cutaneous toxicities, 12 patients with grade 1-2 nausea/vomiting, and 2 patients with mild fluid retention. No toxic death was noted. One patient developed a grade 2 hearing loss and cisplatin was subsequently stopped after 3 cycles. At the time of these preliminary results, 13 patients were evaluable for response. Eight patients had a partial response (OR 61%) and responses occurred at any site. Three patients experienced disease stabilization and 2 patients progressed while on treatment. Response sites included liver, chest and soft tissue.

Llombart-Cussac et al [93] enrolled 41 patients with anthracycline-resistant breast cancer in a phase I/II study looking at maximum tolerated dose and activity profile of docetaxel and cisplatin. The dose-limiting toxicity was found to be febrile neutropenia seen in 2 of 9 patients at level 75/80 mg/m^2 of docetaxel and cisplatin, respectively, and 3 of 5 in the level 85/80-mg/m^2 docetaxel and cisplatin, respectively. Patients experiencing grade 3-4 toxicities were neutropenia 93% (febrile 20%), nausea/vomiting 17%, peripheral neuropathy 10%, stomatitis 7%, thrombocytopenia 5%, fluid retention 2%. One patient died of septic shock. Five patients experienced a CR (12%), and 18 patients a PR (44%) with liver responses in 14 (54%). Median response duration was 4.5 months and median overall survival in 13 months. Investigators in Florida have reported a 96% rate of objective response for the combination of cisplatin and docetaxel (70 mg/m^2 each) in patients with locally advanced breast cancer.

The combination of carboplatin and docetaxel has also been extensively studied in ovarian and lung cancer. Doses of carboplatin of approximately AUC 5-6 mg/mL/min can readily be combined with docetaxel at a dose of 75 mg/m^2. At higher doses, myelosuppression, especially thrombocytopenia becomes dose limiting. Severe neurotoxicity or other non-hematopoietic toxicities are rare.

2.4.4 Docetaxel, Herceptin® clinical experience (TH)

Docetaxel and Herceptin® in combination have recently been studied in 4 phase II trials [94-96, 28]. In the first study by Burris et al, docetaxel was delivered at a dose of 75 mg/m^2 for six 3-weekly cycles while Herceptin® was initiated as a 4mg/kg on day 1 (90-min IV infusion) followed by 2mg/kg weekly (30-min IV infusion) until disease progression. Patients with metastatic breast cancer overexpressing HER2 (IHC 2+/3+) were eligible for this trial. Twenty-two patients have received 120 cycles of docetaxel (median

6 cycles) and more than 500 doses of Herceptin® (median 26 doses). Toxicity has been minimal with 1 episode of febrile neutropenia and 3 cases of dermatitis (2 pts with grade 2 and 1 pt with grade 3). No significant cardiac toxicity was observed. Antitumor activity assessment is reporting an overall response rate of 45% and clinical benefit of 65% so far. Patients with HER2 IHC 3+ status presented with responses in 54% of cases and clinical benefit in 69% of treated patients [94].

The next 3 studies assessed weekly docetaxel with Herceptin® in patients with metastatic breast cancer. The first study [95] looked at weekly 35-mg/m2 IV docetaxel (6 of 8) with weekly Herceptin® in 1st line metastatic breast cancer patients with no prior exposure to taxanes. Twenty-one patients have received 69 cycles (1 cycle = 8 weeks). Grade 3 or greater toxicities included 1 patient with neutropenia, 3 patients with fatigue, 3 patients with diarrhea, 1 patient with nausea and vomiting, 1 with neuropathy, 1 with dyspepsia/ulcer, and 2 patients with hypersensitivity reactions. Preliminary showed 2 patients having a CR (11%) and 10 patients having a PR (52 %) in 19 evaluable patients, with an overall response rate of 63%. Median TTP was 12 months and median survival is 18.3 months [95].

The 2nd study looked at the same weekly dosing of docetaxel and Herceptin® as described above, but allowed for previous metastatic chemotherapy [96]. Of 12 patients evaluable for response and toxicity, 8 patients had received one metastatic chemotherapy regimen and 3 had received 2 prior metastatic regimens. Seventy-six doses of docetaxel and 80 doses of Herceptin® had been administered. No grade 3 or 4 toxicity was observed. The most frequent non-hematologic toxicities observed were fatigue (4 patients), dyspepsia (4 patients), diarrhea (4 patients), nausea (4 patients). Six patients achieved a PR (50%), 5 patients had stable disease and 1 patient had her disease progress. Median duration of response was 3.8 months.

The final study looked at weekly docetaxel and Herceptin® in metastatic HER2 2+, HER2 3+ or FISH positive patients [28]. Of 20 patients, 17 had received prior chemotherapy, either as adjuvant or metastatic. One cycle is defined as 3 weekly administrations of docetaxel and Herceptin® followed by 1 week of rest. A median of 7 cycles was given. Grade 3, 4 neutropenia was observed in 6 patients. No febrile neutropenia, anemia or thrombocytopenia was observed. Grade 3 or 4 nonhematologic toxicity included 1 patient with catheter-related bacteremia, 1 patient with diarrhea, 1 patient with neuropathy, 5 patients with fatigue, 1 patient with pleural effusion, 1 patient with asymptomatic transitory decrease in LVEF below 50%, and 1 patient with congestive heart failure. Twelve patients (60%) had a PR, 5 patients had stable disease for at least 4 months. Median TTP is 7 months.

2.4.5 Docetaxel, Platinum salt (carboplatin or cisplatin) and Herceptin® Multicentric Pilot Phase II Trials (TCH)

Based on biologic data demonstrating pharmacologic synergy between Herceptin® and both docetaxel and platinum analogs in terms of antitumor activity, and to avoid the cardiac toxicity associated with anthracycline-Herceptin®-based combination regimens, BCIRG has proceeded with 2 pilot TCH phase II trials, one combining docetaxel/Herceptin® and carboplatin (BCIRG 102) and one combining docetaxel/Herceptin® and cisplatin (BCIRG 101).

The primary objectives of these pilot studies [97, 98] are to evaluate the efficacy and safety of TCH as therapy for patients (pts) with HER2 -positive advanced breast cancer. Secondary objectives are duration of response, time to disease progression and survival. A total of 120 HER2 positive (immunohistochemistry and/or fluorescence in situ hybridization [FISH]) stage IIIb/IV breast cancer pts were planned to be treated (60 pts per trial). Eligible patients were treated with Herceptin® 4mg/kg on day 1 (90-min IV infusion) followed by 2mg/kg weekly (30-min IV infusion) plus docetaxel 75mg/m^2 (1-h IV infusion) and either cisplatin 75mg/m^2 (1-h IV infusion) or carboplatin (AUC of 6 mg/mL/min) on day 1 every 3 weeks (for 6-8 cycles). All patients are to continue weekly Herceptin® until disease progression. A total of 62 patients were registered into the BCIRG 101 pilot (docetaxel, cisplatin and Herceptin®), with results currently available on 62 patients for safety and efficacy [97]. A total of 62 patients were registered into the docetaxel, carboplatin and Herceptin® pilot (BCIRG 102) with results currently available on 58 patients for efficacy and 62 patients for safety [Baseline patient and tumor characteristics are found in Table 2. Data presented is effective as of October 2001.

Table 2 Patient and Tumor Baseline Characteristics, TCH Pilots

	BCIRG 101 Pilot T Cisplatin H	BCIRG 102 Pilot T Carboplatin H
N	62	62
Median age (range)	52 (29 – 76)	54 (31 – 76)
ECOG PS 0 1 2	40 (65%) 20 (32%) 2 (3%)	36 (58%) 25 (40%) 1 (2%)
Organs Involved 1-2	40 (65 %)	42 (68 %)

≥ 3 organs	22 (35 %)	20 (32 %)
Organ Involvement		
Visceral	43 (69 %)	43 (70 %)
- Liver	24 (39 %)	16 (26 %)
- Lung	25 (40 %)	31 (51 %)
Brain	1 (2%)	3 (5%)
Bone Metastases	29 (47 %)	28 (46 %)
Bone Lytic Only	4 (6 %)	5 (8 %)
Prior Adjuvant Chemotherapy	36 (58 %)	35 (56 %)
- anthracycline CT	20 (32 %)	28 (45 %)
- taxane CT	0	9 (15 %)
Prior Metastatic Chemotherapy	0	3 (5 %)

Of note, patients treated with TCarboH had a higher percentage of lung metastases, prior adjuvant treatment with taxanes and anthracycline, prior chemotherapy for metastatic disease, and presence of brain metastases than patients treated with TCisH. On the other hand, patients treated with TCisH had a higher percentage of liver metastases.

Overall, both treatment regimens were feasible and well tolerated. A total of 389 cycles of chemotherapy (docetaxel-cisplatin) and 1,937 doses of Herceptin® were administered to 62 patients for the TCisH pilot population. In the TCisH pilot, the median number of cycles given was 6 (range 3-8). Two patients had received ≤ 3 cycles, 3 patients had received 4 cycles, 4 had received 5 cycles, 34 (55%) had received 6 cycles, and 19 (31%) had received > 6 cycles. There were 9 (15 %) chemotherapy discontinuations, 2 patients for progressive disease, 3 for adverse events (2 patients for grade 3 neurosensory at cycle 5 and 1 patient who developed congestive heart failure at cycle 4), 3 patients went to surgery, and one patient withdrawal. Of the 389 cycles of chemotherapy given, there were 8 dose reductions with docetaxel (4 for non-hematological toxicity, 1 with hematological toxicity only, and 3 with both hematological and non-hematological toxicities), and 11 dose reductions with cisplatin, 7 of which were for non-hematological toxicity, 3 of which were for both hematological and non-hematological reasons, and 1 which was not study drug related.

A total of 385 cycles of chemotherapy (docetaxel-carboplatin) and 1, 956 doses of Herceptin® have been administered in 62 patients in the TCarboH pilot population. Median number of cycles given was 6 (range 2-13). Of 62 patients, six patients had ≤ 3 cycles, 2 had 4 cycles, 2 had 5 cycles, 35 (56%) had 6 cycles, and 16 (26%) patients had > 6 cycles. There were 10 discontinuations (16%) in the TCarboH pilot, 6 with progressive disease, 1 patient withdrawal without experiencing any severe toxicity, and 3 patients with adverse events (1 patient with grade 3 diarrhea and edema at cycle 2, 1 patient with cardiac tamponade probably related to tumor progression as cytologic examination pericardial effusion was positive for malignancy, 1 patient with pancytopenia and electrolyte imbalance). Of the 385 cycles of chemotherapy given, there were 18 dose reductions with docetaxel (10 for hematological toxicity, 6 for non-hematological toxicity, 2 for both), and 16 dose reductions with carboplatin (10 for hematological, 4 for non-hematological toxicities and 2 for both hematological and non-hematological toxicities).

Of the 62 patients in the TCisH pilot, 8 (13%) had a febrile neutropenia event, compared to 10 of 62 patients evaluable for safety (16%) in the TCarboH pilot. There were 2 (3%) infectious episodes in the TCisH pilot, and no infectious episode in the TCarboH population. There were no septic deaths in either pilot. There were 6 grade 3 / 4 anemia events (9%) in the TCisH pilot and 4 events (6%) in the TCarboH pilot. No patient developed a grade 3 or 4 thrombocytopenia in the TCisH pilot compared to 7 events (12%) in the TCarboH pilot.

Non-hematological toxicities are found in Table 3. Although the TCisH regimen showed a less favorable overall non-hematological toxicity profile compared to that of the TCarboH, there was no substantial difference between the 2 regimens when considering grade 3 / 4 toxicities.

Table 3 Non-Hematological Toxicity

	BCIRG 101 TCisH		BCIRG 102 TCarboH	
N	62		62	
	Overall	Grade 3 / 4	Overall	Grade 3 / 4
Alopecia	58 (94 %)	n/a	**43 (69 %)**	n /a
Asthenia	**58 (94 %)**	11 (18 %)	**50 (81 %)**	**11 (18 %)**
Gastrointestinal				
- Nausea	56 (90 %)	11 (18 %)	**43 (69 %)**	**7 (11 %)**
- Vomiting	**45 (69** %)	7 (11 %)	**26 (42 %)**	**5 (8 %)**
- Diarrhea	**45 (73 %)**	7 (11 %)	**32 (52 %)**	**3 (5 %)**
- Stomatitis	29 (47 %)	2 (3 %)	**31 (50 %)**	2 (3 %)
- Constipation	**16 (26 %)**	**0**	**18 (29 %)**	0
Myalgia / arthralgia	**18 (29 %)**	0	**14 (23 %)**	**3 (5 %)**
Nail Changes	17 (27 %)	0	**9 (15 %)**	0
Neurologic				
- Sensory	**37 (60 %)**	**2 (3 %)**	**26 (42 %)**	0
- Motor	**7 (11 %)**	**1 (2%)**	**9 (15 %)**	1 (2%)
Ototoxicity	**23 (37 %)**	1 (2%)	2 (3%)	0
Peripheral Edema	**25 (40 %)**	1 (2%)	**20 (32 %)**	1 (2 %)
Renal	25 (40 %)	2 (3%)	**1 (2%)**	0
Skin rash / erythema	**17 (27 %)**	1 (2%)	**18 (29 %)**	1 (2 %)

Left ventricular ejection fraction (LVEF) by MUGA or echo was required at baseline, every 12 weeks, at completion of chemotherapy and during Herceptin® therapy at any suspected change (TCarboH) or every 3 months in follow-up (TCisH). In addition to LVEF monitoring, cardiac toxicity was recorded using the NCI Common Toxicity Criteria, version 1.0. In the TCisH population, one 60-year-old patient developed congestive heart failure, with an absolute LVEF decrease of ≥ 15 points from baseline and below the institution's lower limit of normal. Of note, this patient had a prior history of coronary disease and had received radiation therapy to the left chest wall. Ten patients had asymptomatic decreases of LVEF. Four of these patients had an absolute decline by more than 20 points from baseline, 4 had a decline of ≥ 15 points from baseline and below the lower limit of normal, and 2 had asymptomatic decreases ≥ 10 points from baseline and below the institution's lower limit of normal. Two patients developed a grade 1 and grade 2-dysrhythmia toxicity, respectively.

In the TCarboH pilot, 1 patient developed congestive heart failure. She had no prior history of cardiac disease. Seven patients had asymptomatic decreases of LVEF. Of these 7 patients, two had an absolute decline by more than 20 points from baseline and below the institution's lower limit of normal. Three of these 7 patients had declines of ≥ 15 points from baseline and below the institution's lower limit of normal, and the remaining 2 had declines of ≥ 10 absolute points, respectively. One patient developed a grade 3-dysrhythmia toxicity.

The TCH regimen avoids the potential cardiac toxicity when Herceptin® is used with, or after, anthracycline based regimens. As noted earlier in the H0648g, study patients treated with concurrent administration of Herceptin® and AC had an increased risk of class III/IV cardiac dysfunction (16%) compared to patients treated with doxorubicin and cyclophosphamide alone (3%). Only 1 incident of Grade 3 cardiac dysfunction was found in each of the TCH studies and appears favorable when compared with the H0648g results [(Table 4).

Table 4 H0648g and TCH Pilots: Severe Toxicities

	H0648g		TCH Pilots	
	AC+H	Taxol®+H	TCisH	TCarboH
Febrile Neutropenia	NA	NA	13 %	16 %
Infection	2 %	1%	3 %	0
Nausea	6 %	3 %	18 %	11 %
Vomiting	3 %	9 %	11 %	8 %
Stomatitis	1 %	0	3 %	3 %
Neurosensory	0	2 %	3 %	0
Neuromotor	NA	NA	2 %	2 %
Arthralgia / Myalgia	< 1 %	9 %	0	5 %
Asthenia	7 %	8 %	18 %	18 %
Class III/IV Cardiac dysfunction	16%	2 %	*1.6 %*	*1.6 %*

AC= anthracycline and cyclophosphamide; H=Herceptin®; T=docetaxel; Cis=Cisplatin; Carbo=Carboplatin

Preliminary response data are found in Tables 5 and 6, respectively. In the TCarboH (Table 5) pilot, three patients had received prior treatment for metastatic disease. Of the 59 patients who were treated as first line in the pilot trial, 55 were evaluable for efficacy and had a FISH result available. In the TCisH (Table 6) pilot, of the 62 patients evaluable for efficacy, 54 had a FISH result available only.

Table 5 TCarboH Pilot Preliminary Response Data in Metastatic Breast Cancer Patients

	1st and 2nd line patients			**1st line patients only**		
	FISH Positive	**FISH Negative**	**Fish Pending**	**FISH Positive**	**FISH Negative**	**Fish Pending***
CR	*7*	*1*	*0*	7	1	0
PR	***16***	*6*	***1***	**16**	6	**1**
MR	**2**	**1**	**1**	**2**	**1**	**1**
SD	***7***	***7***	***0***	**6**	**7**	**0**
PD	***7***	*2*	*0*	**5**	2	0
ORR	***23/39 (59%)***	***7/17 (41%)***	***1/2 (50%)***	**23/36 (64%)**	**7/17 (41%)**	**1/2 (50%)**
(Not evaluable)	**2**	**2**	**0**	**2**	**2**	**0**

*FISH testing is still ongoing

Table 6 TCisH Preliminary Response Data in 1st Line Metastatic Breast Cancer Patients

	FISH Positive	FISH Negative	FISH Pending	TOTAL
CR	**2**	**1**	**0**	**3**
PR	**25**	**15**	**6**	**46**
SD	**8**	**2**	**2**	**12**
PD	0	**1**	**0**	**1**
ORR	**27/35 (77%)**	**16/19 (84%)**	**6/8 (75%)**	**49/62 (79%)**

Response rates in the H0648g study are lower than seen in the available TCH pilot results in a very similar patient population. See Table 7. Efficacy data based on those patients who are FISH positive is also presented. The TCH regimens show promising response activity. Of note, the difference is more evident in the FISH positive subpopulation.

Table 7 Efficacy Data, HO648g Pivotal Study versus TCH Pilots in 1st Line Metastatic Breast Cancer

	H0648g AC – H	H0648g Taxol® - H	TCisH Pilot	TCarboH Pilot
Pts IHC 2+ or 3+	143	92	62	54
ORR	56 %	41%	84%	57%
95% CI	[48-64]	[31-51]	[72-92]	[43-71]
Pts Fish Positive	107	69	**35**	**36**
ORR	57%	49%	**77%**	**64%**
95% CI	[48-67]	[38-61]	**[59-90]**	**[46-79]**
Pts IHC 2+ or 3+	**143**	**92**	**62**	**59**
TTP	**7.8**	**6.9**	**9.9**	**12.0**
95% CI	**7.3-9.4**	**5.3-9.9**	**8.3-13.1**	**7.4-16.3**
Pts Fish positive	**107**	**69**	**35**	**38**
TTP	**7.6**	**7.1**	**12.7**	**17.0**
95% CI	**7.1-9.4**	**3.9-14.1**	**9.2-13.1**	**9.1-NE***

***NE: Not Estimate**

^ TCarboH Pilot: data only from the 1st line metastatic patients is presented in this table.

In conclusion, the TCisH and TCarboH phase II multicenter studies in this metastatic HER2 positive patient population have shown that these regimens are feasible, very active with an acceptable toxicity profile without any enhancement of the expected toxicity of the individual agents. TCH avoids the potential cardiac toxicity when Herceptin® is used in combination with anthracycine.

2.5 Rationale for the Present BCIRG 007 Trial

2.5.1 Rationale, General

This trial represents a unique design based on molecular, biologic and clinical data rather than the historic approach of adding a new therapeutic to what is already used regardless of the concern or potential contradictions. The cardiotoxicity risks associated with AC - Herceptin® regimen limit the combination of Herceptin®- and anthracycline- based therapies, which according to the results of the pivotal HO648g trial (see Table 1), appear to be more active than the Paclitaxel + Herceptin® regimen. Therefore, new regimens integrating Herceptin® with non-anthracycline drugs are warranted in order to further improve the time to progression and, ultimately, the survival of HER2 positive metastatic breast cancer patients.

2.5.2 Justification of the Comparator Docetaxel (Taxotere®)+Herceptin®

The comparator arm of the BCIRG 007 study is docetaxel + Herceptin®, which consists of 8 cycles of docetaxel at the recommended dose of 100 mg/m^2 and Herceptin® given weekly and continued after the 8th cycle until progression. The rationale for the selection of this comparator is as follows:

1. Paclitaxel + Herceptin® has recently been approved worldwide as first line treatment for HER2 positive metastatic breast cancer patients.
2. Single-agent docetaxel appears to be more active than paclitaxel in metastatic breast cancer (see section 2.4.1).
3. Preclinical in vitro and in vivo studies have demonstrated synergistic effects with docetaxel when combined with Herceptin® [29] while additive effects have been noted with paclitaxel [30]. See section 2.3.4.
4. The combination of docetaxel and Herceptin® is a new Herceptin®-containing regimen, which avoids the cardiac toxicity associated with anthracycline-Herceptin® based combination regimens (see section 2.3.2).
5. The available phase II experience with docetaxel in combination with Herceptin® in HER2 positive metastatic breast cancer patients shows that this regimen is at least as effective as paclitaxel in combination with Herceptin® (see 2.4.4).

2.5.3 Justification of Docetaxel (Taxotere®) + Carboplatin + Herceptin®

1. The combination of either Cisplatin or Carboplatin with docetaxel is highly active in metastatic breast cancer with an acceptable toxicity profile (see sections 2.4.2 and 2.4.3).
2. Preclinical studies have demonstrated that the most significant interaction is a synergistic therapeutic effect between cisplatin or carboplatin and Herceptin® (see section 2.3.3).
3. Based on these above data, 2 pilot studies (BCIRG 101 and BCIRG 102) have been conducted and are showing that both treatments were feasible, well tolerated and very active in metastatic breast cancer.
4. Preclinical data suggests that cisplatin and carboplatin are equally active and synergistic when combined with Herceptin® [29]. The efficacy data of the pilot phase II studies described in section 2.4.5, show that both regimens (TCarboH) and (TCisH) have a similar activity in HER2+ metastatic breast cancer patients, particularly in term of Time to Progression. On the other hand, although both regimens are safe and feasible (more than 80% of patients in both regimens received at least 6 cycles), the safety profile of TcarboH was better than that of TcisH: TcarboH showed less nausea, vomiting and diarrhea. There is no grade III-IV oto or renal toxicity with TcarboH regimen.

   In addition, it should be noted that more than 90% of the participating centers have chosen carboplatin. Therefore, the selection of carboplatin in the TCH arm will definitely homogenize TCH regimen and will make the analysis easier to interpret.

   The centers that have started treating patients with Cisplatin in the TCH combination prior the protocol being amended will treat those specific patients with Cisplatin for their remaining cycles.

2.5.4 Justification of qWeekly and q3Weekly Herceptin® Administration

Two studies are looking at the safety, efficacy and pharmacokinetics of Herceptin® when administered every 3 weeks in patients with HER2 positive (by immunohistochemistry or FISH) metastatic breast cancer [35]. The data indicates that the higher doses of Herceptin® are well tolerated and the q3weekly administration of Herceptin® is feasible. Despite the fact that the peak serum concentrations and AUC of the q3weekly schedule were higher than the peak of serum concentration and AUC of the weekly schedule (see section 2.3.3), the safety profile of the q3weekly Herceptin® (as monotherapy or in combination with paclitaxel) did not differ from that seen with the weekly schedule. Therefore it seems that the peak of serum concentration and the AUC at the doses explored with the two different schedules do not have a significant impact on the safety of Herceptin®. In addition, a recent study, conducted in 114 patients with HER2 overexpression metastatic breast cancer [36], comparing two different doses of Herceptin® (i.e. loading dose of 4 mg/kg followed by 2 mg/kg weekly versus loading dose of 8 mg/kg followed by 4 mg/kg weekly) did not show a clear evidence of a dose response relationship for adverse events including cardiac toxicity, as well as response or survival. It is interesting to note that the half-life of Herceptin® is similar in the two schedules and that the predose concentrations as week 3 with the q3weekly schedule were lower than seen with the weekly schedule. Response rates from the paclitaxel and Herceptin® study were also very similar. We thus propose to administer Herceptin® every 3 weeks instead of every week during the follow-up period starting 3 weeks after the last chemotherapy infusion, in order to reduce the frequency of visits and improve the compliance with Herceptin® administration. On the other hand, weekly schedule of Herceptin® will be maintained during chemotherapy since there are no efficacy and safety phase II data with q3 weeks Herceptin® in combination with Taxotere® and Platinum salts.

2.5.5 Justification of Central Pathology Review

Some markers may be considered predictors of response to certain anticancer agents (see Appendix 3). By predetermining the

biological characteristics of a patient's tumor, therapies may be specifically targeted to those patients whose tumor has a characteristic, which predicts an increased response to the anticancer agent. The FISH test is able to predict the type of tumor that will benefit from Herceptin® (see section 2.5.5).

Although the tumor block is mandatory for the FISH and central pathology review, testing for the designated tumor markers and future testing is not mandatory. Refusal to grant permission for further testing will not affect the quality of care the participant is to receive.

2.5.5.1 Mandatory Tests on Tumor Sample

A central pathology review will be performed on sections derived from the paraffin block submitted for FISH testing. Hormone receptor analysis will also be performed.

2.5.5.2 Optional Tests on Tumor Sample

Additional testing for markers on the tumor sample is proposed. These markers include: p53, members of the bcl family (Bcl-2, bax, Bcl-X and Bag-1), MUC1 and Tubulin isoforms (particularly II, III, IV and Tau). Those factors, which are proven to have predictive utility in ongoing trials, will be tested in the current trial in order to ensure comparability between groups.

The area of research into the identification of tumor markers and biological processes / targets to aid in the identification of clinical benefit in certain subsets of populations or even in the identification of anticancer therapies to target the marker, is rapidly growing. Following the mandatory FISH testing and central pathology review for the study, BCIRG wishes to store the tumor sample for future testing. As more development and information is revealed to us in the future, we would like to use these blocks for measurement of the new markers. The blocks will be stored in the central laboratory until future use is required. BCIRG may collaborate in the future with experts in the field, and the blocks (or portions thereof) may be shared with other researchers. A current example of this is the collaboration with Dr. J.C. Reed from the Burnham Institute who will be researching the blocks for the Bcl family.

2.5.5.3 Optional Tests on Serum Sample for ECD Determination

Serum assays for HER2 are currently being investigated. This may prove to be a more practical means of testing for HER2 and thus targeting those patients who will benefit most from Herceptin®. Serum samples will be collected prior to treatment in order to detect the levels of shed extracellular domain (ECD) of HER2 in peripheral blood for comparison with the FISH test as a predictive factor in a patient's outcome with Herceptin®-containing regimens. Serum samples will also be collected at the timing of tumor assessments during chemotherapy treatment, in follow-up and at disease progression in order to correlate changes in ECD levels with the objective tumor progression.

Additional testing of molecular markers and assays for HER2 may be performed on the serum sample in the future as new developments become available.

Provision of the serum sample to the central laboratory is not mandatory. Refusal to grant permission for collection and release of the blood samples for the above mentioned purpose will not affect the quality of care the participant is to receive.

2.5.6 Justification of New Response Evaluation Criteria in Solid Tumors (RECIST) guidelines for use in BCIRG 007.

The RECIST criteria to assess the response to antitumor therapy will be used in this study [99]. These guidelines are the result of a large international collaboration for a homogeneous evaluation of the tumor response. Participants to this consensus meeting included representatives from academia, industry, and regulatory authorities. 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.

2.5.7 Optional Cardiovascular Substudies

This trial affords a unique opportunity to prospectively follow and evaluate the cardiovascular effects of two chemotherapeutic regimens that include Herceptin®. Analysis of outcomes in this large clinical trial holds the potential for the future development of guidelines to prevent the development of symptomatic heart failure from chemotherapeutic agents and, in particular, regimens containing Herceptin®. Initial steps in prevention of cardiotoxicity include:

1) Identification of patients at high risk of developing heart failure who may not be good candidates for Herceptin® therapy and
2) Early detection of ventricular dysfunction, before clinical heart failure develops. Early detection of ventricular impairment may open the window for early treatment, which has been previously shown to improve outcomes in heart failure.

In addition to the serial monitoring of left ventricular ejection fraction by echocardiography or radionuclide imaging, we propose the examination of genetic and biochemical markers as an adjunct to the serial LVEF determinations.
The objectives of the cardiovascular substudy include:

1) The potential for development of pretreatment screening tools to identify patients at high risk of developing LV dysfunction through assessment of genetic markers, and
2) The potential for early detection of ventricular dysfunction, before clinical heart failure develops through serial measurements of Troponin I and brain natriuretic peptide (BNP).

These strategies would allow for the safe identification of patients best suited for Herceptin® treatment and tailored treatment strategies.

2.5.7.1 Genetic Markers

The human population is biologically diverse and genetically heterogeneous. Therefore, it is not surprising that differences in susceptibility to disease among individuals exist. The etiologies of many diseases including heart failure are due to a combination of factors, including genetic susceptibility and environmental exposures. Subtle differences in the genes that regulate cellular growth and development, DNA replication and repair, the metabolism of endogenous agents in the body, and the metabolism and excretion of exogenous agents that the body comes in contact with, contribute to the risk of developing a disease. Identification and characterization of human genetic variation is providing new risk factors for disease in the form of DNA sequence variation. Single-nucleotide polymorphisms (SNPs) are common variations among the DNA of individuals, which can increase the risk of developing disease. Identifying these SNPs and the genes in which they reside is an important area in human genomics.

Recently genetic polymorphisms involving pathways mediating cardiac function, such as the β-adrenergic, angiotensin, and endothelin receptors, have been identified, which are associated with increased risk of cardiomyopathy and heart failure death [100-102]. The results of these studies are summarized in Table 1. Polymorphisms in a host of other genes including likely candidates such as BNP, IL-10, TNFα, TGFβ1, NOS3, Endothelin 1, Endothelin B receptor have been tested but have not demonstrated any association with heart failure incidence or prognosis. Likewise, polymorphisms in the HER2 signaling pathway itself may predispose to the development of cardiac dysfunction in response to Herceptin®. It has been shown that polymorphisms in HER2 are linked to the risk of breast cancer although its effects on cardiac function are unknown [103].

Table 1. Proposed Polymorphisms

Polymorphism	Type of Mutation	Effects on CHF Mortality or Morbidity	Reference
Angiotensin Converting Enzyme			
I/D	Insertion/Deletion	↑	[101]
β2-adrenoreceptor			
Gly16/Gln27	SNP	↓	[104]
Ile164	SNP	↑	[100]
ET Receptor A			
ETA C1363T	SNP	↑	[102]
HER2	SNP	?	[103]

SNP= single nucleotide polymorphism

Analyzing these genetic polymorphisms and correlating them with the development of LV dysfunction in the study population will allow identification patients at high risk of developing cardiac dysfunction secondary to chemotherapy with or without Herceptin®. To identify patients susceptible to Herceptin®-induced left ventricular dysfunction, we will examine polymorphisms previously associated with heart failure (ACE, β2-adrenoreceptor receptor, and the Endothelin A receptor) and HER2 polymorphism. A sample of whole blood will be requested prior to treatment administration. UCLA will isolate genomic DNA from these samples. UCLA will assay each subject's DNA for the five genetic polymorphisms described above using conventional PCR or a TaqMan assay. The SNP alleles will be analyzed for association with susceptibility to develop cardiomyopathy in response to Herceptin® and anthracyclines.

2.5.7.2 Biochemical Markers

2.5.7.2.1 Brain Natriuretic Peptide

Natriuretic peptides, brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) are released in response to myocardial stretch and injury. ANP and BNP, promote natriuresis and vasodilation as well as suppressing the renin-angiotensin system, attenuating the hemodynamic disturbances seen in heart failure. The levels of these peptides are elevated in both patients with heart failure and patients with asymptomatic cardiac dysfunction Indeed, BNP is elevated before heart failure symptoms develop and may permit early detection of early cardiac dysfunction [105]. In a comparative study, levels of ANP, N-terminal ANP, and BNP were measured in patients referred to a heart failure clinic. Levels of all three peptides were significantly higher in patients found to have heart failure by clinical assessment and echocardiography. However, BNP was reported to have the highest sensitivity, specificity, and positive predictive value compared to ANP and N-terminal ANP for the diagnosis of heart failure. BNP also has been used to predict the development of heart failure in healthy subjects [106].

Preliminary studies have looked at the utility of the BNP assay in detection of chemotherapeutic cardiotoxicity. A study from Japan measured several biochemical markers before and after anthracycline chemotherapy including BNP, ANP, norepinephrine, aldosterone, angiotensin II and CK-MB. Only BNP had significantly elevated post-chemotherapy values [107]. Elevations in BNP levels have also been correlated with subclinical myocardial dysfunction [108].

2.5.7.2.2 Cardiac Enzymes

Troponins are proteins involved in the regulation of both cardiac and skeletal muscle contraction, via their calcium-mediated interaction with actin and myosin. Cardiac troponins (cTnT and cTnI) are encoded by different genes than skeletal troponins and thus have unique amino acid sequences easily distinguished by immunologic assays. Troponins are not normally found in the circulation and their presence in the sera is indicative of myocardial injury and loss of cell membrane integrity. Circulating levels of the Troponins are specific indicators of myocardial damage, more sensitive than the creatinine phosphokinase MB isoenzyme. The troponin assay (cTnT and cTnI) are widely used to aid in diagnosis of myocardial ischemia and holds prognostic value. Elevated levels of circulating Troponins are independent predictors of both short- and long-term mortality.

Recent studies have demonstrated that circulating troponin levels are associated with the presence and severity of heart failure of both ischemic and nonischemic etiology [109]. Mechanisms of release of troponins from the myocytes into the circulation are unknown but may include recurrent ischemia, impaired subendocardial perfusion, apoptotic cell death, and myocardial remodeling. Furthermore, there is a recently evolving role for troponins in heart failure prognosis. Cardiac troponins have been shown to predict the development of myocardial dysfunction and heart failure in patients receiving chemotherapeutic agents that are potentially cardiotoxic. A 1999 study demonstrated elevated troponin T in close to 30% of children receiving anthracycline-based chemotherapy for ALL. Higher troponin elevation correlated with higher cumulative anthracycline dose and future elevated troponin values, suggesting chronically active cardiac injury [110]. Initial studies in rats show troponin T to be a sensitive means of predicting anthracycline cardiotoxicity in rats [111]. A recent study from Italy demonstrated troponin I to be a significant predictor of future development of significant and prolonged cardiac dysfunction. Patients with positive troponin values had significantly decreased mean left ventricular ejection fraction at end of 7 month follow up compared to those with negative troponin values who did not. Furthermore, a LVEF of less than 50% was seen during follow up in 30% of positive troponin patients but none of troponin negative patients [112].

Studies to date have shown elevations in BNP and Troponin to be predictors of the later development of anthracycline-induced cardiac dysfunction. To determine prospectively if these markers are useful for the early detection of LV dysfunction related to Herceptin®, we propose to make serial measurements of cTnI throughout the study. The assays are also to be drawn at time of any clinical evidence of cardiac failure (chest pain, dyspnea, fluid overload, sinus tachycardia).
Plasma samples are to be collected the same time as LVEF one, at baseline, end of cycles 3, 6, end of chemotherapy and then every 4 months during the first 2 years of follow-up and at any time of clinical evidence of cardiac failure (chest pain, dyspnea, fluid overload, arrhythmias).

III STUDY OBJECTIVES

Primary Objective

To evaluate time to disease progression after treatment with either Herceptin® in combination with single-agent docetaxel (TH) or Herceptin® with carboplatin and docetaxel (TCH) in advanced breast cancer patients previously untreated with chemotherapy for advanced disease and whose cancer contains the HER2 HER2 gene amplification.

Secondary Objectives

To compare response rate, duration of overall response and overall survival.

To evaluate and compare the rate of clinical benefit, defined as CR, PR, or stable disease > 24 weeks.

To compare toxicity between the 2 arms.

To evaluate pathologic and molecular markers for predicting efficacy.

To correlate baseline peripheral levels of shed HER2 extracellular domain (ECD) with baseline FISH results and to determine whether peripheral levels of shed HER2 ECD constitute a prognostic and/or predictive factor vis-à-vis time to progression and survival.

To evaluate genetic and biochemical markers for predicting risk of developing cardiac dysfunction and later cardiac events in these patient groups.

IV PATIENT DEFINITION

4.1 NUMBER OF PATIENTS / ENROLLMENT / FOLLOW-UP PERIOD

This is a multicenter, international randomized study involving two hundred and fifty (250) patients enrolled by centers throughout the BCIRG network. Enrollment starts in December 2001 and is expected to last 27 months, until March 2004. The exact period of follow-up will be determined as per the statistical analyses.

4.2 DURATION OF TREATMENT

All included patients in each arm will be randomized to one of the follow treatments:

TH: Docetaxel single agent 100 mg/m^2 q3weeks x 8 cycles. Herceptin® will be administered weekly during treatment with chemotherapy. Three weeks after the last infusion of chemotherapy, Herceptin® will then be administered every 3 weeks.

TCH: Docetaxel 75 mg/m² and carboplatin at target AUC=6 mg/mL/min q3weeks x 8 cycles. Herceptin® will be administered weekly during treatment with chemotherapy. Three weeks after the last infusion of chemotherapy, Herceptin® will then be administered every 3 weeks.

Treatment will continue until disease progression, second primary malignancy (except for curatively treated non-melanoma skin cancer or carcinoma in situ of the cervix), unacceptable toxicity or withdrawn consent.

4.3 INCLUSION CRITERIA

1. Written informed consent prior to beginning specific protocol procedures including expected cooperation of the patients for the treatment and follow-up must be obtained and documented according to the local regulatory requirements.

2. Histologically or cytologically proven breast adenocarcinoma at first diagnosis.

3. Metastatic breast cancer.

4. Patients must have either measurable or nonmeasurable lesions according to the RECIST criteria.
   Patients having truly nonmeasurable lesions (see exclusion criteria # 4) as their only site of disease will not be eligible, with the following exception: osteolytic bone lesions as the only manifestation of the disease having at least two lytic sites present and confirmed by bone X-ray, MRI or CT scan.

5. Primary tumor or metastatic tumor must show the presence of the HER2 gene amplification by Fluorescence In-Situ Hybridization (FISH analysis) by a designated central laboratory (see Appendix 3A for complete details).

6. Age $\geq$ 18 years and age $\leq$ 75 years. The upper age limit is not meant to be exclusionary but rather is based on the lack of safety data for the TCH regimen in women >75 years of age.

7. Karnofsky Performance status index $\geq$ 60%.

8. Previous Therapy

   a. Hormonal therapy

   Patients may have had previous hormonal therapy as adjuvant treatment and/or as treatment for metastatic disease provided that the patient has progressive disease at study entry and the hormonal agent has been stopped at the time of randomization.

   b. Chemotherapy

   Patients may have had adjuvant and/or neoadjuvant chemotherapy.
   Patients having received a taxane, as prior adjuvant and/or neoadjuvant therapy are eligible providing the relapse occurred at least 6 months following discontinuation of the taxane.

   Patients having received a taxane and Herceptin® as prior adjuvant and/or neoadjuvant therapy are eligible providing the relapse occurred at least 12 months after the last administration of Herceptin®.

   Patients having received an anthracycline or anthracenedione containing regimen as prior adjuvant and/or neoadjuvant therapy for any past or current neoplasm are eligible provided the total cumulative dose received is as follows: doxorubicin $\leq$ 360 mg/m^2 or epirubicin $\leq$ 720 mg/m^2 or mitoxantrone $\leq$ 72 mg/m^2 and treatment stopped at least 4 weeks prior to study registration.

   Patients CANNOT have had chemotherapy for locally advanced or metastatic breast cancer i.e. the treatment allocated in this study should be first line chemotherapy for metastatic disease.

   c. Herceptin®

   Patients having received a Herceptin®-containing regimen (except Herceptin® and taxane combination) as prior adjuvant and/or neoadjuvant therapy are eligible providing the relapse occurred at least 6 months following discontinuation of Herceptin®.

   Patients CANNOT have had Herceptin® for locally advanced or metastatic breast cancer.

d. Radiotherapy

Previous radiation therapy may have been given providing at least 4 weeks has elapsed from the end of radiotherapy and study registration unless radiotherapy involved only one single field to treat one single metastatic bone lesion. For evaluation of any previously irradiated lesion in the study, clear progression must have been shown at study entry.

9. Patients must have fully recovered from toxic effects of previous antitumor therapy, excluding alopecia.

10. Normal cardiac function must be confirmed by LVEF (MUGA scan or echocardiography) and ECG within 1-month prior o registration. Result for the LVEF must be above or equal to the lower limit of normal for the institution.

11. Laboratory requirements: (within 7 days prior to registration)

a. Hematology:
Neutrophils $\geq 1.5 \times 10^9$/L
Platelets $\geq 100 \times 10^9$/L
Hemoglobin ≥ 10 x g/dL

b. Hepatic function:
Total bilirubin $\leq$ 1 UNL
ASAT (SGOT) and ALAT (SGPT) $\leq$ 5 UNL
Alkaline phosphatase $\leq$ 5 UNL; except in presence of bone metastases or any non-malignant bone disease and in absence of any liver disorders.
Patients with ASAT and/or ALAT > 1.5 x UNL **associated** with alkaline phosphatase > 2.5 x UNL are not eligible for the study.
Patients with prior history of viral hepatitis (B, C) (serology performed) with transaminases (ASATand ALAT) and Alkaline Phosphatase and total bilirubin > 1 UNL are not eligible for the study.

c. Renal function:
Creatinine $\leq$ 175 µmol/L (2 mg/dL)
If creatinine is between 140 – 175 µmol/L (1.6-2.0 mg/dL), the creatinine clearance (calculated or measured) should be $\geq$ 60 mL/min.

12. Complete radiology and tumor measurement work up within 4 weeks prior to registration.

a. Chest (AP and Lateral)
Chest X-ray and/or chest CT scan and/or MRI.

b. Abdomen
Abdominal CT scan and/or MRI and/or ultrasound. If abdominal ultrasound is positive, abdominal CT scan and/or MRI must be performed and will be used to follow the patient throughout the entire duration of the trial.

c. Bone

Patients with tumor lesions other than only bone metastases are allowed to have only bone scintigraphy as the sole method to detect bone metastases at baseline. If the bone scintigraphy is positive, bone scintigraphy alone can be used to follow the patient throughout the entire duration of the trial.

Patients having bone lesions as their only site of disease must have bone scintigraphy as bone radiological work-up within the 4 weeks prior to registration. Bone X-ray and/or CT scan and/or MRI of hot spots detected on bone scintigraphy also must be performed and must be used to follow the patient throughout the entire duration of the trial.

13. Negative pregnancy test (urine or serum) within 7 days prior to registration for all women of childbearing potential. Patients of childbearing potential must implement adequate non-hormonal contraceptive measures during study treatment.

14. Patients must be accessible for treatment and follow-up. Patients registered in this trial must be treated and followed in a participating center.

4.4 EXCLUSION CRITERIA

1. Prior chemotherapy for locally advanced (stage IIIB) disease, local recurrence or metastatic disease.

2. Pregnant or lactating patients.

3. Prior treatment with Herceptin® for advanced breast cancer.

4. Prior Platinum salt containing regimen as adjuvant and/or neoadjuvant therapy for any past or current neoplasm.

5. One lytic bone metastasis, blastic bone metastases, mixed bone metastases, lymphangitic carcinomatosis, ascites, pleural/pericardial effusion, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses that are not confirmed and followed by imaging techniques, cystic lesions and/or irradiated not progressive lesions as only manifestation of metastatic disease.

6. Prior history or known clinical manifestation of brain or leptomeningeal involvement.

7. Non-metastatic disease as evidenced by local recurrent lesion within partially resected breast.

8. Concurrent treatment with any other anti-cancer therapy.

9. Pre-existing neuropathy-motor or sensory of a severity ≥ grade 2 by NCI CTC criteria, version 2.0.

10. Other serious illness or medical condition:
    a. Previous history of myocardial infarction within 1 year from registration;
    b. Unstable angina pectoris;
    c. Any history of documented congestive heart failure;
    d. Concomitant grade 3 or grade 4 cardiovascular arrhythmia (NCI CTC, version 2.0);
    e. Patients with poorly controlled hypertension i.e diastolic greater than 100 mm/Hg;
    f. History of significant neurologic or psychiatric disorders including psychotic disorders, dementia or seizures that would prohibit the understanding and giving of informed consent;
    g. Active uncontrolled infection;
    h. Active peptic ulcer, unstable diabetes mellitus;
    i. Patients with severe dyspnoea due to complications of advanced malignancy or respiratory insufficiency requiring supplemental O_2

11. Past or current history of neoplasm other than breast carcinoma, except for:
    a. Curatively treated non-melanoma skin cancer;
    b. Carcinoma in situ of the cervix;
    c. Other cancer curatively treated and with no evidence of disease for at least 10 years.

12. Chronic treatment with corticosteroids **unless** initiated > 6 months prior to study entry **and** at low dose (≤ 20 mg methylprednisolone or equivalent).

13. Concomitant therapy with any hormonal agent such as raloxifene, tamoxifen, or other selective estrogen receptor modulators (SERMs), given for breast cancer prevention or for osteoporosis. Patients must have discontinued these agents prior to registration.

14. Concomitant treatment with bisphosphonates may be used in patients with tumor lesions other than only bone lesions or for non-oncologic indications.

15. Definite contraindications for the use of corticosteroids.

16. Concurrent treatment with other experimental drugs. Participation in another clinical trial with any investigational not marketed drug within 30 days prior to study entry.

17. Known allergy reactions to any of the drugs used in the study.

18. Male patients, as no clinical efficacy or safety data are available from phase I-II studies.

V PLAN OF THE STUDY

5.1 General Study Plan

This is a prospective, *non-blinded, randomized*, phase III trial. Patients will be stratified at inclusion according to institution and prior adjuvant and/or neoadjuvant chemotherapy (none, chemotherapy with adjuvant and/or neoadjuvant taxane, chemotherapy without adjuvant and/or neoadjuvant taxane), and will be randomly assigned to receive treatment with TH or TCH until disease progression, second primary malignancy (except curatively treated non-melanoma skin cancer or carcinoma in situ of the cervix), unacceptable toxicity, or withdrawn consent.

- **TH: Docetaxel with Herceptin®:** Herceptin® 4 mg/kg loading dose by IV infusion over 90 minutes on Day 1 of Cycle 1 only, followed by Herceptin® 2 mg/kg by IV infusion over 30 minutes weekly starting on Day 8 until three weeks after the last cycle of chemotherapy. Beginning three weeks after the last cycle of chemotherapy, Herceptin® 6 mg/kg by IV infusion over 30 minutes will be given every 3 weeks. Docetaxel 100 mg/m^2 administered on Day 2 of Cycle 1, then on Day 1 of all subsequent cycles by IV infusion over 1 hour will be administered every 3 weeks for a total of 8 cycles. For all cycles except for cycle 1, docetaxel will be administered first followed by Herceptin®.

- **TCH: Docetaxel / Carboplatin / Herceptin®:** Herceptin® 4 mg/kg loading dose by IV infusion over 90 minutes on Day 1 of Cycle 1 only, followed by Herceptin® 2 mg/kg by IV infusion over 30 minutes weekly starting on Day 8 until three weeks after the last cycle of chemotherapy. Beginning three weeks after the last cycle of chemotherapy, Herceptin® 6 mg/kg by IV infusion over 30 minutes will be given every 3 weeks. Docetaxel 75 mg/m^2 will be administered on Day 2 of Cycle 1, then on Day 1 of all subsequent cycles by IV infusion over 1 hour followed by carboplatin at target AUC = 6 mg/mL/min administered by IV infusion over 30-60 minutes repeated every 3 weeks. A total of eight cycles of docetaxel and carboplatin will be administered every 3 weeks. For all cycles except for cycle 1, docetaxel followed by carboplatin will be administered first followed by Herceptin®.

The chemotherapy doses will be calculated according to baseline body surface area (BSA) for all cycles. If there is a 10% or greater decrease in body weight compared to baseline, the BSA will be recalculated.

If the calculated BSA of the patient is > 2.2 m², the dose to be given to the patient will be calculated according to BSA = 2.2 m². No ideal body weight should be used for the calculation of BSA.

Herceptin® dosing will be based on the baseline weight. Weekly weight measurements will be required for those patients receiving Herceptin® during chemotherapy and q3weekly weight measurements will be required for patients receiving Herceptin® during the follow-up phase. In case of a >10% increase or decrease in weight, Herceptin® dose should be recalculated using the new weight.

Dose reduction and/or treatment delay and treatment discontinuation are planned for each arm in case of severe hematological and/or non-hematological toxicities. See Section 5.4

- **Each Arm:** No more than 8 days should elapse between the date of randomization and the start date of the first cycle of chemotherapy.

5.2 Study Medication

For the purpose of this study, study medication will be defined as the chemotherapy in each of the study arms for the duration of the active treatment. Herceptin® will be included in the definition of study medication.

5.3 Study Treatment

Study treatment will be administered as follows unless unacceptable toxicity, disease progression, second primary malignancy (except curatively treated non-melanoma skin cancer or carcinoma in situ of the cervix), unacceptable toxicity or withdrawn consent.

5.3.1 TH Arm

A total of 8 cycles of docetaxel will be administered every 3 weeks. Herceptin® will be administered weekly during treatment with chemotherapy and then every three weeks during the follow-up period.

First cycle of Docetaxel / Herceptin® only

Day 1: Herceptin®* 4 mg/kg administered by IV infusion over 90 minutes.

Day 2: Docetaxel 100 mg/m^2 by IV infusion (in minimum 250 mL of normal saline or dextrose 5% solution) over 1 hour. During the first 5 minutes, the infusion must be done drop by drop in order to reduce the incidence of acute hypersensitivity reaction (AHSR).

Day 8: Herceptin®* 2 mg/kg administered by IV infusion over 30 minutes.

Day 15: Herceptin®* 2 mg/kg administered by IV infusion over 30 minutes.

* *See Table 8 for Herceptin® infusion times and post-infusion observation periods.*

Subsequent cycles (to start 3 weeks after Day 1 of 1st cycle)

Day 1: Docetaxel 100 mg/m² as 1 hour IV infusion, given every 3 weeks, followed by Herceptin®* 2 mg/kg IV infusion over 30 minutes.

Day 8: Herceptin®* 2 mg/kg administered by IV infusion over 30 minutes.

Day 15: Herceptin®* 2 mg/kg administered by IV infusion over 30 minutes.

Last cycle

Day 1: Docetaxel 100 mg/m² as 1 hour IV infusion followed by Herceptin®* 2 mg/kg IV infusion over 30 minutes.

Day 8: Herceptin®* 2 mg/kg administered by IV infusion over 30 minutes.

Day 15: Herceptin®* 2 mg/kg administered by IV infusion over 30 minutes.

Day 22: Herceptin®* 6 mg/kg administered by IV infusion over 30 minutes. (=EOC visit)

Herceptin®* will then be administered at 6 mg/kg by IV infusion over 30 minutes every 3 weeks. Initiation of the q3weekly infusion of Herceptin®* will correspond to the end of chemotherapy (EOC) visit.

Herceptin®* to continue until disease progression, second primary malignancy (except for curatively treated non-melanoma skin cancer or carcinoma in situ of the cervix), unacceptable toxicity or withdrawn consent.

TABLE 8 Herceptin® Infusion Times and Post-Infusion Observation Period (Refer to section 5.5.9 for further information)

Infusion of Herceptin®	Herceptin® Dose *Do not administer as i.v push or bolus*	Infusion Time (minutes)	**Total Observation Period starting at the time of the infusion[b].**
During Chemotherapy Cycles: (weekly infusions) • First Infusion	4 mg / kg	90	**According to local prescribing information and local Health authorities recommendation.** **For example:** • **European Union and Canada: 6 hours** • **US: 2 ½ hours**
c) Second Infusion	2 mg / kg	30 [a]	**According to local prescribing information and local Health authorities recommendation** **For example:** • **European Union and Canada: 2 hours[c]** • **US: 1 hour[c]**
d) Third and Subsequent infusions	2 mg / kg	30 [a]	**According to local prescribing information and local Health authorities recommendation.** **For example:** **European Union and Canada : 2 hours[c]** **US: 30 minutes[c]**
During Follow-Up Visits (q3weekly infusion)	6 mg / kg	30 [a]	**According to local prescribing information and local Health authorities recommendation.** **For example:** • **European Union and Canada : 2 hours[c]** • **US: 30 minutes[c]**

[a] Only if previous dose was well tolerated. In the first cycle, the docetaxel infusion should be started only after all acute toxicities from Herceptin® infusion have resolved.

[b] For those countries where longer observation periods are required, investigators should continue to monitor their patients according to local prescribing information or local Health authorities recommendation i.e: After receiving her first infusion patient should stay at Hospital for an additional period in compliance with the local prescribing information or local Health authorities recommendation

[C] Only if previous dose was well tolerated.

5.3.1 TCH Arm

TCH will consist of eight q3 weekly cycles of docetaxel and carboplatin. Herceptin® will be administered weekly during treatment with chemotherapy then every three weeks during the follow-up period.

First cycle of Docetaxel/Carboplatin/Herceptin® only

Day 1: Herceptin®*4 mg/kg loading dose administered by IV infusion over 90 minutes.

Day 2: Docetaxel 75 mg/m^2 by IV infusion (in minimum 250 mL of normal saline or dextrose 5% solution) over 1 hour followed by carboplatin at target AUC = 6 mg/mL/min administered by IV infusion over 30 – 60 minutes

Day 8: Herceptin®* 2 mg/kg administered by IV infusion over 30 minutes.

Day 15: Herceptin®* 2 mg/kg administered by IV infusion over 30 minutes.

***See Table 8 for Herceptin® infusion times and post-infusion observation periods**.*

Subsequent cycles (to start 3 weeks after Day 1 of 1st cycle)

Day 1: Docetaxel 75 mg/m^2 by IV infusion (in minimum 250 mL of normal saline or dextrose 5% solution) over 1 hour followed by carboplatin at target AUC = 6 mg/mL/min administered by IV infusion 30 – 60 minutes every 3 weeks followed by Herceptin®* 2 mg/kg administered by IV infusion over 30 minutes.

Day 8: Herceptin®* 2 mg/kg administered by IV infusion over 30 minutes.

Day 15: Herceptin®* 2 mg/kg administered by IV infusion over 30 minutes.

Last cycle

Day 1: Docetaxel 75 mg/m^2 by IV infusion over 1 hour followed by carboplatin at target AUC = 6 mg/mL/min administered by IV infusion 30 – 60 minutes followed by Herceptin®* 2 mg/kg administered by IV infusion over 30 minutes.

Day 8: Herceptin®* 2 mg/kg administered by IV infusion over 30 minutes.

Day 15: Herceptin®* 2 mg/kg administered by IV infusion over 30 minutes.

Day 22: Herceptin®* 6 mg/kg administered by IV infusion over 30 minutes. (=EOC visit)

Herceptin®* will then be administered at 6 mg/kg by IV infusion over 30 minutes every 3 weeks. Initiation of the q3weekly infusion of Herceptin®* will correspond to the end of chemotherapy (EOC) visit.

Herceptin®* to continue until disease progression, second primary malignancy (except for curatively treated non-melanoma skin cancer or carcinoma in situ of the cervix), unacceptable toxicity or withdrawn consent.

5.3.2 Carboplatin Dose

Carboplatin dose is calculated using a modified Calvert formula (creatinine clearance is substituted for GFR) as follows:

Total dose (mg) = (Target AUC) x (Creatinine Clearance + 25)

Note: 1. Carboplatin dose is calculated in mg, not mg/m^2

2. Target AUC = 6 mg/mL/min, initially. It may be decreased due to toxicity as per section 5.4

3. Creatinine clearance can either be measured or estimated using the Cockroft-Gault formula, as follows:

$$\text{Creatinine Clearance (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight in kg})}{72 \times \text{serum creatinine in mg/dL}} \times 0.85$$

For the dosing of carboplatin using the modified Calvert formula, the calculation of the creatinine clearance will be done according to baseline weight. If there is a 10% or greater decrease in body weight compared to baseline, the calculation should be revised according to the new actual weight.

If a patient has a BSA more than 2.2, the weight to be used to calculate the estimated creatinine clearance in the Cockroft-Gault formula should be the weight, which results in a BSA of 2.2.

In case of serum creatinine value ≤ 0.9 mg/dL, it is strongly advise to measure the creatinine clearance. If the creatinine clearance value cannot be measured, the serum creatinine value can be adjusted to 1mg/dl in the Cockroft-Gault formula, if the investigator considers that there is a risk of over dosing the patient by using her actual serum creatinine value.

5.3.3 Prophylactic Premedication Regimen for Docetaxel-Related Hypersensitivity Reactions and Fluid Retention

The following premedication regimen must be administered for all patients treated with docetaxel.

Dexamethasone 8 mg p.o. for total of 6 doses.

1. Night before chemotherapy;
2. Immediately upon waking the morning of chemotherapy;
3. One hour before infusion of docetaxel (may be given oral or intravenous);
4. Night of chemotherapy;
5. Morning the day after chemotherapy;
6. Evening the day after chemotherapy.

Dexamethasone 8 mg equivalent may be used
Dexamethasone 8 mg or Methylprednisolone 40 mg or Prednisone 50 mg or Prednisolone 50 mg.

5.3.4 Use of Prophylactic Antibiotics

Primary prophylactic use of antibiotics is not allowed in either arm. Prophylactic use of antibiotics will be used in subsequent chemotherapy cycles for those patients who have experienced a serious or life-threatening infection only. (See Section 5.5.1.6)

5.3.5 Use of Prophylactic G-CSF

Primary prophylactic use of G-CSF will be permitted, although not mandated by the protocol. Prophylactic G-CSF must be used in subsequent cycles for those patients who have experienced an episode of febrile neutropenia or infection during chemotherapy. (See section 5.5.1.5)

5.3.6 Use of Prophylactic Antiemetics

Antiemetic prophylaxis is mandatory for all patients. Selection of antiemetics is at the discretion of the investigator.

5.4 Treatment Delays and Dose Reduction / Modification

5.4.1 Treatment Delays

Treatment with chemotherapy may be delayed no more than 2 weeks (up to Day 35) to allow recovery from acute toxicity.

Herceptin® treatment may continue while chemotherapy is being withheld due to chemotherapy-related toxicity at the investigator's discretion.

If a patient misses a Herceptin® dose for any reason, the missed dose may be rescheduled later in that same calendar week or not given that week at all. A patient may not be given 2 Herceptin® doses in the same calendar week.

Clarification on the meaning of the calendar week.
If Herceptin® administration is due on a Monday but for any reason cannot be performed that day, the infusion can be made up to the Sunday of the same week (same calendar week) and the date of the following administration can be back to the initial schedule (Monday the week after).

Example: Infusion #1 planned on Monday Feb 4, 2002 delayed due to logistic issue
Infusion #1 administered on Sunday Feb 10, 2002 (same calendar week)
Infusion #2 can be administered on Monday Feb 11, 2002 (next calendar week)

If the patient does not suffer from any Herceptin®-related events which may cause Herceptin® to be stopped permanently, Herceptin® administration is to continue until disease progression, second primary malignancy (except curatively treated non-melanoma skin cancer or carcinoma in situ of the cervix), unacceptable toxicity, or withdrawn consent regardless of the number of doses of Herceptin® the patient may have received or missed.

Herceptin® regardless of Herceptin treatment period should be held for grade 3 or 4 non-hematologic toxicity which is related to Herceptin® until recovery to grade ≤ 2, excluding cardiac dysfunction (refer to section 5.5.12). If patients experience Herceptin® related toxicity that does not resolve (to grade 1 or 2) continuing Herceptin administration will be left at the discretion of the investigator. Uncertain cases should be discussed with the sponsor. If the same non-hematologic toxicity recurs at a grade of 3 or 4, treatment should be permanently discontinued. The Herceptin® dose should not be held for hematologic toxicity.

Should the patient's disease progress, all study treatment must be discontinued, including Herceptin®.

5.4.2 Treatment Dose Adjustments

Chemotherapy dose adjustments are to be made according to the system showing the greatest degree of toxicity. Toxicities will be graded using the NCI Common Toxicity Criteria, version 2.0 (see Appendix 12).

Dose reduction is planned for each arm in case of severe hematological and/or non-hematological toxicities as follows:

Docetaxel Single Agent: from 100 mg/m^2 to 75 mg/m^2, then 75 to 60 mg/m^2
Docetaxel in Combination: from 75 mg/m^2 to 60 mg/m^2, then 60 to 50 mg/m^2
Carboplatin: from AUC 6 mg/mL/min to AUC of 5 mg/mL/min

Doses, which have been reduced for toxicity, must not be re-escalated with the exception of liver function tests that improve within ranges given.

There will be no dose modifications for Herceptin®. If a patient misses a dose by less than a week, give the usual dose (2 mg/kg for the weekly schedule, 6 mg/kg for the 3 weekly schedule) as soon as possible (don't wait until the next planned cycle). Carry on the maintenance doses (2 mg/kg for the weekly schedule, 6mg/kg for the 3 weekly schedule) according to the original schedule.

If a patient misses a dose by more than a week from the due date, re-start the treatment as if she were a new patient. The treatment should be re-started as soon as possible (don't wait until the next planned cycle) with a loading dose (4 mg/kg for the weekly schedule, 8mg/kg for the 3 weekly schedule) given over 90 minutes. The usual maintenance schedule (2 mg/kg for the weekly schedule, 6mg/kg for the 3 weekly schedule) should follow, as for a new patient (weekly starting one week after loading for the weekly schedule; 3 weekly, starting 3 weeks after loading for the 3-weekly schedule).

IF A PATIENT EXPERIENCES SEVERAL TOXICITIES AND THERE ARE CONFLICTING RECOMMENDATIONS, THE MOST CONSERVATIVE DOSE ADJUSTMENT SHOULD BE IMPLEMENTED.

5.5 Toxicity Related Guidelines for Dose Reduction and Dose Modification

5.5.1 Hematological Toxicities

5.5.1.1 Febrile Neutropenia

Febrile neutropenia shall be defined as oral or tympanic fever of ≥ 38.5° C or 101.3 ° F in the presence of neutropenia (where neutropenia is defined as ANC < 1.0 x 10^9 /L). See NCI CTC, version 2.0 (Appendix 12).

A therapeutic intervention should proceed immediately following the diagnosis of febrile neutropenia. Therapeutic interventions can be as per the institution's guidelines, or may include

- hospital admission
- pre-antibiotic evaluation
- CBC with differential and blood culture should be performed
- start of an empirical antibiotic therapy

In case of febrile neutropenia, blood counts must be done every 2 days until recovery of ANC 1.0 or oral temperature < 38.5 C. This must be documented in the specific adverse event section in the CRF.

For all subsequent chemotherapy cycles, prophylactic G-CSF will be added as per guidelines outlined in section 5.4.1.5. Antibiotics are not allowed as prophylaxis for febrile neutropenia.

5.5.1.2 Infection With (or Without) Neutropenia

For severe (Grade 3) or life-threatening (Grade 4) infection during chemotherapy, with or without neutropenia, prophylactic G-CSF and prophylactic antibiotics will be added to all remaining cycles.

Ciprofloxacin is recommended at 500 mg orally twice daily for 10 days starting day 5 of each cycle for remaining chemotherapy cycles. If ciprofloxacin is not available or not tolerated, another oral antibiotic **must** be used. The choice of antibiotic is at the discretion of the investigator.

G-CSF will be added to all subsequent chemotherapy cycles as per guidelines outlined in section 5.5.1.5.

5.5.1.3 2nd Febrile Neutropenia and 2nd Infection Event

In the case of a second febrile neutropenia or infection event, patient will continue with the prophylactic G-CSF for all subsequent cycles. In addition, all chemotherapeutic drug doses will be reduced (see Section 5.4.2) for all remaining cycles. Herceptin® dose will not be adjusted.

In the case of a 3rd event, there will be no further dose reduction. Patient will go off study (into regular follow-up). Herceptin® may continue at discretion of investigator.

5.5.1.4 Delayed ANC Recovery on Day 21

BLOOD COUNTS ON DAY 21

Neutrophils (x 10^9/L)	Action to be taken
1.5	Treat on time
< 1.5	1) CBC should be repeated every other day till day 35 Proceed with full dose chemotherapy as soon as ANC 1.5. Consider curative treatment with G-CSF Add G-CSF in remaining cycles if recovery occurred after day 28. 2) If there is no recovery on day 35, (ANC < 1.5 x 10^9/L), the patient will go off chemotherapy. Herceptin® may continue at the discretion of the investigator.

5.5.1.5 Use of Recombinant Granulocyte Colony Stimulating Factor (Granocyte®/Neupogen®/Neulasta®)

a) G-CSF Indications

The use of G-CSF is permitted only:

- As curative treatment in case of febrile neutropenia or infection.
- As prophylactic treatment in patients with a prior episode of febrile neutropenia or infection in earlier cycle (see dose modification sections 5.5.1.2 and 5.5.1.3).
- As treatment for delayed recovery of absolute neutrophil count at day 21 and as prophylactic treatment for subsequent cycles if recovery occurred after day 28 (see section 5.5.1.4).
- If the investigator wishes to use G-CSF as primary prophylaxis, i.e. from 1st cycle onwards, he/she may do so. **Its use as primary prophylaxis is not MANDATORY, but is an option for investigators to use at their discretion.**

b) Dose and Schedule for G-CSF Prophylaxis

	Granocyte®	**Neupogen®**	**Neulasta®**
Dose	150 µg (19.2 MIU)/m²/day	5µg/kg/day	6 mg / cycle
Route	Subcutaneous	Subcutaneous	Subcutaneous
Schedule	Day 4 to Day 11* At Day 11 if ANC < 1.0 X 10^9 / L continue until Day 13 (10 days in total)	Day 4 to Day 11* At Day 11 if ANC < 1.0 X 10^9 / L continue until Day 13 (10 days in total)	One single injection per cycle on Day 2*.

* Day 1 being the day of the infusion, day 4 means 72 h after the day of the infusion.

5.5.1.6 Prophylactic Antibiotics

a. Indication for Prophylactic Antibiotics

No primary prophylactic administration (from first cycle) is permitted.

The use of prophylactic antibiotics is permitted only:

- As prophylactic treatment in patients with a prior episode of infection (grade 3 or grade 4) in an earlier chemotherapy cycle

NOTE: Prophylactic antibiotics will **not** be used in subsequent cycles for patients who have had a prior episode of febrile neutropenia.

b. Dose and Schedule for Prophylactic Antibiotic Prophylaxis

For patients where a serious or life-threatening infection has occurred, a prophylactic antibiotic is required for all subsequent chemotherapy cycles. Ciprofloxacin is recommended at 500 mg orally twice daily for 10 days starting day 5 of each cycle for remaining chemotherapy cycles. If ciprofloxacin is not available or not tolerated, another oral antibiotic **must** be used. The choice of antibiotic is at the discretion of the investigator.

5.5.1.7 Thrombocytopenia

The following dose adjustments are based on the hematologic counts **on the day of or day prior to chemotherapy** treatment.

Platelet Count TH or TCH (cells/μL)	
> 100,000	No change
< 100, 000	Hold for a maximum of 2 weeks. If after 2 weeks, and no recovery above 50,000, all chemotherapy is permanently discontinued. If after 2 weeks and recovery above 50,000, treat with dose reduction above for all subsequent doses. Herceptin® may continue in all cases above. If during TH, reduce docetaxel from 100 to 75 mg/m^2 If during TCH with carboplatin, decrease carboplatin to AUC of 5 mg/mL/min and docetaxel from 75 to 60 mg/m^2.

5.5.1.8 Anemia

In case of ≥ grade 2 decrease in hemoglobin, treatment with blood transfusion or erythropoietin should be given. The use of prohylactic erythropoietin for grade < 2 anemia is not allowed. The choice of the type of erythropoietin used (long acting or regular) is at the investigator's discretion.

In the case where the next cycle of chemotherapy is due, chemotherapy to be administered if hemoglobin is > 10 g/dL.

In case of ≥ grade 3 or 4 decrease in hemoglobin, doses should be reduced as follows:
With docetaxel as single agent in TH, docetaxel dose to be decreased from 100 mg/m^2 to 75 mg/m^2.

If during TCH (carboplatin), docetaxel to be reduced from 75 mg/m^2 to 60 mg/m^2 and carboplatin reduced from an AUC of 6 mg/mL/min to an AUC of 5 mg/mL/min.

- Herceptin® may continue in all cases above.

5.5.2 Nausea and Vomiting

Antiemetic prophylaxis is mandatory for all patients. Selection of antiemetics is at the discretion of the investigator.

Acute episodes of nausea and vomiting should be controlled with adequate antiemetics. In case of grade 4 vomiting that persists despite antiemetics, patient will go off chemotherapy.

- Herceptin® to continue at investigator discretion. .

5.5.3 Diarrhea

No primary prophylactic treatment for diarrhea is recommended.

In case of grade 2 to 3 diarrhea, the patient should be treated with loperamide. For subsequent cycles, give loperamide the day of the first episode of diarrhea, including grade 1. If despite this treatment, patient still experiences grade 3 or more diarrhea, reduce the dose of docetaxel from 75 to 60 mg/m² (TCH) or from 100 to 75 mg/m² (TH) in the subsequent cycles.

If despite this dose reduction diarrhea still occurs at grade 3, investigator should consider taking patient off chemotherapy and Herceptin® should be continued.

In case of grade 4 diarrhea patient should go off chemotherapy and Herceptin® should be continued.

5.5.4 Stomatitis

In case of grade 4 stomatitis patient should go off chemotherapy and Herceptin® should be continued.
In case of grade 3 stomatitis (and/or oesophagitis) the following dose modification should be applied:

During TH

Docetaxel will be reduced from 100 to 75 mg/m². If despite dose reduction, stomatitis still occurs at grade 3, docetaxel will be further reduced from 75 to 60 mg/m². No further dose reduction is planned.

During TCH

Docetaxel will be reduced from 75 to 60 mg/m². If despite dose reduction, stomatitis still occurs at grade ≥ 3, docetaxel will be further reduced from 60 to 50 mg/m². No further dose reduction is planned.

- Herceptin® may continue in all cases above.

5.5.5 Bilirubin and Impaired Liver Function Tests

Docetaxel doses shall be modified for hepatic toxicity. If docetaxel is delayed due to hepatic toxicity, other drugs being used in combination at that time shall also be delayed and administered when docetaxel is resumed.

Since no data in patients with abnormal bilirubin level treated with lower dose of docetaxel are available, in the event that bilirubin levels are abnormal during the study, the next cycle will be delayed by a maximum of two weeks. If no recovery, the patient should be taken off chemotherapy and Herceptin® should be continued.

In the event that ASAT and/or ALAT and/or alkaline phosphatase levels are abnormal in the absence of progression, the following dose modifications should apply:

ASAT / ALAT Values	Alkaline PhosphataseValues	Dose Modification
≤ 1.5 x UNL	≤ 5 x UNL	no dose modification
> 1.5 x UNL to 5 x UNL	≤ 2.5 x UNL	no dose modification
> 1.5 x UNL to 5 x UNL	> 2.5 x UNL to 5 x UNL	**TCH:** Reduce dose of docetaxel from 75 to 60 mg/m² **TH:** Reduce dose of docetaxel from 100 to 75 mg/m²
> 5 x UNL	> 5 x UNL	**Each Arm:** Dose delay by a maximum of 2 weeks. If no recovery to the above figures, patient should go off chemotherapy.

Once the dose is reduced due to impaired liver function, no further dose reduction is recommended if no worsening of the parameters is observed.

In case of recovery of liver function tests on the following cycle, the dose should be re-escalated to the previous dose-level.

Patients with prior history of viral hepatitis (B, C) should stop chemotherapy when transaminases (ALAT and ASAT) or Alkaline Phosphatase increase by ≥ 1.5 UNL and/or bilirubin level increases > 1UNL.
Herceptin may continue.

5.5.6 Peripheral Neuropathy

In case of peripheral neuropathy grade 0-1, no dose modification is needed. If the patient experiences peripheral neuropathy of grade 2 the following dose modifications should be performed:

TCH (carboplatin):
Delay carboplatin and docetaxel treatment by maximum of two weeks.
As soon as patient recovers, treatment should continue with the following dose recommendations:

If patient recovers to Grade 1 toxicity, dose of docetaxel will be decreased from 75 to 60 mg/m^2.
If grade ≥ 2 persists for > 2 weeks, patient will go off chemotherapy and Herceptin® should be continued.

In case of 2nd episode, reduce docetaxel dose from 60 to 50 mg/m^2.

No further dose reduction is planned.

TH:
Delay docetaxel treatment by maximum of two weeks.
As soon as patient recovers, treatment should continue with the following dose recommendations:
If patient recovers to Grade 1 toxicity, dose of docetaxel will be decreased from 100 to 75 mg/m². If grade ≥ 2 persists for more than 2 weeks, patient will go off chemotherapy and Herceptin® should be continued.

In case of 2nd episode, reduce dose from 75 to 60 mg/m².
No further dose reduction is planned.

- For Grade 3: patient will go off chemotherapy and Herceptin® should be continued.

The same guideline also applies for patients with grade 1 neuropathy at baseline once she moves to grade 2.
- Herceptin® may continue in all cases above.

5.5.7 Cutaneous Reactions

- For grade 0, 1, 2:

  Each Arm: no change

- For grade 3: delay for a maximum of two weeks until recovery to grade 1 then for subsequent cycles of
  TCH:
  Reduce dose of docetaxel from 75 to 60 mg/m²;
  Second reduction allowed of docetaxel from 60 to 50 mg/m^2
  TH:
  Reduce dose of docetaxel from 100 to 75 mg/m²
  Second reduction allowed of docetaxel from 75 to 60 mg/m²

  If no recovery to grade 1 within the two-week delay period, patient will go off chemotherapy and Herceptin® should be continued.

- For grade 4: Patient will go off chemotherapy

Herceptin® may continue in all cases above.

5.5.8 Docetaxel Anaphylactoid Type and Hypersensitivity Reactions

In the event that a hypersensitivity reaction occurs despite premedication, it is then very likely to occur within few minutes of start of the first or of the second infusion of docetaxel. Therefore, during the 1st and the 2nd infusions, the infusion must be given drop by drop for the first 5 minutes, and a careful evaluation of general sense of well being and whenever possible blood pressure and heart rate monitoring will be performed so that immediate intervention would occur in response to symptoms of an untoward reaction.

Facilities and equipment for resuscitation will be immediately available including: antihistamine, corticosteroids, aminophylline, epinephrine.

If a reaction occurs, the specific treatment that can be medically indicated for a given symptom (e.g. epinephrine in case of anaphylactic shock, aminophylline in case of bronchospasm, etc.) will be instituted. In addition, it is recommended to take the measures listed below:

Mild symptoms: localized cutaneous reaction, such as: pruritus, flushing, rash	¨ Consider decreasing the rate of infusion until recovery of symptoms, stay at bedside. ¨ Then, complete docetaxel infusion at the initial planned rate. ¨ At subsequent cycles use the same premedication outlined in section 5.3.4
Moderate symptoms: any symptom not listed above (mild symptoms) or below (severe symptoms), such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic blood pressure (BP) > 80 mm Hg	¨ Stop docetaxel infusion. ¨ Give i.v. dexamethasone 10 mg (or equivalent) and i.v. diphenhydramine 50 mg (or equivalent). ¨ Resume docetaxel infusion after recovery of symptoms. ¨ At subsequent cycles, give i.v. dexamethasone 10 mg (or equivalent) and i.v. diphenhydramine 50 mg (or equivalent) one hour before infusion, in addition to the premedication planned in section 5.3.4
Severe symptoms: such as bronchospasm, generalized urticaria, hypotension with systolic BP 80 mm Hg, angioedema	¨ Stop docetaxel infusion. ¨ Give i.v. dexamethasone 10 mg (or equivalent) and i.v. diphenhydramine 50 mg (or equivalent), add epinephrine as needed. ¨ Whenever possible resume docetaxel infusion within 3 hours after recovery or reinfuse the patient within 72 hours using i.v. dexamethasone 20 mg (or equivalent) and i.v. diphenhydramine 50 mg (or equivalent) one-hour prior to resumption of infusion. ¨ At the subsequent cycles, dexamethasone (or equivalent) will be given at 20 mg orally the evening before chemotherapy, the morning of chemotherapy and one hour before docetaxel infusion. Additionally diphenhydramine (or equivalent) will be given at 50 mg i.v. 1 hour before docetaxel infusion. ¨ If a severe reaction recurs, patient will go off chemotherapy.
Anaphylaxis (NCI grade 4 reaction)	NO FURTHER DOCETAXEL SHOULD BE ADMINISTERED

5.5.9 Herceptin® Infusion-Associated Reactions

During the first infusion with Herceptin®, chills and/or fever are commonly observed in patients. Other signs and/or symptoms may include nausea, vomiting, pain, rigors, headache, cough, dizziness, rash, and asthenia. These symptoms are usually mild to moderate in severity and occur infrequently with subsequent Herceptin® infusions. These symptoms can be treated with an analgesic/antipyretic such as meperidine/pethidine or acetaminophen/paracetamol, or an antihistamine such as diphenhydramine.

Some adverse reactions to Herceptin® infusion, including dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, respiratory distress, urticaria, and angioedema can be serious and potentially fatal. The majority of these events occur during or within 2.5 hours of the start of the first infusion. Patients who experience severe or moderate infusions symptoms may be managed by slowing or stopping the Herceptin® infusion and supportive therapy with oxygen, beta agonists, antihistamines, corticosteroids. The patient must be monitored for a minimum of 4 ½ hours after the infusion is stopped until resolution of any observed symptoms. If the patient is an outpatient, it is strongly recommended she be admitted to the hospital for monitoring if the toxicity does not resolve within 3 hours. If a grade 3 or 4 toxicity occurs during the post-infusion observation period, the patient must be evaluated for a minimum of 1 hour from the time the toxicity was first noticed until resolution of any observed severe symptoms. If the patient is being treated as an outpatient, she must be admitted to the hospital for monitoring if the toxicity does not resolve during that hour.

Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, may be at greater risk of severe reactions. Therefore, these patients should be treated with extreme caution and observed appropriately upon administration of Herceptin®.

On very rare occasions, patients have experienced the onset of infusion symptoms or pulmonary symptoms more than six hours after the start of the Herceptin® infusion. Patients should be warned of the possibility of such an event and be instructed to contact their physician if these symptoms occur.

Patients who experience severe or moderate infusion symptoms may be managed by slowing or stopping the Herceptin® infusion and supportive therapy with oxygen, beta agonists, antihistamines, corticosteroids. The patient must be monitored for a minimum observation period required by the local prescribing information (see Table 8) until resolution of any observed symptoms.

5.5.10 Docetaxel Related Fluid Retention (peripheral edemas and/or effusions)

In case fluid retention occurs during the treatment with docetaxel, the signs and symptoms should be graded as mild or moderate or severe as recommended in Appendix 4. NO DOSE REDUCTION IS PLANNED.

The weight will be recorded and followed as frequently as possible to document any weight gain, which could be related to edema.

Recommended curative treatment for fluid retention:

Curative treatment should commence when signs and/or symptoms of fluid retention are observed, including weight gain from baseline grade 1 not otherwise explained.
The following treatment is recommended in case fluid retention occurs:

* Furosemide 20 mg p.o. o.d.

If the symptoms cannot be controlled adequately, i.e. worsening of the fluid retention or spread to another area, the dose of furosemide should be increased to 40 mg. The addition of metolazone p.o. at the recommended dose together with potassium magnesium supplement may be useful.

The clinical tolerance of the patient and the medical judgment of the investigator will determine if it is in the patient's best interest to continue or to discontinue the study drug. It is recommended, however, that patients with fluid retention of grade 3 severity (Appendix 4) should be withdrawn from chemotherapy.

In case of difficulty to make a judgment whether an effusion would be disease related or study drug related, the treatment should be continued until progressive disease in other organs is documented.

Nail changes will not motivate dose-modification.

5.5.11 Renal Toxicity

Carboplatin doses shall be modified for renal toxicity. Dose modifications are based on test results at the time of planned treatment (i.e. Day 1) of each cycle. No dose reduction for docetaxel or Herceptin® will be made for renal toxicity. However, drugs may be delayed if the creatinine is > 2 mg/dL (> 175 μmol/L).

Dose Modifications for TCH Arm Only

Creatinine Clearance mL/min	Carboplatin Dose to be Administered
50 mL/min	AUC 6 mg/mL/min (regular dose as in protocol)
49 – 31 mL/min	AUC 5 mg/mL/min
30 mL/min	Delay until > 30mL/min (max 2 weeks) then treat with AUC 5 mg/mL/min

Creatinine clearance can either be measured or estimated using the Cockroft-Gault formula, as follows

Calculated creatinine clearance (Cockroft-Gault formula) for dose reduction:

$$\text{Creatinine Clearance (mL/min)} = \frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times \text{serum creatinine in mg/dL}} \times 0.85$$

Carboplatin dose is calculated using a modified Calvert formula (creatinine clearance is substituted for GFR) as follows:

Total dose (mg) = (Target AUC) x (Creatinine Clearance + 25)

If either carboplatin is delayed for any length of time (1-2) weeks, the next dose should be decreased.

- Herceptin® may continue in all cases above.

5.5.12 Cardiotoxicity and Cardiac Monitoring

5.5.12.1 Determination of LVEF Status by MUGA or Echocardiography

Measurements of left ventricular ejection fraction as outlined in the protocol will be performed by either MUGA or echocardiography. The same examination technique should be used in the patient throughout the study. **We strongly advise that all LVEFs be determined at the same radiology facility used at baseline.**

NOTE: ECHOCARDIOGRAPHY WILL BE PREFERRED, AS IT WILL ALLOW US TO COLLECT DETAILED INFORMATION ON THE CARDIAC CHANGES THAT MAY OCCUR.

5.5.12.2 Echocardiography Guidelines (for those sites using echocardiography)

Elements necessary for this assessment include:

1) standard echocardiographic equipment including a machine capable of 2 dimensional imaging and spectral Doppler imaging,
2) sonographer trained in standard adult transthoracic imaging
3) cardiologist with experience in interpretation of 2D and Doppler imaging
4) VCR attachment on echo machine and tape.

2D Imaging should include:

1. Parasternal Long Axis View: assessment of left ventricular end systolic and end diastolic dimensions
2. Parasternal Short Axis View: (at the papillary muscle level) assessment of the left ventricular dimensions at end systole and end diastole and assessment of overall left ventricular systolic function (LVEF)
3. In the apical 4 chamber view, an assessment of left ventricular systolic function

The software available on echocardiography machines usually performs the calculation of LVEF.

Calculations: Ejection fraction (EF%) = (EDV – ESV) / EDV x 100

Doppler Imaging should include:

1. In the apical 4 chamber view and the apical 2 chamber view spectral Doppler assessment of mitral valve inflows including IVRT (isovolumic relaxation time), DT (deceleration time), E/A ratios

Other abnormalities noted during this limited echo (e.g. pericardial effusions, significant mitral regurgitation, etc), should be reported in the patient's chart and CRF.

All echocardiology exams will be recorded on videotape, placed in the patient's file, and must be made available for review on request by BCIRG.

5.5.12.3 Timing of LVEF Determinations

Left ventricular ejection fraction assessments by MUGA or echocardiography will be performed at baseline, at the end of cycle 3, at the end of cycle 6, at the end of chemotherapy visit and every 4 months until Herceptin® discontinuation.

Additional assessments of LVEF over and above the LVEF determinations required by the protocol are left to the discretion of the investigator.

In cases where a delay in chemotherapy has occurred and a MUGA or echocardiography is due, the MUGA or echocardiography may be rescheduled up to 3 weeks following the last dose of chemotherapy.

5.5.12.4 Management of Asymptomatic Decreases in LVEF While Patient on Herceptin®

If Herceptin® is held or discontinued during therapy with either docetaxel, or docetaxel and carboplatin due to cardiotoxicity, chemotherapy may be continued at the investigator's discretion.

For patients with an asymptomatic decrease in LVEF, the treatment decision with respect to Herceptin® and repeat LVEF determinations will be defined by the measured left ventricular ejection fraction as it relates to the radiology facility's lower limit of normal and the absolute change in LVEF from baseline, according to the cardiac guidelines developed by Schwartz et al [100].

GUIDELINE ACCORDING TO SCHWARTZ CRITERIA

HERCEPTIN® ADMINISTRATION MUST BE HELD AND LVEF DETERMINATIONS WILL BE REPEATED AFTER 4 WEEKS IN CASE OF AN ABSOLUTE DECREASE OF LVEF ACCORDING TO THE SCHWARTZ CRITERIA

- **< Lower limit of normal for the institution AND**
- **> 10% absolute decrease from baseline.**

RULES for Interpreting and Applying "repeat" MUGA or Echocardiography Scan Results.

1. Herceptin® must be permanently discontinued following two consecutive "hold" categories

2. Herceptin® must be permanently discontinued following three intermittent "hold" categories. At the investigator's discretion, Herceptin® may also be permanently discontinued prior to the occurrence of three intermittent "hold" categories.

Example:	Patient randomized to TCH	
	MUGA Insitution LLN	50%
	Baseline MUGA	60%
	MUGA at Cycle 3	48%
	Treatment Decision	Hold Herceptin® Continue with docetaxel and carboplatin Repeat MUGA after 4 weeks
	Repeat MUGA	51%
	Treatment Decision	Restart Herceptin® Continue with docetaxel and carboplatin
	MUGA at Cycle 6	49%
	Treatment Decision	Hold Herceptin®Repeat MUGA after 4 weeks Continue with docetaxel and carboplatin
	Repeat MUGA	53%
	Treatment Decision	Restart Herceptin®
	MUGA at EOC	51%

Treatment Decision	Continue with Herceptin®
MUGA at 4 month Follow-Up	45%
Treatment Decision	Permanently discontinue Herceptin® (3 intermittent "hold" as per Above Rules)

5.5.12.5 Follow-up for asymptomatic decreases in left ventricular ejection fraction (LVEF)

For patients having discontinued Herceptin® for asymptomatic decreases in LVEF, LVEF assessment will be required in follow-up every 4 months in the first year or until resolution, then every year until the end of follow-up or otherwise as clinically indicated.

5.5.12.6 Congestive Heart Failure

Clinical signs and symptoms suggesting congestive heart failure (dyspnea, tachycardia, cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, etc) must be further investigated.

The suspicion of congestive heart failure, based on the signs and symptoms mentioned above, must be confirmed by a decrease in left ventricular ejection fraction, with a chest X-ray. LVEF should be repeated 4 to 7 days afterwards to confirm a diagnosis of congestive heart failure.

If congestive heart failure is confirmed, Herceptin® will be permanently discontinued. Chemotherapy may continue at investigator's discretion.

All congestive heart failure events (grade 3 or grade 4 cardiac left ventricular function, NCI CTC version 2.0) must be reported as a serious adverse event.

For patients having developed congestive heart failure, LVEF assessment will be required in follow-up every 4 months in the first year or until resolution, then every year until the end of follow-up or otherwise as clinically indicated.

5.5.12.7 Cardiac Arrhythmias.

If grade 1 cardiovascular arrhythmia occurs during either the docetaxel or Herceptin®, the infusion should be stopped or slowed. Subsequent cycles should be under continuous cardiac monitoring.

If grade 2 cardiovascular arrhythmia, TCH and TH should be held and a cardiac evaluation should be conducted. Based on these results, continuation of either docetaxel (with or without Herceptin®) or docetaxel and carboplatin (with or without) Herceptin® will be at the discretion of the investigator.

If grade 3 or grade 4 cardiovascular arrhythmia occurs, TCH or TH will be discontinued.

5.5.12.8 Cardiac Ischemia / Infarction

If grade 1 or 2 develops during either the docetaxel or Herceptin® infusion, the infusion should be stopped or slowed. Both chemotherapy and Herceptin® may continue but with increased cardiac monitoring.

If grade 3 or 4 develops, Herceptin® must be permanently discontinued. Docetaxel +/- Carboplatin may continue at investigator discretion.

5.5.13 Other Toxic Effects

Other toxic effects should be managed symptomatically if possible.

- For grade 3 toxicities, in general drug should be held for a maximum of two weeks from the planned date of reinfusion until resolution to grade 1, then reinstituted, if medically appropriate. A dose reduction will be discussed between the investigator and sponsor.

- If grade 4 toxicity occurs, the patient will go off chemotherapy and Herceptin® may continue at investigator discretion.

5.6 Collection of Serum Samples for Shed Extracellular Domain (ECD) of HER2

A sample of serum for detection of peripheral shed extracellular domain of HER2 will be requested at the same time as the tumor evaluation required by the potocol:

- At baseline
- At the end of cycle 3
- At the end of cycle 6
- At the end of chemotherapy
- Every 2 months for the first 2 years of follow-up until disease progression, second primary malignancy (except curatively treated non-melanoma skin cancer or carcinoma in situ of the cervix) or death whichever comes first.
- At disease progression.

The serum sample will be collected and shipped to UCLA laboratory (see Appendix 3B, 3C for more details). Provision of the serum sample to the central laborary is not mandatory. Refusal to grant permission for collection and release of the samples for the above mentioned purpose will not affect the quality of care the participant is to receive.

5.7 Cardiac Genetic and Biochemical Marker Studies

As outlined in Section 2.5.9, we propose extra collection of blood and plasma samples for the purpose of assessing a patient's genetic predisposition to the development of cardiac dysfunction and to assay specific biochemical markers through serial assays that may potentially detect early ventricular dysfunction. The cardiac genetic and biochemical marker study is not mandatory. Refusal to grant permission for further testing will not affect the quality of care the participant is to receive.

5.7.1 Cardiac Genetic Markers

A sample of whole blood will be collected prior to study start in order to analyze the following polymorphisms: angiotensin converting enzyme I/D, β2-adrenoreceptor (Gly16/Gln27 and Ile164), ET Receptor A (ETA C1363 T) and HER2. See Appendix 3E for details on the collection, storage and shipment procedure.

5.7.2 Biochemical Markers

Plasma samples for the serial analysis of troponin I and brain natriuretic peptide (BNP) will be collected at the following times for the first 2 years of follow-up. See Appendix 3D for details on the collection, storage and Shipment procedure.

- At baseline
- At the end of Cycle 3
- At the end of Cycle 6
- At the end of Chemotherapy visit
- Every 4 months for the first 2 years of follow-up
- At any time of clinical evidence of cardiac failure.

5.8 Treatment Duration and Follow-up

5.8.1 Treatment Duration (Chemotherapy and Herceptin®)

Study treatment will be administered as follows until disease progression, 2nd primary malignancy (except curatively treated non-melanoma skin cancer or carcinoma in situ of the cervix), unacceptable toxicity, or withdrawn consent.

If a patient is randomized to the TH arm, 8 cycles of single agent docetaxel 100 mg/m^2 every 3 weeks will be administered.

If a patient is randomized to the TCH arm, 8 cycles of TC every 3 weeks are to be administered.

For both regimens during chemotherapy treatment, Herceptin® 4 mg/kg load followed by 2 mg/kg weekly will be administered. In follow-up beginning three weeks after the last infusion of chemotherapy, Herceptin® will be administered every 3 weeks at a dose of 6 mg/kg. Initiation of the q3weekly infusion of Herceptin® will correspond to the end of chemotherapy (EOC) visit.

In case of disease progression during treatment (see section 6.2 for efficacy definitions), second primary malignancy, unacceptable toxicities or withdrawn consent, treatment shall finish earlier.

5.8.2 End of Chemotherapy (EOC) Definition

End of chemotherapy (EOC) is defined as 21 days after the last infusion of chemotherapy (docetaxel or docetaxel/carboplatin).

Patients will be observed 3 weeks after last study drug infusion until end of study to document outcome of ongoing side effects. Clinical adverse experiences requiring further ongoing evaluation include:

- Ongoing clinical adverse experiences possibly or probably related to study drug at the time of End of Chemotherapy.
- Relevant non cancer related signs and symptoms occurring after completion of chemotherapy (i.e. congestive heart failure,...).
- Serious adverse event (SAE) and adverse event (AE) reporting for Herceptin® related events will continue for the entire duration of the Herceptin® administration (up to 30 days after last infusion).

5.8.3 Follow-up After End of Chemotherapy

Patients will be followed for 5 years after the last patient has been accrued according to the schedule described below.

Follow-up visits will be every 2 months until disease progression, second primary malignancy (except curatively treated non-melanoma skin cancer or carcinoma in situ of the cervix), other anti-tumor therapy administration, or death. The following will be documented:
-Disease progression or 2nd primary malignancy
-Further therapy.
-Late side effects, including congestive heart failure.
-Serious adverse event (SAE) and adverse event (AE) reporting for Herceptin® related events will continue for the entire duration of the Herceptin® administration (up to 30 days after last infusion).
- Survival.

In case of administration of any other anti-tumortherapy given for disease progression or for second primary malignancy (except curatively treated non-melanoma skin cancer or carcinoma in situ of the cervix) patients will go into an abbreviated follow-up schedule. The abbreviated follow-up visits will be every 4 months and will capture the following data:
-Survival
-Cardiac disease

5.9 Concomitant Treatment

Allowed:

1. G-CSF: treatment of febrile neutropenia/infection, prophylactic use following a febrile neutropenia or infectious episode for all subsequent cycles, delayed neutrophil counts, and primary prophylaxis (at investigator discretion). See sections 5.5.1.5.
2. Antiemetics (section 5.3.7)
3. Antiallergic measures (section 5.5.8)
4. Antibiotics (section 5.5.1.6)
    - Oral prophylactic in case of prior infectious episode
    - IV curative in case of febrile neutropenia or documented infection.
5. Palliative radiotherapy may be given for control of pain or for other reasons with no curative intent. Before radiotherapy is given, the possibility of tumor progression should be ruled out by physical, biological and radiological assessments of the tumor lesions. The irradiated area should be as small as possible and should never involve more than 20% of the bone marrow (Appendix 10) in any given four week period. If all target and non-target lesions are included in the irradiated field, the patient must be taken off study.
6. Concomitant treatment with bisphosphonates may be used in patients with tumor lesions other than ONLY bone metastases or for non-oncologic indications.
7. Ancillary treatments will be given as medically indicated. They must be specified in the Case Report Form.

Not permitted:

1 The patients will not receive other investigational drugs and anticancer treatment while on study (until disease progression, unacceptable toxicity or consent withdrawn).

2 Corticosteroids are not allowed, except as outlined in previous sections as premedication, antiemetics, given for acute hypersensitivity reaction during the course of active treatment with chemotherapy and Herceptin® and in cases of chronic treatment at low dose (≤ 20 mg methylprednisolone or equivalent) initiated at least 6 months prior to study entry.

3 Concomitant treatment with bisphosphonates for patients where osteolytic bone metastases are the only site of disease will not be allowed until disease progression, second primary magignancy (except curatively treated non-melanoma skin cancer or carcinoma in situ of the cervix) or other anti-tumor therapy administration.

4 Concomitant treatment with amifostine (Ethyol®) will not be allowed during the course of active treatment with chemotherapy and Herceptin®.

5 Concomitant treatment with cardioprotectors (e.g. Dextrazoxane®) will not be allowed during the course of active treatment with chemotherapy and Herceptin®.

5.10 Reasons for Discontinuation or Withdrawal

Reasons for premature withdrawal or discontinuation criteria include

1. Unacceptable Toxicity (see Section 5.5 Toxicity Related Guidelines for Dose Reduction)
2. Withdrawn Consent (see Informed Consent, Appendix 6 "Withdrawal From Study")
3. Progression, second primary malignancy (with the exception of curatively treated non-melanoma skin cancer or carcinoma in situ of the cervix – see Exclusion Criteria 10a, 10b), death or administration of any further anticancer treatment (Section 5.7 Treatment Duration and Follow-up, Section 5.9 Therapy After Protocol Treatment is Discontinued)

The reason and date of chemotherapy discontinuation for all patients will be documented in the case report form (e.g. completed study, adverse event, lost to follow-up, etc.).

The investigator will attempt to complete all discharge procedures at the time a patient is discontinued from the study.

For patients who drop out because of chemotherapy related toxicities, Herceptin® may continue until progression or Herceptin® related toxicity. These patients are to be followed in regular follow-up.

Patients who stop chemotherapy for any reason OTHER THAN having been administered a further anticancer therapy for disease progression or 2nd primary malignancy (except curatively treated non-melanoma skin cancer or carcinoma in situ of the cervix) must be followed in a regular follow-up.

5.11 Therapy after protocol treatment is discontinued

Except for study chemotherapy and Herceptin® as per protocol, no further antitumor therapy is allowed (surgery, chemotherapy, immunotherapy, etc.) before tumor progression is documented.

If patients are removed from the study because of disease progression, further treatment is at the discretion of the investigator. The metastatic regimen (s) used will be collected in the Case Report Form.

Note: Since the half-life of Herceptin® is now estimated to be approximately 28.5 days (95% confidence interval, 25.5 – 32.8 days), Herceptin® may persist in the circulation for up to 24 weeks (18-24 weeks) after stopping Herceptin® treatment. It is already known that, when used in combination, Herceptin® and anthracyclines are associated with an increased risk of cardiotoxicity. Considering the above mentionned new pharmacokinetic data, the use of anthracyclines after stopping Herceptin® may possibly be at increased risk of cardiotoxicity. If possible, physicians should avoid anthracycline base therapy for up to 24 weeks after stopping Herceptin® therapy. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

5.12 Study Evaluations

5.12.1 Prestudy Evaluations

	INVESTIGATIONS	TIMING Within (time) prior to registration or randomization
1 Patient informed consent*	Obtained (written)	**Before study registration**
2 History and physical exam, including clinical tumor assessment	**History** - including: diagnosis of breast adenocarcinoma, prior antitumor therapy and outcome, menopausal status, receptor status at diagnosis, general medical history including cardiac history and allergy, concurrent illness and existing signs and symptoms. Concomitant medications, and their indication, used within one month prior to study entry. **Physical Exam** – complete physical examination including: height and weight, Karnofsky index for performance status/vital signs.	14 days
3 Hematology **	Hemoglobin WBC and neutrophil count Platelet count	7 days
4 Biochemistry **	**Liver function:** • Alkaline phosphatase, • ASAT (SGOT), ALAT (SGPT), • Bilirubin **Renal function:** • Serum creatinine, • Creatinine clearance (if indicated)	7 days Liver function tests are to be repeated within 3 days, if abnormal results.
5 HER2 Assessment	Positive FISH test (BCIRG central lab confirmation)	Prerandomization
6 Pregnancy test	Urine or serum (if applicable)	7 days

	INVESTIGATIONS (Cont.)	TIMING (Cont.) Within (time) prior to registration or randomization
7 Radiology and Tumor Measurement ***	Chest X-ray (AP and lateral) and/or Chest CT scan and/ or MRI. Abdominal ultrasound/CT scan/ MRI. If ultrasound is positive, CT scan or MRI is to be performed. If a chest CT scan with upper abdomen is performed, it is not necessary to perform an abdominal CT scan or ultrasound. Bone scintigraphy/X-rays/CT-scan or MRI. Hot spots observed on Bone scintigraphy must be confirmed by X-rays/CT-scan or MRI for patients having bone lesions as only site of disease. Other instrumental examinations as indicated The same examination technique should be used for baseline through follow-up..	Within 4 weeks prior to registration.
8 ECG		Within 4 weeks prior to registration.
9 LVEF	MUGA or Echocardiography Please note the same method of examination should be used in the sample patient throughout the study.	Within 4 weeks prior to registration.
10 Serum Sample+ (optional)	For detection of HER2 shed extracellular domain	Prior to first study drug administration (at time of hematology tests)
11 Blood Sample+ (optional)	For cardiac genetic marker	Prior to first study drug administration (at time of hematology tests)
12 Plasma Sample+ (optional)	For cardiac biochemical markers	Prior to first study drug administration (at time of hematology tests)
13 Other investigations	As clinically indicated	prerandomization
* Informed Consent should be obtained prior to any tests specified in this clinical protocol that are not part of the patient's routine care		
** Laboratory assessments will be performed whenever possible by the same laboratory throughout the study.		
***** To ensure comparability, the BASELINE x-rays/scans/MRI and SUBSEQUENT x-rays/scans/MRI to assess response must be performed using identical techniques (i.e. scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner).**		
+***Please see Appendix 3 for more details.***		

5.12.2 Study Entry – Registration

All eligible patients must be registered **either with the coordinators of the study based in Paris, for Europe and Far East countries, and Los Angeles, for all Canadian and US centers or by the ANZ BCTG statistical center based in Sydney, for all ANZ BCTG centers,** prior to start of treatment.
A patient who has not been registered before the first treatment administration will not be accepted for the study at a later date.

The registration forms should be faxed to **the coordinators of the study or to the Cancer Trials Co-ordinator at the ANZ BCTG statistical center**. A registration package outlining the exact process for registering a patient and the registration forms will be forwarded and reviewed to all sites at the initiation site visit, by the site CRA.

Registration Fax#:	**Europe and Far East countries:** +	33 (1) 58 10 09 10 or 33 (1) 58 10 09 11
	Canada and USA:	310 478 8025 or 310 479 5745
	Australia:	02 9562 5026
	New Zealand:	+61 800 0279 2999

The following information will be requested:

1 Protocol number
2 Institution name
3 Caller's name
4 Investigator's name
5 Patient's identifiers
6 Patient's birth date (day/month/year)
7 Date treatment planned.
8 Verification of selected inclusion and exclusion criteria as identified in the patient registration form.
9 Date when the paraffin block of the primary tumor was sent to the designated BCIRG laboratory for HER2 determination.

HER2 screening will be performed by a regional BCIRG designated central laboratories. The result of the test will be sent directly from the central lab to the BCIRG Study Registration Officer (within a maximum of 5 working days), who will determine patient eligibility based on the registration form received from the clinical site and from the result of the HER2 test, received from the designated lab. See Appendix 3A for more details on the process.

Each eligible patient will be randomized according to a center specific randomization block to receive either docetaxel with Herceptin® (TH) or docetaxel and carboplatin with Herceptin® (TCH).

Investigators will be notified by fax immediately after ALL information has been received from the site as per the Registration Form. This fax will contain the patient's study number, the strata and the randomly allocated treatment group.

Note 1: Treatment must start within 8 days from the time of randomization.

Note 2: If further tests or results are needed to be performed at the time of registration, we will allow a maximum of 5 working days from the time of registration to the time of randomization.

5.12.3 Evaluation During Chemotherapy

All patients during the study must be evaluated according to the schedule outlined in Appendix 5 until they come off chemotherapy.

Schema during chemotherapy	INVESTIGATIONS	TIMING
1 History and physical Exam	**Clinical History since previous infusion** **Physical Exam -** including: Weight, Karnofsky Performance Status, Clinical Tumor assessment	every 3 weeks (day 1 or day -1 of each cycle before chemotherapy)
2 Hematology*	Hemoglobin, WBC, neutrophils, and platelet count.	every 3 weeks (day 1 or day -1 of each cycle before chemotherapy)
3 Biochemistry*	Alkaline phosphatase, ASAT (SGOT), ALAT (SGPT), bilirubin, serum creatinine, creatinine clearance (if indicated),	every 3 weeks (within 3 days prior to chemotherapy)
4 Radiology and Tumor Measurement**	X-rays, CT scans or MRI of ALL lesions to assess response. Bone X-rays or CT scan or MRI of osteolytic bone lesions in patient having bone lesions as only site of disease. Bone scintigraphy in patients with tumor lesions other than only bone metastases. Bone scan to be repeated in patients with suspicion of bone metastases at baseline (i.e. positive bone scintigraphy and negative x-ray of hot spots, without other benign conditions). Otherwise, bone scan to be repeated as indicated by increase of clinical (pain) or biological (alkaline phosphatase, calcium) parameters. Other instrumental examinations as indicated. The same examination technique should be used for baseline through follow-up.	At the end of cycles 3, 6 and EOC
5 LVEF	MUGA or Echocardiography	At the end of cycles 3, 6 and EOC.
6 Adverse events***	Investigations as indicated. Serious Adverse Events should be reported within 24 hours anytime	Every 3 weeks (day 1 before infusion)
7 Serum Sample+ (optional)	For HER2 shed extracellular domain	At the same time as the tumoe evaluation, at the end of cycles 3, 6 and EOC.
8 Plasma Sample+ (optional)	For cardiac biochemical markers	At the end of cycles 3, 6 and EOC
9 Other Investigations		as clinically indicated
* Laboratory assessments will be performed whenever possible by the same laboratory throughout the study.		
****To ensure comparability, the BASELINE x-rays/scans/MRI and SUBSEQUENT x-rays/scans/MRI to assess response must be performed using identical techniques (i.e. scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner). ULTRASOUND should not be used to measure lesions that are clinically not easily accessible**		
*** Toxicities will be recorded and graded according to the NCI CTC criteria, version 2.0 (Appendix 12). In case NCI-CTC criteria are not applicable the event should be defined as 1 = mild, 2 = moderate, 3 = severe and 4 = life-threatening. +***Please see Appendix 3 for more details***		

5.12.4 Evaluation at the End of Chemotherapy (EOC)

To be performed 21 days after the last infusion.

Examinations will include **physical exam, hematology, biochemistry, complete radiology for tumor evaluation** (chest X-ray and/or chest CT-scan and/or chest MRI, abdominal CT-scan and/or MRI and/or ultrasound and bone scan), **ECG, LVEF, record of toxicity.** Reason for patient going off study is to be documented. All evaluations for the End of Chemotherapy will be captured in the CRFs of the last cycle.

Serum samples for detection of HER2 shed extracellular domain and plasma samples for cardiac biochemical markers will be collected at the end of chemotherapy visit.

5.12.5 Evaluation during Follow-up after End of Chemotherapy

All patients must be evaluated for 5 years after the last patient has been accrued according to the schedule outlined in Appendix 5.

Patients will be followed every 2 months until disease progression, second primary malignancy (except curatively treated non melanoma skin cancer or carcinoma in situ of the cervix), other antitumor therapy administration or death.

Exams performed at each follow-up include: physical examination (with Karnofsky Performance Status), **hematology, biochemistry, complete radiology for tumor evaluation** (chest X-ray and/or chest CT-scan and/or chest MRI, abdominal CT-scan and/or MRI and/or ultrasound and bone scan), **record of toxicity.**

Serum sample will be collected every 2 months in follow-up at the same time as the tumor evaluation for detection of shed extracellular domain of HER2 in peripheral blood until disease progression, second primary malignancy (except curatively trated non melanoma skin cancer or carcinoma in situ of the cervix), other antitumor therapy or death, whichever comes first, for the first 2 years of follow-up. A serum sample will be collected at the time of disease progression. Serum samples will be shipped to UCLA laboratory (see Appendix 3B, 3C for more details) on an every 6 months basis until disease progression.

Plasma sample will be collected every 4 months in follow-up for the first 2 years of follow-up and at any time of clinical evidence of cardiac failure (chest pain, dyspnea, fluid overload, arrhythmias) for the serial analysis of troponin I and brain natriuretic peptide (BNP).

LVEF determinations will be every 4 months until Herceptin® discontinuation, unless otherwise indicated as outlined in section 5.5.12.

Other diagnostic tests (i.e. abdominal ultrasound, bone scan) should be performed only in presence of signs and/or symptoms suggestive of cancer progression.

VI Safety and Efficacy Parameters

6.1 Safety Evaluations

6.1.1 Clinical Safety

The following tests will be performed prior to and/or on specified days during and following therapy:

- Complete history of malignant and non-malignant diseases including known hypersensitivity reactions and cardiac history.

- Full clinical examination, height, weight, assessment of any residual toxicity due to previous therapy, assessment of performance status according to Karnofsky Performance Status Index.

- Electrocardiogram (ECG), Left Ventricular Ejection Fraction (LVEF) either by MUGA or echocardiography.

Adverse events: assessed regularly for potential adverse events according to the NCI Common Toxicity Criteria, version 2.0 (Appendix 12).

Toxicities, which cannot be graded using the NCI Common Toxicity Criteria, version 2.0, will be graded as follows:

1= mild (asymptomatic)
2= moderate (symptomatic but not interfering significantly with function)
3= sever (causing significant interference with function)
4= life threatening

6.1.2 Laboratory Determinations

The following tests will be performed prior to and on specified days during and following therapy

Hematology:	WBC, neutrophils, platelet count, hemoglobin
Biochemistry:	alkaline phosphatase, SGOT, SGPT, total bilirubin, serum creatinine, creatinine clearance.
Pregnancy test:	urine or serum, if applicable. Results must be known prior to randomization.
FISH test:	Results must be known prior to randomization.

HER2 shed extracellular domain in peripheral blood: not mandatory, but preferred for comparison of levels throughout the patient's on-study course.

Cardiac Genetic Markers: This is not mandatory.

Cardiac Biochemical Markers: This is not mandatory.

6.2 Efficacy Evaluation

6.2.1 General

Assessment and reporting of tumor response will be done in accordance with the model established by the Response Evaluation Criteria in Solid Tumors (RECIST) group [99].

6.2.2 Reporting of response in this study

All patients included in the study must be assessed for response to treatment, even if there are major protocol 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) non-evaluable including early death from malignant disease, early death from toxicity, early death because of other cause, not assessable, insufficient data.

All efficacy analysis will be performed both on the intent to treat population and eligible populations.

6.2.3 Disease Measurability

Patients must have measurable and/or nonmeasurable lesions according to the RECIST criteria.

Patients having truly nonmeasurable lesions (see exclusion criteria # 4) as their only site of disease will not be eligible, with the following exception: osteolytic bone lesions as the only manifestation of the disease having at least two lytic sites present and confirmed by bone X-ray, MRI or CT scan.

6.2.3.1 Measurable lesions

Measurable lesions are defined as lesions that can be accurately measured in at least one dimension, longest diameter to be recorded as $\geq$ 20 mm with conventional techniques or as $\geq$10 mm with spiral CT scan.

6.2.3.2 Non-Measurable lesions

Non-measurable lesions are defined as all other lesions, including small lesions, (longest diameter< 20 mm with conventional techniques or<10 mm with spiral CT scan) and truly nonmeasurable lesions.

Lesions considered to be truly nonmeasurable include the following:

-Bone lesions.
-Leptomeningeal disease.
-Ascites.
-Pleural/pericardial effusions.
-Inflammatory breast disease
-Lymphangitis cutis/pulmonis.
-Abdominal masses that are not confirmed and followed by imaging techniques.
-Cystic lesions.

6.2.4 Baseline documentation and measurement of lesions

6.2.4.1 Target lesions

These include all measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs. 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 response.

6.2.4.2 Non-Target lesions

These include all non-meaurable lesions and measurable lesions if there are more than 10 measurables lesions.
Measurement of all these lesions is not required, but the presence or absence of each should be noted throughout follow-up.

6.2.5 Timing of Measurements

6.2.5.1Baseline

Baseline evaluations will be performed within 4 weeks prior to randomization.

6.2.5.2 During Cycles and Follow-up

Tumor assessment will occur at baseline, after cycles 3, 6 and end of chemotherapy. The same method of assessment and the same technique should be used to characterize each identified and reported lesion. In follow-up, assessments will occur every 2 months. The same type of imaging and the same method e.g. physical examination, CT scans, MRI, X-ray, used at baseline and throughout to assess response will be used at each of the follow-up visits. If progression occurs, patient will be followed every 4 months for survival and cardiac disease only.

6.2.5.3 Confirmation of Response

Because time to disease progression is the primary objective of this study, a repeat of tumor assessment at 28 days of either a complete or partial response will not be necessary. Confirmation of responses will be performed at the next tumor assessment required by the protocol.

6.3 Response Criteria

6.3.1 Evaluation of Target-Measurable Lesions

The measurement of the longest diameter only for all target-measurable lesions is to be used and assessed at baseline, and again cycles 3, 6, at end of chemotherapy (EOC) and in follow-up. Table 9 summarizes the criteria to be used in evaluating the response of target-measurable lesions.

Table 9: Summary of Response Criteria for Target-Measurable Lesions

Best Response	Change in Sum of Longest Diameters of Target-Measurable 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**.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD providing it is measured at least 6 weeks after the treatment start.
Progression (PD)	At least a **20%** increase in **the sum of LD** of target lesions taking as **reference the smallest sum LD** recorded since the treatment started or the appearance of one or more new lesions.

LD = Longest Diameter

6.3.2 Evaluation of Non Target-Non Measurable Lesions

Definitions of the criteria used to determine the objective response for non-target lesions are as follows, and summarized in Table 10.

Table 10: Summary of Response Criteria for Non Target-Non Measurable Lesions

Response	Appearance/Disappearance/Persistence of non target-non measurable lesions
Complete Response (CR)	Disappearance of all non target-non measurable lesions
Incomplete Response/Stable Disease	Persistence of one or more non target-non-measurable lesion.
Progression (PD)	Appearance of one or more new lesions. Unequivocal progression of existing non target-non-measurable lesions. NB: In the case of radiological evidence of progression in bone at cycle 3, the tumor flare phenomenon should be considered and excluded prior to assigning progression "PD" to the patient's disease.

6.3.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of treatment until disease progression taking as reference for progressive disease the smallest measurements recorded since the treatment started. The determination of the overall response should be done according to the following table.

Table 11 summarizes all possible combinations of tumor responses in target-measurable and non target-non-measurable lesions with or without the appearance of new lesions.

Table 11: Overall Responses for all possible combinations of tumor responses in target-measurable and non target –non measurable lesions with or without the appearance of new lesions

Target- Measurable Lesions	Non target-Non measurable 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

6.3.4 Definitions

Time to Disease Progression: The TTP is defined as the interval from the date of randomization to the date of disease progression or 2nd primary malignancy (except curatively treated non melanoma skin cancer or carcinoma in situ of the cervix) or death except if the cause of death is definitely unrelated to malignant disease. In these cases, the TTP will be censored at the date of death.

If a patient is lost to follow-up or receives other antitumor therapy before documented progression, that patient will be censored as of the last date of contact or start date of antitumor therapy, respectively.

Duration of overall response: Measured from the time that measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

Duration of overall complete response: Measured from the time measurement criteria are first met for complete response until the first date that progressive disease is objectively documented.

Response Rate: Response Rate is defined as the percentage of patients in the group who achieve a complete or partial response.

Clinical Benefit: Clinical benefit will consist of complete response, partial responses and stable disease lasting > 24 weeks.

Survival: Survival is defined as the interval between the date of randomization and the date of death. If a patient is lost to follow-up, that patient will be censored as of the date of last contact.

VII DATA ANALYSIS / STATISTICAL CONSIDERATIONS

7.1 Sample Size Determination

The primary objective of this trial is to show that TCH differs from TH in terms of time to progression (TTP). The following assumptions are made:

- the median TTP of HER2 FISH positive metastatic patients receiving TH will be around 7 months
- there will be a 50% improvement in median TTP for patients receiving TCH
- the error rate for a false positive outcome (α) is set to 5%, using two- sided significance tests
- the error rate for a false negative outcome (β) is set to 20%, i.e. the power of the trial is set to 80% for the difference of clinical interest

The above assumptions yield a required a sample of 238 eligible patients. Assuming that about 5% of the patients will be found ineligible after randomization, the total sample size needed in the trial is 250 (125 patients per treatment arm).

7.2 Randomization

The randomization will be stratified by institution and prior adjuvant and/or neoadjuvant chemotherapy (none, chemotherapy with adjuvant taxane, chemotherapy without adjuvant taxane) to avoid a chance imbalance between the treatment arms with respect these factors. The treatment assignment will be based on a dynamic minimization procedure, which will use a stochastic treatment allocation algorithm based on the variance method [114].

7.3 Efficacy Evaluation

7.3.1 Efficacy Parameters

Primary

The primary efficacy parameter will be Time to Progression (TTP). The TTP is defined as the interval from the date of randomization to the date of disease progression or 2nd primary malignancy (except curatively treated non melanoma skin cancer or carcinoma in situ of the cervix) or death except if the cause of death is definitely unrelated to malignant disease. In these cases, the TTP will be censored at the date of death.

If a patient is lost to follow-up or receives other antitumor therapy before documented progression, that patient will be censored as of the last date of contact or start date of antitumor therapy, respectively.

Secondary

Secondary efficacy parameters will be overall survival (OS), response rate, and duration of overall response. Secondary endpoint also includes comparing and evaluating clinical benefit. These terms are defined in section 6.3.4.

7.3.2 Populations to be analyzed

The analysis of TTP, OS, clinical benefit and duration of overall response will be performed on the Intention-to-Treat (ITT) population, defined as the population of all randomized patients analyzed in the treatment arm they were assigned to. Randomized patients who did not receive chemotherapy will be analyzed in their group of randomization. These analyses will also be performed on the eligible patients population, defined as the ITT population patients less patients who were randomized but did not, upon evaluation, meet all inclusion and exclusion criteria as outlined in the protocol and were considered as having a major protocol deviation.

7.3.3 Statistical methods

The Kaplan-Meier product limit method will be used to estimate the TTP and the OS. The logrank test, stratified prior adjuvant chemotherapy (none, chemotherapy with adjuvant taxane, chemotherapy without adjuvant taxane) will be used to compare the two treatment arms with respect to TTP and OS.

The interim analysis of overall survival will be done using a Haybittle-Peto pragmatic boundary with significance level of 0.001. The main survival analysis would then be performed with significance level of 0.049.

Cox's proportional hazards models will be assessed for TTP and OS in order to adjust the treatment comparison for the major prognostic factors. These factors include clinical baseline parameters, pathological markers and molecular markers. Such adjusted analyses will be considered secondary to the main analysis. Any subset analyses will be reported with appropriate caveats.

A Mantel-Haenszel λ^2 test, stratified for prior adjuvant chemotherapy (none, chemotherapy with adjuvant taxane, chemotherapy without adjuvant taxane) will be used to compare the two treatment arms with respect to objective tumor response.

Logistic regression analysis will be performed for objective response in order to adjust the treatment comparison for the major prognostic factors. These factors include clinical baseline parameters, pathological markers and molecular markers. Such adjusted analyses will be considered secondary to the main analysis. Any subset analyses will be reported with appropriate caveats.

All tests of hypotheses will be two-sided. Confidence intervals of the median survival will be calculated using the method of Brookmeyer and Crowley [115].

In the statistical analysis, a center will correspond to a participating institution. It is expected to have at the end of the study a large number of centers with few patients per center. Therefore, it is not planned to include any center effect in the analyses. However, should there be centers with a large recruitment, it is planned to compare the consistency of the results between this (these) large center(s) and the entire study results, in terms of major baseline characteristics and primary endpoint.

7.3.4 Interim analysis

An overall survival interim analysis is planned at time of the main TTP, with data cut-off when the 204th (TTP) event occurred.

7.3.5 Main analysis

The main TTP analysis will take place when at least 204 events (disease progression, second primary malignancy with the exception of curatively treated non-melanoma skin cancer or carcinoma in situ of the cervix, or death) are observed. This number is adjusted for the expected 5% ineligibility rate. This is expected to occur approximately 24 months after the last patient is accrued.

The main survival analysis will take place at 12 months after the main TTP analysis. Survival analysis will be updated 12 months after the main survival analysis i.e 24 months after the TTP analysis. Subsequent survival analyses will be done as "exploratory update analyses".

7.3.6 Extension of follow-up

An overall survival (OS) update will take place 12 months after main survival analysis i.e. 24 months after the TTP analysis (48 months after the last patient is accrued). Subsequent overall survival analyses will be done as “exploratory update analyses”.

7.4 Safety Evaluation

7.4.1 Grading of adverse events

The National Cancer Institute Common Toxicity Criteria (NCI-CTC Version 2.0) and the corresponding grading system will be used to grade adverse events for recording in the CRF. For all adverse events not classified by the NCI-CTC, a COSTART grading classification (FDA 1989) will be performed (severity as 1: mild, 2: moderate, 3: severe, and 4 life threatening).

Please refer to Appendix 12 for the standard ranges that will be used to analyse the hematological parameters for the study.

Cardiac toxicity events will be defined and graded as per the NCI Common Toxicity Criteria, version 2.0. Classifications such as cardiac ischemia/infarction, cardiac left ventricular function, cardiac arrythmias, etc will be used. A comparison of the asymptomatic decreases in left ventricular ejection fraction will be made according to the Schwartz criteria: an absolute decline of > 10 percentage points from baseline and < the lower limit of normal for the institution (both for confirmed i.e. repeat LVEF determinations after 4 weeks and nonconfirmed decreases).

7.4.2 Populations to be analyzed

The safety analysis will be conducted on all patients who started at least one infusion of the study treatment.

7.4.3 Statistical methods

Adverse events will be compared using two-tailed λ^2 tests or, when expected counts are low, Fisher's exact test or one of its generalizations. In view of the anticipated large number of statistical tests, p-values will not be interpreted in the usual sense but will be used as a "flagging device" to highlight differences worth further attention.

Descriptive statistics will be given on the number of patients in whom the study medication had to be reduced, delayed or permanently stopped.

7.5. Independent Data Monitoring Committee

7.5.1 Composition and mission of the IDMC

In addition to the Steering Committee, an Independent Data Monitoring Committee (IDMC) will be set up. It will be composed of at least two oncologists and one cardiologist. These members will be independent of the trial and familiar with the methodology of oncology trials. They must be aware of the dangers of conclusions based on immature data and agree with the design and the goals of this protocol.
The mission of the IDMC will be to ensure the ethical conduct of the trial and to protect the safety interests of patients in this study. This committee ensures the feasibility and monitors the progress of the trial. The IDMC will be responsible for review of the trial safety.

7.5.2 Meetings of the IDMC

No meeting of the IDMC members will be scheduled before the happening of any major event. In the case where an unanticipated serious event or incidence is reported prior to the scheduled meeting, a meeting will be called immediately to address and assure the safety of the patients in the study. The latter may also include data that has come in from other studies but involves the same agents being administered in this study. The latter may also include newly presented efficacy data from another relevant study whose data in some way may influence the current BCIRG 007 study. The IDMC will have written operating procedures and will maintain records of all its meetings.

7.5.3 Documentation provided to the IDMC

In absence of meeting, the BCIRG Pharmacovigilance & Safety Department should provide the IDMC with a SAE summary table per treatment arm including relationship. The information will be provided on a monthly basis by e-mail directly to the IDMC members.

In addition before any meeting of the IDMC, the BCIRG Data Center should provide the IDMC with at least the following key documents:

- Eligibility data
- On study protocol deviations (i.e. error in treatment allocation, early discontinuation of chemotherapy without any reason, unacceptable concomitant treatment, etc.)
- Patient accrual
- Lost to follow-up patients
- Summary of patient and tumor characteristics
- Summary of drug delivery
- Toxicity data
- And any other major problems encountered.

All results are confidential and must not be divulged to nonmembers of the IDMC.

7.5.4 Recommendations of the IDMC

After each meeting, the IDMC will provide the Steering Committee with a written recommendation to either modify the trial (with reasons), or discontinue the trial (with reasons) or continue the trial unchanged. The final decision to amend the protocol or to discontinue the trial will be taken only by the Steering Committee.

VIII Adverse Events / Safety

8.1 Definitions

8.1.1 Adverse Event

The term **adverse event** covers any sign, symptom, syndrome, or illness that appears or worsens in a subject during the period of observation in the clinical study and that may impair the well being of the subject. The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically relevant (e.g., that require unscheduled diagnostic procedures or treatment measures, or result in withdrawal from the study).

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 Serious adverse event).

Surgical procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an adverse event. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not adverse events.
Worsening of a sign or symptom of the disease under study (advanced breast cancer) will normally be measured by efficacy parameters and should only be recorded as an Adverse Event if the outcome is serious (see section 8.1.2 Serious adverse event).

8.1.2 Serious Adverse Event

A serious adverse event is one that at any dose:

- Results in death
- Is life-threatening[1]
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity[2]
- Is a congenital anomaly/birth defect
- Is an medically significant event[3].

[1]"Life-threatening," means that the subject 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.

[3] Medical and scientific judgement 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. The List of Critical Terms (1998 adaptation of WHO Adverse Reaction Terminology Critical Terms List) should be used as guidance for adverse events that may be considered serious because they are medically important.

Cases of overdose with an adverse event that meets one of the criteria given above should be reported as "serious".

Congestive heart failure (CHF) is considered as a Protocol Defined Serious Adverse Event for this study. CHF should be reported as a serious adverse event regardless of causality and time of occurrence.

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. Severity of the adverse events should be graded according to the NCI Common Toxicity Criteria, version 2.0 (see Appendix 12).

8.1.3 Alert Terms and Other Reasons for Expedited Reporting

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

Cases in which a "significant overdose" 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 form, "Serious Adverse Event Report" form (Appendix 9).

A "significant overdose" includes any overdose in which either a serious adverse event, a non-serious adverse event, or no adverse event occurs and is considered by the investigator as clinically relevant, i.e. poses an actual or potential risk to the subject's well being.

8.2 Period of Observation

For the purposes of this study, the period of observation for collection of Adverse Events extends from the time the subject starts treatment with the study medication until 30 days after the last infusion of study treatment (chemotherapy or Herceptin®).

Note since the half-life of Herceptin® is estimated to be approximately 28.5 days (95% confidence interval, 25.5-32.8 days), Herceptin® may be present in the circulation for up to 24 weeks (range 18-24 weeks) after stopping Herceptin ®treatment.

Cancer progression (defined as component of the clinical efficacy endpoint) will not be reported as serious adverse event unless it satisfies the Serious Adverse Event definition during the period of observation (refer to section 8.1.2). After the end of the observation period, cancer progression will not be reported as a serious adverse event.

Second primary malignancies, that satisfy the Serious Adverse Event definition (refer to section 8.1.2) will be reported as a serious adverse event regardless of causality and regardless of time of occurrence (during or after the period of observation).

Death from any cause that satisfy the Serious Adverse Event definition (refer to section 8.1.2) will be reported as a serious adverse event during the observation period. They will not be reported as a serious adverse event after the observational period unless study drug related.

8.3 Documentation and Reporting of Adverse Events by Investigator

All adverse events that occur after the start of the observation period set in this protocol (see Section 8.2 - Period of observation) must be documented on the pages provided in the case report form in accordance with the "AEs and SAEs process" guidelines.

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 case report form.

If the adverse event is serious (see Section 8.1.2 - Serious adverse event), the investigator must complete, in addition to the "Adverse Event" page in the case report form, a "Serious Adverse Event Report" form at the time the serious adverse event is detected (See Appendix 9). This form must be sent to BCIRG

For all countries outside Canada and USA
BCIRG Safety Manager
13, rue Martin Bernard
75013 Paris FRANCE
Tel: 33 (0) 1 58 10 08 98 or 33 (0) 1 58 10 08 80
Fax: 33 (0) 1 58 10 09 05

For Canada and USA
Fax: 310 478 7085

who will forward it to the sponsor.

- In the situation when a "significant overdose" had occurred without any adverse event (see Section 8.1.3 -Alert terms and other reasons for expedited reporting to Pharmacovigilance), the investigator should only complete a "Serious Adverse Event Report" form. This form must be sent to the sponsor's representative – BCIRG Safety & Pharmacovigilance Manager.

Every attempt should be made to describe the adverse event in terms of a diagnosis. If appropriate, component symptoms should also be listed below the diagnosis. If only non-specific signs or symptoms are present, then these should be recorded as a diagnosis.

All subjects who have adverse events, whether considered associated with the use of the study medication 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 autopsy'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's representative – the BCIRG Safety & Pharmacovigilance Manager.

8.4 Immediate Reporting to Sponsor

Serious adverse events and adverse events that fulfill a reason for expedited reporting to Pharmacovigilance (alert term and/or "significant overdose", as defined in Section 8.1.3 -Alert terms and other reasons for expedited reporting to Pharmacovigilance) must be documented on a "Serious Adverse Event Report" (Appendix 9**)** form in accordance with the "Instructions for reporting serious adverse events (SAEs) occurring in clinical trials". This form must be completed and supplied to the BCIRG Safety Manager within 24 hours or at the latest on the following working day. The "Serious Adverse Event Report" (Appendix 9) form and the instructions are provided in the investigator's study file.

The sponsor will ensure that all legal reporting requirements are met (see Appendix 9A).

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 medication.

Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up "Serious Adverse Event Report"(Appendix 9) form.

The "Aes and SAEs Process" guidelines 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 becomes serious. In the latter situation, when a non-serious event becomes serious, details must be forwarded immediately to the sponsor's representative – the BCIRG Safety & Pharmacovigilance Manager on a "Serious Adverse Event Report" form (Appendix 9).

IX MEDICATION

9.1 Drug Packaging, labeling, dispensing and storage

9.1.1 Packaging and Labeling

A) HERCEPTIN® (see Appendix 7 for detailed information)

For the purpose of this study, Roche and Genentech when necessary will supply Herceptin®.

Packaging:

There are 2 preparations available for Herceptin®, the 440 mg multi dose vials, and the 150 mg unit dose vials. The preparation available for your site will vary depending on the country. See Appendix 7 for more details.

Labeling:

The label attached to the Herceptin® will contain the following information:

Manufacturer's name and address
Sponsor's name and address
Product name
Study code number
Contents
Directions for Use
Storage Conditions
Batch number and packaging numbers
Legal requirements (expiry dates)

B) DOCETAXEL (see Appendix 8 for detailed information)

For the purpose of this study, docetaxel will be supplied when necessary.
Packaging:

Docetaxel will be provided as a sterile concentrate for infusion (concentration = 40 mg/mL).
The appropriate solvent for diluting the docetaxel concentrate for infusion will also be provided.
Vials are intended for single administration only.

Labeling:

The label attached to the Taxotere® (docetaxel) will contain the following information:

Manufacturer's name and address
Product name
Study code number
Contents
Directions for Use
Storage Conditions
Batch number and packaging numbers
Legal requirements (expiry dates)

9.1.2 Dispensing and Storage

9.1.2.1. Herceptin® (see Appendix 7)

For preparation of the Herceptin® solution and storage of the vials, please refer to Appendix 7.

See section 5.3 for administration guidelines.

9.1.2.2 Carboplatin

See preparation instructions on the package insert.

9.1.2.3 Docetaxel (see Appendix 8)

For preparation of the docetaxel solution and storage of the vials, please refer to Appendix 8.

9.2 Drug Accountability

The person responsible for drug dispensing is required to maintain adequate records of all study drugs (docetaxel, Herceptin®, Carboplatin and G-CSF when supplied). These records (e.g., drug movement form) include the dates the study medications are received from the manufacturer (if applicable), the dates dispensed for the individual patient, and the dates destroyed at the site as per each country's policy and guidelines (or returned to manufacturer) Patient number, date of infusion, investigator name, lot number, expiry date of the study medication must be placed in the CRF.

The person responsible for drug administration to the patient will record precisely the date and the time the drug is administered to the patient. In case the drug infusion has to be stopped, the exact date and time that the infusion has been stopped and restarted will be carefully recorded.

X ADMINISTRATIVE ASPECTS

10.1 Monitoring, Auditing, and Inspecting

The study will be monitored by regular site visits and telephone calls to the investigator by members of or personnel designated by the BCIRG Clinical Operations Department. During site visits, the monitor should review original patient records, drug accountability records and document retention. Additionally, the monitor should observe study procedures and will discuss any problems with the investigator. During the course of the study BCIRG and/or Roche & Genentech, or any third party entitled by BCIRG and Roche & Genentech jointly, may conduct site audits. The investigator will provide direct access to source data/documents for trial related monitoring, audits, IRB/EC review and regulatory inspections.

10.2 Patient Identification

All patients screened for the study will have their initials and birth date entered chronologically on the patient log at the initial visit. In the event a patient is excluded from study participation, the reason is to be documented in the space provided on the patient log.

Each patient will be assigned a Patient Randomization Number on registration. This number and the patient initials are to be entered on the Case Report Form.

10.3 Recording of Data

The study will be conducted using paper based CRFs. NCR™ Case Report Forms will be supplied by BCIRG providing white original and colored copies. These forms must be typewritten or *PRINTED LEGIBLY* using black ballpoint pen when prepared for submission to BCIRG.

The forms should be verified against all original records (and workbooks, if applicable) by the BCIRG Clinical Monitor before submission. The bottom copy will be retained in the investigator's files, and all other copies will be returned to the BCIRG central Data management office in Edmonton, Canada by the BCIRG Clinical monitor. No case report forms are to be mailed to the BCIRG without specific authorization. Case Report Forms and all original data should be readily available for review during scheduled monitoring visits. Any data to be recorded directly on the Case Report Forms will be considered to be source data.

10.4 Record Retention

1. The investigator will retain copies of all pertinent information for a period of at least 15 years from study completion. Additional considerations must be made about complying with applicable local laws, guidelines, etc.
2. A study document binder will be provided by BCIRG for all required study documents.

10.5 Confidential Follow-up

The investigator will be responsible for retaining sufficient information about each patient (e.g. name, address, phone number, social security number/identity number, and identity in the study) so that regulatory agencies, BCIRG, or Roche & Genentech may access this information should the need to do so arise. These records should be retained in a confidential manner for as long as legally mandated according to local requirements.

10.6 Patient Informed Consent (Appendix 6)

Prior to the screening evaluation, the patient will be informed of the nature of the study drug and will be given pertinent information as to the intended purpose, possible benefits, and possible adverse experiences. The procedures and possible hazards to which the patient will be exposed will be explained.

An approved informed consent statement will then be read and signed by the patient, and, when required, a witness, and the investigator. The patient will be provided with a copy of the signed informed consent statement. The patient may withdraw from the study at anytime without prejudicing future medical treatment.

10.7 Ethics Committee/Institutional Review Board

The final approved protocol and the informed consent statement will be reviewed by a properly constituted Ethics Committee/IRB. The Ethics Committee's/Board's decision concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to BCIRG and Roche & Genentech.

Particular attention is drawn to the FDA's regulation regarding the IRBs. By signing the "Statement of Investigator" form (Form 1572), the investigator provides BCIRG and Roche & Genentech with the necessary assurance that an IRB is responsible for the initial and continuing review and approval of the proposed clinical study in accordance with these regulations when applicable.

The investigator will agree to make required progress reports to the Ethics committee/IRB, as well as report any serious adverse events, life-threatening problems or deaths. The investigator will also inform the Ethics Committee/IRB of reports of serious adverse events (provided to him/her by the sponsor) in other clinical studies conducted with the study drug. The Ethics Committee/IRB must be informed by the investigator of the termination of the study.

10.8 Declaration of Helsinki

This study is to be performed in accordance with the Declaration of Helsinki (Edinburgh Scotland Amendment, 2000), as described in Appendix 1.

10.9 Insurance of Liabilities

If required, the investigator may forward the Ethics Committee/IRB a copy of the Insurance that the sponsor has to take out covering his and any other participating parties liabilities.

10.10 Modification of the Protocol

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by BCIRG and Roche & Genentech, and approved by the Ethics Committee/IRB prior to implementation and notified to the health authorities in accordance with local regulations.

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be agreed upon by BCIRG, Roche & Genentech and the investigator and will be documented in a memorandum. The Ethics Committee/IRB may be notified of administrative changes at the discretion of BCIRG.

10.11 Use of Information and Publication

All information concerning the study drug supplied by Roche & Genentech in connection with this study and/or by any other party collaborating with BCIRG and Roche & Genentech within this Study, and not previously published, is considered confidential and proprietary information. This information includes the Investigator's Brochure, clinical protocol, workbooks if applicable, Case Report Forms, assay methods, BCIRG technical methodology, and basic scientific data. This confidential information shall remain the sole property of BCIRG and Roche & Genentech or the respective collaborating party and, shall not be disclosed to others without prior written consent from BCIRG and Roche & Genentech and shall not be used except in the performance of this study.

To allow for the use of the information derived from this clinical study and to insure compliance to current regulations, the investigator is obliged to provide BCIRG with complete test results and all data developed in this study. Only BCIRG and Roche & Genentech or any third party entitled by BCIRG and Roche & Genentech jointly, may make information obtained during this study available to the physicians and to regulatory agencies, except as required by regulation.

No publication, abstract or presentation of the study will be made without approval of the advisory board of the BCIRG and Roche & Genentech. BCIRG and Roche & Genentech will review the manuscript to prevent forfeiture of patent rights to data not in the public domain. The investigators prior to publication will agree the authorship list. The names on the author list will be given according to the participation in the design of the protocol as well as taking into consideration the input of the number of eligible and evaluable patients accrued by the investigators in each center. The study will only be published once it is completed and the final analysis has been performed by BCIRG. Interim abstracts will be presented according to the statistical plan and in agreement with BCIRG.

In the event BCIRG and Roche & Genentech choose to publish the data from this study, BCIRG and Roche & Genentech may provide the advisory board of the study with a manuscript at least 30 days prior to the expected date of submission to the intended publisher.

XI INVESTIGATOR'S AGREEMENT

I have read the preceding protocol

BCIRG 007
(WO16437)

A MULTICENTER PHASE III RANDOMIZED TRIAL COMPARING DOCETAXEL (TAXOTERE®) AND TRASTUZUMAB (HERCEPTIN®) WITH DOCETAXEL, CARBOPLATIN AND TRASTUZUMAB (HERCEPTIN®) AS FIRST LINE CHEMOTHERAPY FOR PATIENTS WITH METASTATIC BREAST CANCER CONTAINING THE HER2 GENE AMPLIFICATION.

1. And agree that it contains all necessary details for conducting this study. I will conduct the study as outlined in the preceding protocol and in compliance with GCPs. I will attempt to complete the enrollments into the study by March 2004. I will provide copies of the protocol and all drug information relating to preclinical and prior clinical experience furnished to me by Roche & Genentech and BCIRG, to all physicians responsible to me who participate in this study. I will discuss this material with them to assure that they are fully informed regarding the drug and the conduct of the study. I agree to keep records on all patient information (case report forms and patient's informed consent statement), drug shipment and return forms, and all other information collected during the study in accordance with legal regulations

_____
Investigator (PRINT NAME)

_____
Investigator Signature Date

_____
Global Project and Medical Director
BCIRG Date

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APPENDIX 1 - DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects**.** Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best-proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best-proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

APPENDIX 2 - KARNOFSKY INDEX FOR PERFORMANCE STATUS

100	Normal, no complaints: no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort, some signs or symptoms of disease.
70	Cares for self but unable to carry on normal activity or to do work.
60	Requires occasional assistance but is able to care for most of personal needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospitalization is indicated although death not imminent.
20	Very ill; hospitalization and active supportive care necessary.
10	Moribund.
0	Dead.

APPENDIX 3 - PATHOLOGY REVIEW AND MOLECULAR MARKER TESTING

Appendix 3A - FISH TESTING; PATHOLOGY AND MOLECULAR MARKER REVIEW (MANDATORY)

A. HER2 FISH Testing

Human Epidermal Growth Factor Receptor 2 (HER2)

Abnormal expression of human epidermal growth factor receptor 2 (HER2) is frequently observed in a number of primary tumors, suggesting that the over expression of this growth factor receptor may contribute to transformation and tumorigenesis. In most cases, HER2 protein over expression is thought to result from gene amplification and has been correlated with poor clinical outcome in patients with breast and ovarian cancers that over express HER2. Approximately 25% to 30% of patients with breast and ovarian cancers over express HER2.

The BCIRG 007 study requires, as one of the patient eligibility criteria, HER2 amplification which represents ¼ to 1/3 of the breast cancer patient population. Approximately 1,000 patients are expected to be screened in order to identify 250 patients whose breast cancer amplify the HER2 gene.

A representative paraffin block from potentially eligible women with breast cancer will be tested for c-erbB-2 status using Fluorescence In-Situ Hybridization (Vysis kit) in one of the BCIRG designated central laboratories.

Dr. Michael Press, University of Southern California, Los Angeles, U.S.A. will be responsible for the HER2 screening procedure. The two BCIRG central laboratories are as follows:

For Sites in North America, Australia
Dr. Michael F. Press
University of Southern California
Norris Cancer Centre
Suite # 5409 1441 Eastlake Avenue,
Los Angeles, CA, 90033
Telephone: (323) 865-0563

For All Other Countries
Dr. Guido Sauter
Institute of Pathology
University of Basel
Schonbeinstrasse 40
CH-4003 Basel, Switzerland
Telephone: (+41) 61 265 28 89

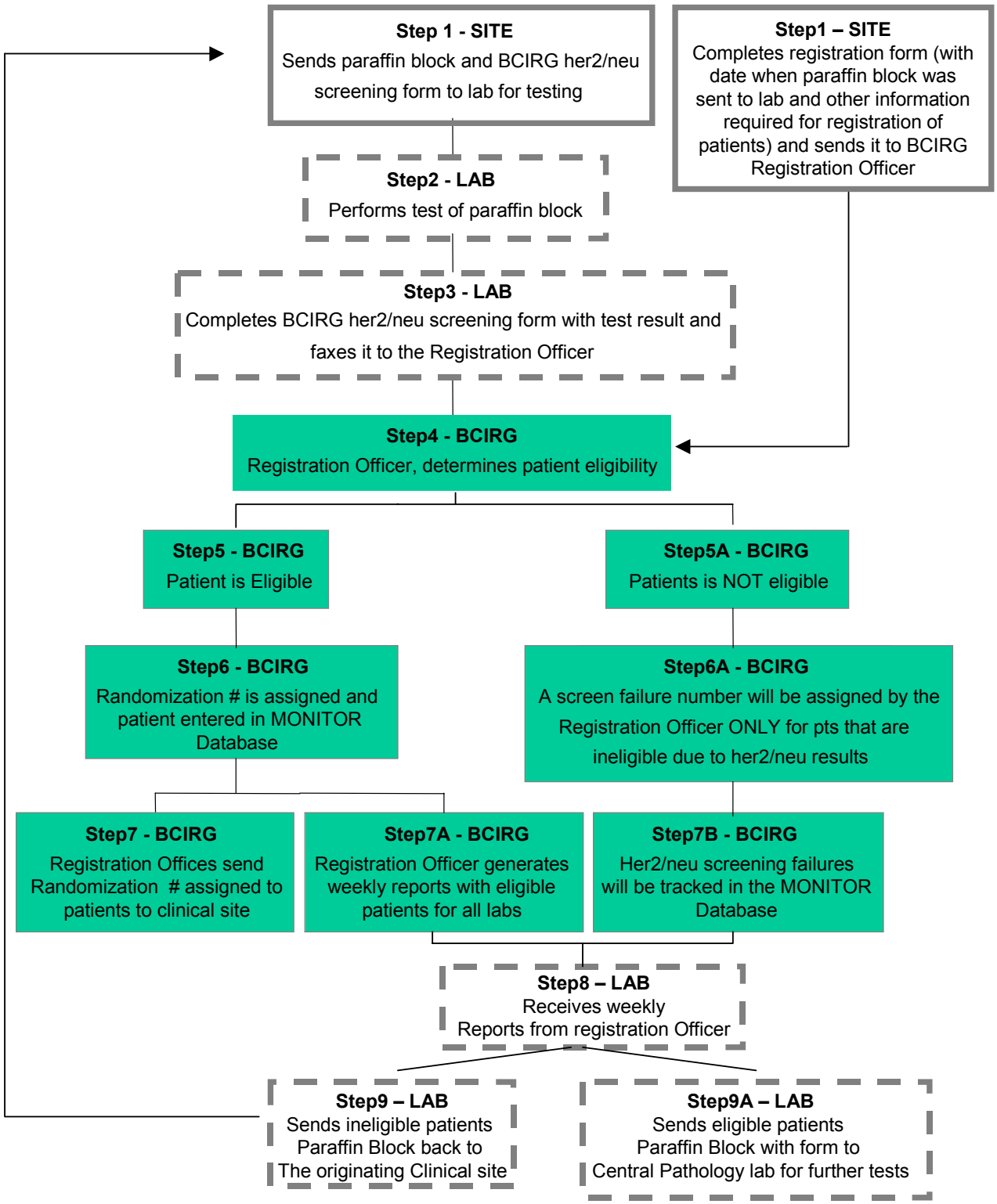
1. Procedure:

All patients identified by the participating center as potentially eligible will start the study screening procedures as per study protocol.
A representative tumor block will be sent by the clinical site to one of the BCIRG designated labs. The block will be sent accompanied by a HER2 screening form provided by BCIRG to the clinical site. This form will include a patient identifier such as patient initials, patient's date of birth and clinical site number.
The BCIRG laboratories will perform the *c-erb*B-2 analysis using the Vysis FISH kit and report the result to the BCIRG Registration Officer. The lab will then be informed by the Registration Officer if the patient was eligible and will either send the block back to the originating centre (if patient is not accrued to the BCIRG 007 trial) or to the BCIRG designated Central Pathology laboratory (if the patient is accrued to the BCIRG trial).
See Flow chart HER2 screening and central pathology process.

2. Operating Principles for the Designated Labs:

1. Use of the Vysis kit.
2. Quality control and standardized procedure as determined by Dr. Michael Press.
3. Turn-around time of 5 working days for faxing results to the BCIRG Registration Officer.
4. The disposal procedure for the blocks is as follows:
   - All cases not accrued to the BCIRG 007 trial (as informed by the BCIRG Registration Officer) should have their blocks returned directly to the contributing centre.
   - All cases enrolled post HER2 screening for the BCIRG 007 will have their blocks forwarded to the BCIRG designated Central Pathology Laboratory for molecular studies

Flow Chart of HER2 Screening and Central Pathology process



B. Pathology and Marker Review

The purpose of this investigation is to establish the baseline characteristics of the tumors and ensure comparability between experimental arms. Each tumor will be tested for a number of accepted histo-pathologic and molecular marker prognostic factors and

i. A number of accepted histo-pathologic and molecular marker prognostic factors and

ii. Several other factors with proven utility in predicting response to Taxotere®.

Due to the well-described difficulty in obtaining inter-observer reproducibility in the assessment of pathologic factors, a central lab will perform the assessments of these prognostic and predictive factors.

1. Methodology

Hematoxylin and Eosin stained slides prepared from the paraffin block submitted for FISH testing will be assessed for Histologic subtype, grade and vascular invasion. Additional unstained slides from the same block will be assayed for *ER, PR, p53* and *MIB-1* using automated immunohistochemistry at the BCIRG designated Central Pathology Laboratory. Histopathologic and immunohistochemical assessment of these factors will be performed by a single reference pathologist with external review of 30% of the material by a second observer. If indicated, the investigation of the *Bcl* family (Bcl-2, bax, Bcl-X and Bag-1) will be done in collaboration with Dr. J. C. Reed MD, Ph.D., Scientific Director, The Burnham Institute (formerly, The La Jolla Cancer research Foundation), La Jolla, California. If indicated, the investigation of the tubulin isoforms (II, III, IV and Tau) will be done in collaboration with Drs. C. Dumontet and I. Treilleux in Lyon, France. If indicated, the investigation of MUC1 will also be performed at the Central Pathology Laboratory.

2. The pathology materials which must be supplied are:

One paraffin block from a representative area of the tumor. If insufficient material remains in this original block, the center will be contacted for an alternate block. The blocks will be kept in the central registry for the duration of the trial. They can be accessed during this period by the original lab. The block may be returned to the original pathology lab at the close of the trial if desired so by the patient. Blocks will otherwise be stored in a tumour bank for future investigations.

Appendix 3B - SUMMARY OF OPTIONAL ECD AND CARDIAC SUBSTUDIES PROCESS

	ECD substudy	Biochemichal markers	Genetic markers
Time of collection	Baseline, at the end of cycles 3, 6, EOC and then every 2 months during the first 2 years of follow-up, until disease progression or second primary malignancy or death, whichever occurs first.	Baseline, at the end of cycles 3, 6, EOC and then every 4 months during The first 2 years of follow-up and at any clinical evidence of cardiac failure	Baseline
Number of specimens	5	9	1
Number of tubes/collection	2	2	1
Type if tubes	Red top tubes	Purple top tubes	Purple top tubes
Material	Serum	Plasma	Whole blood
Storage	-20°C or –80°C	–80°C (-20°C is acceptable under shipment time condition below)	Fridge
Anticoagulants	EDTA	EDTA	EDTA or Heparin
Shipment time	Every 4 or 6 months (within 4 months if stored at -20°C)	Every 4 to 6 months (within 4 months if stored at -20°C)	Within 1 month
Condition of shipment	Dry ice	Dry ice	Dry Ice

Appendix 3C - SHED HER2 ECD SUBSTUDY (OPTIONAL)

Collection, storage and shipping instructions for serum for shed extracellular domain (ecd) of her2 and serum bank specimen

This optional study will also ask for a serum sample to be provided to the central lab prior to study start and at the time of tumor assessment i.e. at the end of cycles 3, 6, at EOC, every 2 months until progression and at the time of disease progression for the first 2 years of follow-up. Serum assays for HER2 are currently being investigated. We wish to collect serum samples prior to treatment in order to review the levels of shed extracellular domain (ECD) of HER2 in peripheral blood for comparison with the FISH test as a predictive factor in a patient's outcome with Herceptin-containing regimens. We will also ask that a serum/ sample be sent to our lab at the time of disease relapse for comparison of levels. Additional testing of molecular markers and assays for HER2 may be performed on the serum sample in the future. Refusal to grant permission for collection and release of the serum samples for the above mentioned purpose will not affect the quality of care the participant is to receive.

1. Procedures:

1. Specimens will be collected at baseline and at the same time as tumor assessment i.e. at the end of cycles 3, 6, EOC, every 2 months until progression and at time of progression for the first 2 years of follow-up.
2. Please note the expiration date on the kit box. The expiration date on the kit box corresponds to the expiry date on the red top tube. The red top tube tends to loose its vacuum after this date. It is safe to use the tubes after its expiration date; however, it may not fill to the desired volume, resulting in the need to collect multiple tubes in order to obtain the required volume of serum.
3. Remove the gel cold pack from the kit box and place it in the freezer.
4. Obtain the two 10mL red top tubes (with serum separator gel) to draw the blood specimens.
5. Label the red top tubes with the patient identification labels provided by BCIRG in the kit box. (BCIRG patient number, patient initials, and date and time sample is collected). **Note: The labels and the label number in each kit pertain to the samples drawn at that one time. Samples drawn at the time of relapse will be labeled with labels having a different number than those drawn at the time of registration.**
6. Label the plastic transport vial with the patient identification labels provided by BCIRG in the kit box. (BCIRG patient number, patient initials, and date and time sample is collected)
7. Attach a label containing the patient information (BCIRG patient number, patient initials, date and time sample is collected) to the "Serum Collection Form".
8. Draw the blood from the patient into two 10mL red top tubes. Allow the tubes to fill completely.
9. Let sample sit for 20 minutes at room temperature. This allows the sample to clot.
10. Centrifuge the samples at 1000 – 1200 g for 15 minutes. Ensure the centrifuge is balanced.
11. Carefully remove stopper from the red top tubes.
12. Using a pipette, aliquot the serum into the plastic transport vial. Vial should contain 2 – 7 mL of serum.
13. Ensure that the lids on the transport vials are secure.
14. Discard the red top tube containing residual serum and cells into a biohazard waste container.
15. Place the transport vial into the biohazard bag (ziplock bag). Please note this bag has an absorbent sheet that must remain in the bag. This absorbent sheet will absorb any serum that leaks from the transport vial. (**Please note - The most common cause for leakage is unsecured caps on the transport vials**.)
16. Place the biohazard bag containing the transport vial at 2 to 8°C until ready to ship to the BCIRG central lab. If the sample cannot be shipped on the same day it is collected, please place the biohazard bag containing the transport vial in the freezer. ***Please note: if sample cannot be shipped within 48 hours, sample should be frozen.***

17. When you are ready to ship the samples, remove the biohazard bag containing the transport vial from the fridge or freezer.
18. Fill half of the Styrofoam lined shipping box with dry ice. Place the biohazard bag containing transport vials and the "Serum Collection Form" on the dry ice. Fill the rest of the Styrofoam lined shipping box with the remaining dry ice.
19. Place the Styrofoam lid securely on the Styrofoam lined shipping box. Do not secure this lid with tape. The dry ice needs to sublimate.
20. Close the corrugated cardboard lid of the shipping box and secure the cardboard lid with packing tape.
21. Attach the shipping label (Please note – dry ice is considered a dangerous goods shipment) and ship this box via the designated Courier Company to:

For all sites
UCLA-Department of Medicine
Dr Slamon's Research Laboratory
675 Charles E.Young Drive South
Room 5/535, Building MRL
Los Angeles, CA
90095 USA
Central Laboratory contact name: Lillian Ramos
Phone: 310-206-1408
Fax: 310-825-3761

2. Serum sample supplies:

You will be provided with a serum sample kit box (1 kit box required for 1 sample collected) and an additional collection of extra supplies (1 extra collection of supplies will be provided for every 3 samples collected).

Serum Collection Forms will be provided to you at the time of the study initiation visit.

If supplies are needed, please fill out the BCIRG 007 Study Supply Order Form. If you have any questions regarding the supplies, please contact your BCIRG study monitor, or the BCIRG general office number at 780 702 0200.

Each Kit Box includes:

Two – 10 mL SST Gel& Clot Activator red top vacutainer tube
Two Plastic Transport Vial
Elastic Band
Pipette

Alcohol, cotton swabs, sterilized plastic strip
21-gauge vacutainer needle, 1-1/2 " (multiple-sampling)

Patient Identification Labels
U Tek Refrigerant Pack
Biohazard Ziplock Bag (with absorbent sheet inside)

Bag of Extra Collection Supplies includes:

10 mL SST Gel& Clot Activator red top vacutainer tube
Plastic Transport Vial
Elastic Band

Alcohol, cotton swabs, sterilized plastic strip
21-gauge vacutainer needle, 1-1/2 " (multiple-sampling)

Biohazard Ziplock Bag (with absorbent sheet inside)

Site (or Lab) Must Have:

Disposable gloves
Refrigerator, Gel cold pack should be cold not frozen.
Needle disposal Container
Biohazard Container
Packing Material (for shipment of sample)
Packing Tape

Appendix 3D – CARDIAC BIOCHEMICAL SUBSTUDY (OPTIONAL)

Collection, storage and shipping instructions for plasma samples for cardiac biochemical markers

This optional study will also ask for a plasma sample to be provided to the central lab prior to study start and specified time intervals outlined in the first step of this procedure. Plasma assays for Cardiac Biochemical Markers, BNP and Troponin I, are currently being investigated. We wish to collect plasma samples prior to treatment in order to review the levels BNP and Troponin I in peripheral blood as a predictive factor in a patient's cardiac health. We will also ask that a plasma sample be sent to our lab at the defined intervals as a comparison of levels. Refusal to grant permission for collection and release of the plasma samples for the above-mentioned purpose, will not affect the quality of care the participant is to receive.

1. Procedures:

2. Specimens will be collected at Baseline, Cycle 3, 6, End of Chemotherapy and every 4 months and at any time of clinical evidence of cardiac dysfunction for the first 2 years of follow-up.
3. Please note the expiry date on the kit box. The expiry date on the kit box corresponds to the expiry date of the EDTA (anti-coagulant) in the purple top tube. Please do not use an EDTA, purple top tube past it's expiry date.
4. Obtain the two 5mL (EDTA) purple top tubes to draw the plasma specimens.
5. Label the purple top tubes with the patient identification labels provided by BCIRG in the kit box. (BCIRG patient number, patient initials, and date and time sample is collected)
6. Label the plastic transport vials with the patient identification labels provided by BCIRG in the kit box. (BCIRG patient number, patient initials, and date and time sample is collected) Secure these labels onto the tubes with transparent tape, by wrapping the tape once around the label. This will prevent the label from falling off in the –80ºC freezer.
7. Attach a label containing the patient BCIRG information (patient number, patient initials, date and time sample is collected) to the "Plasma Collection Form" (Please refer to next page for an example)
8. Draw the blood from the patient into the two 5mL purple top tubes. Allow the tube to fill completely.
9. Gently invert the purple top tubes 4 to 5 times, to allow the EDTA (anti-coagulant) and blood to mix. Do not vigorously shake the tubes. This is cause the red cells to lyse and will result in a hemolytic sample.
10. Centrifuge the sample at 1000 – 1200 g for 15 minutes. Ensure the centrifuge is balanced.
11. Carefully remove stopper from the purple top tubes.
12. Using a pipette, aliquot the plasma into the plastic transport vials. Vials should contain 1 – 3 mL of plasma. (If there is no cell contamination, proceed to step 12) When transferring the sample ensure that you do not shake or disturb the packed red cells with the pipette. This will cause red cell contamination of your plasma sample. If the cells have contaminated the plasma, securely recap the sample with the purple stopper and centrifuge the sample once more. (Return to step 9)
13. Ensure that the lids on the transport vials are secure.
14. Discard the purple top tube containing residual plasma and cells into a biohazard waste container.
15. Place the transport vial into the biohazard bag (ziplock bag). Please note this bag has an absorbent sheet that must remain in the bag. This absorbent sheet will absorb any serum that leaks from the transport vial. (**Please note - The most common cause for leakage is unsecured caps on the transport vials**.)
16. Ensure that the "Plasma Collection Form" is completed and placed in the side pouch of the biohazard bag.
17. Place the biohazard bag containing the transport vials in a –80ºC freezer, until ready to ship to the central laboratory (see address hereafter).
18. When you are ready to ship the samples, remove the biohazard bag containing the transport vial from the –80ºC freezer.

19. Fill half of the Styrofoam lined shipping box with dry ice. Place the biohazard bag containing transport vials and the "Plasma Collection Form" on the dry ice. Fill the rest of the Styrofoam lined shipping box with the remaining dry ice.
20. Place the Styrofoam lid securely on the Styrofoam lined shipping box. Do not secure this lid with tape. The dry ice needs to sublimate.
21. Close the corrugated cardboard lid of the shipping box and secure the cardboard lid with packing tape.

21 Attach the shipping label (Please note – dry ice is considered a dangerous goods shipment) and ship this box via the designated Courier Company to:

For all sites
UCLA-Department of Medicine
Dr Slamon's Research Laboratory
675 Charles E.Young Drive South
Room 5/535, Building MRL
Los Angeles, CA
90095 USA
Central Laboratory contact name: Lillian Ramos
Phone: 310-206-1408
Fax: 310-825-3761

2. Plasma sample supplies:

You will be provided with a plasma sample kit box (1 kit box required for 1 sample collected) and an additional collection of extra supplies (1 extra collection of supplies will be provided for every 3 samples collected).

Plasma Collection Forms will be provided to you at the time of the study initiation visit.

If supplies are needed, please fill out the BCIRG 007 Study Supply Order Form. If you have any questions regarding the supplies, please contact your BCIRG study monitor, or the BCIRG general office number at 780 702 0200.

Each Kit Box includes:

Two - 5 mL (EDTA) purple-top vacutainer tubes
Two Plastic Transport Vial with purple stripe
Pipette

Alcohol, cotton swabs, sterilized plastic strip
21-gauge vacutainer needle, 1-1/2 " (multiple-sampling)

Patient Identification Labels
Biohazard Ziplock Bag (with absorbent sheet inside)

Bag of Extra Collection Supplies includes:

Two - 5 mL (EDTA) purple-top vacutainer tubes
Plastic Transport Vial
Pipette
Alcohol, cotton swabs, sterilized plastic strip
21-gauge vacutainer needle, 1-1/2 " (multiple-sampling)
Biohazard Ziplock Bag (with absorbent sheet inside)
Tourniquet
Yellow Vacutainer Holder

Also Supplied:
One Styrofoam Lined Shipping Box

Site (or Lab) Must Have:
Disposable gloves
Refrigerator, Freezer –80ºC
Centrifuge capable of accommodating 5-mL vacutainer tubes
Needle disposal Container
Biohazard Container
Packing Material (for shipment of sample)
Packing Tape
Dry Ice for shipping

Appendix 3E- CARDIAC GENETIC SUBSTUDY (OPTIONAL)

Collection, storage and shipping instructions for whole blood for the cardiac genetic markers

This optional study will also ask for a whole blood sample to be provided to the central lab prior to study start at Baseline only. Whole blood assays for Cardiac Genetic Markers, to identify patients susceptible to Herceptin®-induced LV dysfunction is currently being investigated. We wish to collect a whole blood prior to treatment in order to review the levels of ACE, 2-adrenergic receptor, and the Endothelin a receptor in blood cells as a predictive factor in a patient's cardiac health. Refusal to grant permission for collection and release of the blood samples for the above-mentioned purpose, will not affect the quality of care the participant is to receive.

1. Procedure for Baseline Collection:

1. Specimens will be collected at Baseline.
2. Please note the expiry date on the kit box. The expiry date on the kit box corresponds to the expiry date on the EDTA (anticoagulant) in the purple top tube. Please do not use an EDTA, purple top tube past its expiry date.
3. Obtain the one 5mL (EDTA) purple top tube to draw the blood specimen.
4. Attach a label containing the patient BCIRG information (patient number, patient initials, date and time sample is collected) to the "Blood Collection Form" (Please refer to next page for an example)
5. Draw the blood from the patient into the 5mL purple top tube. Allow the tube to fill completely.
6. Gently invert the purple top tube 4 to 5 times, to allow the EDTA (anti-coagulant) and blood to mix. Do not vigorously shake the tubes. This is cause the red cells to lyse and will result in a hemolytic sample.
7. ***Do not centrifuge this purple top tube**.
8. Place this purple top EDTA tube, into the bubble pack provided.
9. Place the bubble pack containing the purple top EDTA tube into the biohazard bag (ziplock bag). Please note this bag has an absorbent sheet that must remain in the bag. This absorbent sheet will absorb any blood that leaks from the tube.
10. Ensure that the "Blood Collection Form" is completed and placed in the side pouch of the biohazard bag.
11. Place the biohazard bag containing the transport vial into an insulating material.
12. Fill half of the Styrofoam lined shipping box with dry ice. Place the insulating material containing the biohazard bag with the transport vials and the "Blood Collection Form" on the dry ice. Fill the rest of the Styrofoam lined shipping box with the remaining dry ice
13. Place the Styrofoam lid securely on the Styrofoam lined shipping box. Do not secure this lid with tape. The dry ice needs to sublimate.
14. Close the corrugated cardboard lid of the shipping box and secure the cardboard lid with packing tape.
15. Attach the shipping label (Please note – dry ice is considered a dangerous goods shipment) and ship this box via the **designated Courier Company** to:

For all sites

UCLA-Department of Medicine
Dr Slamon's Research Laboratory
675 Charles E.Young Drive South
Room 5/535, Building MRL
Los Angeles, CA
90095 USA
Central Laboratory contact name: Lillian Ramos
Phone: 310-206-1408
Fax: 310-825-3761

2. Whole Blood sample supplies:

You will be provided with a blood sample kit box (1 kit box required for 1 sample collected) and an additional collection of extra supplies (1 extra collection of supplies will be provided for every 3 samples collected).

Blood Collection Forms will be provided to you at the time of the study initiation visit.

If supplies are needed, please fill out the BCIRG 007 Study Supply Order Form. If you have any questions regarding the supplies, please contact your BCIRG study monitor, or the BCIRG general office number at 780 702 0200.

Each Kit Box includes:

One - 5 mL EDTA purple-top vacutainer tube
Elastic Band

Alcohol, cotton swabs, sterilized plastic strip
21-gauge vacutainer needle, 1-1/2 " (multiple-sampling)

Patient Identification Labels
Bubble Pack
U Tek Refrigerant Pack
Biohazard Ziplock Bag (with absorbent sheet inside)

Bag of Extra Collection Supplies includes:

5 mL EDTA purple-top vacutainer tube
Elastic Band
Alcohol, cotton swabs, sterilized plastic strip
21-gauge vacutainer needle, 1-1/2 " (multiple-sampling)
Biohazard Ziplock Bag (with absorbent sheet inside)
Bubble Pack
Tourniquet
Yellow Vacutainer Holder

Site (or Lab) Must Have:

Disposable gloves
Refrigerator, Gel cold pack should be cold not frozen.
Needle disposal Container
Biohazard Container
Packing Material (for shipment of sample)
Packing Tape

APPENDIX 4 – FLUID RETENTION SEVERITY SCALE

EDEMA	SEVERITY GRADING	EFFUSION
• Asymptomatic *and/or* • Very well tolerated *and/or* • Dependent in evening only	MILD 1	• Asymptomatic • No intervention required
• Moderate functional impairment *and/or* • Pronounced and well tolerated *and/or* • Dependent throughout day	MODERATE 2	• Symptomatic: - Exertional dyspnea *and/or* - Chest pain *and/or* • ECG changes *and/or* • Abdominal distention • Drainage may be required
• Significant impairment of function *and/or* • Pronounced and not well tolerated *and/or* • Generalized anasarca	SEVERE 3	• Symptomatic effusion - Dyspnea at rest *and/or* - Tamponade *and/or* - Pronounced abdominal distention • Drainage urgently required

⇩

FLUID RETENTION
grading
[MILD, MODERATE, SEVERE]
Reporting the highest grade of edema or effusion

APPENDIX 5 - FLOW CHART OF EXAMINATION

Examination	**Prestudy Screen** Within (time) prior to registration	**During Chemotherapy**	***End of Chemotherapy**	**During Follow-up**
Patient informed consent	Before study registration			
History	14 days			
Physical examination Weight Performance Status	14 days	Every 3 weeks X[1]	X	X
Signs and symptoms/ Adverse Events*	14 days	Every 3 weeks X[2]	X	X
Concomitant medication**	1 month	Every 3 weeks X	X	X
Hematology Hemoglobin, WBC, neutrophils, platelets	7 days	Every 3 weeks X[3]	X	X
Biochemistry **Liver function** ASAT/ ALAT alkaline phosphatase bilirubin	7days (Liver function tests repeated within 3 days if abnormal)	Every 3 weeks X[4]	X	X
Renal function creatinine creatinine clearance (if indicated)	7 days	Every 3 weeks X[4]	X	X
HER2 FISH Testing (positive)	Before study registration			
Serum Sample (for shed ECD)	Before 1st administration	After cycles 3 and 6	X	Every 2 months****
Blood Sample (for cardiac genetic markers)	Before 1st administration			
Plasma Sample (for cardiac biochemical markers)	Before 1st administration	After cycles 3 and 6	X	Every 4 months *****
Pregnancy test (urine or serum)	7 days			
ECG	4 weeks	As clinically indicated		
LVEF MUGA scan or echocardiography	4 weeks	After cycles 3 and 6	X	Every 4 months******
Radiology and Tumor measurement	4 weeks	After cycles 3 and 6	X	Every 2 months *******
Chest (AP and Lateral) X-ray and/or CT-scan and/or MRI	X	X[5]	X[5]	X[5]

Examination	Prestudy Screen Within (time) prior to registration	During Chemotherapy	***End of Chemotherapy	During Follow-up
Radiology and Tumor measurement	4 weeks	After cycles 3 and 6	X	Every 2 months *******
Chest (AP and Lateral) X-ray and/or CT-scan and/or MRI	X	X[5]	X[5]	X[5]
Abdomen CT-scan and/or MRI and/or ultrasound. If ultrasound positive, CT-scan and/or MRI are mandatory.	X	X[5]	X[5]	X[5]
Bone Bone scintigraphy. If positive, bone X-ray and/or CT-scan and/or MRI are mandatory.	X	X[5]	X[5]	X[5]
Other investigations	As clinically indicated			

X[1] Physical exam will be performed at day 1 or –1 of the cycle.

X[2] On day 1 before infusion.

X[3] CBC and differential is to be done every three weeks prior to receiving chemotherapy (day –1 or day 1 of each cycle). In case of fever $\geq 38.1°C$, the CBC and differential must be performed and repeated every 2 days until recovery with temperature $< 38.1°C$ or absolute neutrophil count ≥ 0.5

X[4] Biochemistry tests will be performed within 3 days prior to the next infusion of study chemotherapy.

X[5] X-rays, CT scans or MRI of ALL lesions to assess response.
Bone X-rays or CT scan or MRI of osteolytic bone lesions
Bone scan to be repeated only in patients with suspicion of bone metastases at baseline (i.e. positive bone scintigraphy and negative x-ray of hot spots, without other benign conditions).
Otherwise, bone scan to be repeated as indicated by increase of clinical (pain) or biological (alkaline phosphatase, calcium) parameters.

* Signs and symptoms will be recorded for baseline in the appropriate CRF pages and for ALL other visits in the Adverse Experiences pages of CRF.

** Concomitant medication will be recorded for baseline on the appropriate CRF pages, and will include all medication used within one month prior to registration. For ALL other visits concomitant medication will be captured ONLY if related to adverse events.

*** The End of Chemotherapy evaluation will be performed at 21 days after the last dose of chemotherapy (including patients that did not complete all cycles).

**** Specimens will be collected every 2 months in follow-up and at the time of disease progression.

***** Specimens will be collected every 4 months during the first 2 years of follow-up and at any time of clinical evidence of cardiac failure.

****** LVEF determination will be every 4 months until Herceptin® discontinuation, unless additional assessment recommended as outlined in section 5.5.12.

******* Complete radiology for tumor evaluation will be followed every 2 months until disease progression and/or other anti-tumor therapy administration.

APPENDIX 6 - SAMPLE PATIENT INFORMED CONSENT

Note: This is a sample patient informed consent. Each Ethics Committee or Institutional Review Board will revise and adapt according to their own institution's guidelines.

Study number: BCIRG 007 (WO 16437)

A MULTICENTER PHASE III RANDOMIZED TRIAL COMPARING DOCETAXEL (TAXOTERE®) AND TRASTUZUMAB (HERCEPTIN®) WITH DOCETAXEL (TAXOTERE®), CARBOPLATIN AND TRASTUZUMAB (HERCEPTIN®) AS FIRST LINE CHEMOTHERAPY FOR PATIENTS WITH METASTATIC BREAST CANCER CONTAINING THE HER2 GENE AMPLIFICATION.

Study number: BCIRG 007
Sponsor Number: WO 16437

Investigator name:

Address:

Consent Form:

This consent form is part of the informed consent process. It is designed to give you an idea of what this research study is about and what will happen to you if you choose to be in the study. If you would like to know more about something mentioned in this form, or have any questions regarding this research study, please be sure to ask your doctor or nurse. Read this form carefully to make sure you understand all the information it provides. You will get a copy of this form to keep. This study is sponsored by Roche & Genentech and coordinated by the Breast Cancer International Research Group (BCIRG). Roche and Genentech are the companies that manufacture the drug Herceptin® in non-US countries and in the US, respectively. Roche and Genentech will supply this drug free of charge for the purpose of this study where necessary. Aventis is the company that manufactures the drug Taxotere® (docetaxel). This drug will be provided free of charge for the purposes of this study where necessary. This study will take place at various centers throughout Canada, USA, Europe and Australia. Approximately 250 subjects will be participating in this study. Your doctor, who is one of the researchers, will discuss the study with you. Your participation in this study is entirely voluntary. You do not have to take part in this study and your care does not depend on whether you take part or not. This study may not help you directly, but we hope that it will teach us something that will help others in the future.

BACKGROUND Information:

Your doctor has explained to you that you have advanced breast cancer with a risk of progression (cancer may return or spread after it was treated). Approximately 25-30% of breast cancers overexpress the HER2 gene and this overexpression is associated with a much more rapid growth of the cancer cell. Breast cancer can be treated with a combination or sequential schedule of chemotherapy agents such as doxorubicin, cyclophosphamide, docetaxel, paclitaxel and Herceptin®. Taxotere® (docetaxel) has been administered in approximately 2,000 patients with advanced breast cancer in a clinical trial setting and has been approved for commercial use as a single agent for this indication. Studies suggest that a medication called Herceptin® can block the effect of the HER2 gene and slow down the growth of the cancer. Herceptin® has been given safely to many women with advanced metastatic breast cancer and it was found to be effective and to improve survival in combination with chemotherapy as compared to chemotherapy alone. Herceptin® in combination with single-agent docetaxel (the TH regimen) is considered to be one therapeutic approach for your disease. Several studies in small groups of patients are currently being conducted in metastatic breast cancer looking at the combination of Herceptin®, Taxotere® and Platinum Salt, and the results have been encouraging so far in terms of efficacy and safety. Based on the interaction between Herceptin® and chemotherapy, the combination of Herceptin®, Taxotere® and Carboplatin leads us to believe that the cancer growth can be slowed down and relapse significantly delayed or even prevented.

The reason why carboplatin has been selected is because of an increased antitumor activity in preclinical studies seen in breast cancer models when Herceptin® was given with carboplatin.

Study Purpose

The aim of the study is to find out how effective the drug combination of Taxotere®, Carboplatin and Herceptin® (TCH) are for women who have a metastatic breast cancer with large amounts of the HER2 gene compared to the therapeutic regimen Taxotere® and Herceptin® combination (TH).

If the tests and exams show that you can be in the study, you will be randomly assigned (randomized) to one of the two treatments: TCH or TH. This means a computer program will put you into TCH treatment or TH treatment by chance. Neither you nor your doctor will choose which group you are in. You will have an equal chance of being placed in either of the two treatments.

Eligibility

Tissue from your tumor either at the time of your prior surgery or at the present will need to be taken and tested by a central laboratory designated by the BCIRG for the presence of human epidermal growth factor receptor 2 (HER2), a protein. If it is found that you are positive to this test, you will be eligible for this study.

Study Design

If you choose to take part in this study, you have to come to the center every week to receive your Herceptin® dose and at the same time, every 3 weeks you will receive either T or TC for a maximum of 8 cycles (24 weeks of chemotherapy) unless the cancer continues to grow in spite of treatment. Following completion of the 8 cycles of chemotherapy, Herceptin® will be given every 3 weeks at a higher dose unless the cancer continues to grow in spite of treatment:

A cycle of therapy consists of 21 days / 3 weeks.

Chemotherapy Administration:

➢ If you are treated with the TH combination you will receive the following:

First cycle of **TH**

Day 1: Herceptin® 4 mg/kg IV over 90 minutes. You will then be observed for **X** hours before you go home.
Day 2: Taxotere® 100 mg/m² IV over 1 hour.
Day 8: Herceptin® 2 mg/kg IV over 30 minutes. You will be observed for **X** hours before you go home.
Day 15: Herceptin® 2 mg/kg IV over 30 minutes. You will be observed for **X** hours before you go home.
Day 22: Day 1 of Cycle 2.

[Investigator Note: please adapt the Herceptin post-observation period to your local regulations]

Subsequent cycles (to start 3 weeks after Day 1 of 1st cycle)

Day 1: Taxotere® 100 mg/m² IV over 1 hour every 3 weeks followed by Herceptin® 2 mg/kg IV over 30 minutes.
Day 8: Herceptin® 2 mg/kg IV over 30 minutes. You will be observed for **X** hours before you go home.
Day 15: Herceptin® 2 mg/kg IV over 30 minutes. You will be observed for **X** hours before you go home.
Day 22: Day 1 of future cycles

Following completion of the 8 cycles of Taxotere®, Herceptin® will continue every 3 weeks at a dose of 6 mg/kg IV over 30 minutes unless the cancer continues to grow in spite of treatment. You will be observed for **x hours** after the 6mg/kg Herceptin® before you go home if previous dose was well tolerated.

[Investigator Note: please adapt the Herceptin post-observation period to your local regulations]

➢ **If you are treated with the TCH combination you will receive the following:**

First cycle of **TCH**:

Day 1: Herceptin® 4 mg/kg IV over 90 minutes. You will then be observed for **X** hours before you go home.
Day 2: Taxotere® 75 mg/m² IV over 1 hour followed immediately by carboplatin at target AUC = 6 mg/mL/min IV over 30-60 minutes.
Day 8: Herceptin® 2 mg/kg IV over 30 minutes. You will be observed for **X** hours before you go home.
Day 15: Herceptin® 2 mg/kg IV over 30 minutes. You will be observed for **X** hours before you go home
Day 22: Day 1 of Cycle 2.

(Note: AUC stands for the term “area under the curve” and refers to a means of dosing certain drugs.)

Subsequent cycles (to start 3 weeks after Day 1 of 1st cycle):

Day 1: Taxotere® 75 mg/m² IV over 1 hour followed immediately by carboplatin at target AUC = 6 mg/mL/min IV over 30-60 minutes followed by Herceptin® 2 mg/kg IV over 30 minutes.
Day 8: Herceptin® 2 mg/kg IV over 30 minutes. You will be observed for **X** hours before you go home.
Day 15: Herceptin® 2 mg/kg IV over 30 minutes. You will be observed for **X** hours before you go home.
Day 22: Day 1 of future cycles.

Following completion of the 8 cycles of Taxotere®/carboplatin, Herceptin® will continue every 3 weeks at a dose of 6 mg/kg by IV over 30 minutes ® unless the cancer continues to grow in spite of treatment. You will be observed for **x hours** after the 6mg/kg Herceptin® before you go home if previous dose was well tolerated.

[Investigator Note: please adapt the Herceptin post-observation period to your local regulations]

If the side effects are unacceptable, your doctor may reduce the dose of the investigational drug and/or delay the cycle before stopping treatment. You will be offered alternative treatment in case chemotherapy is stopped. Even if your chemotherapy medications are stopped, you will continue to take Herceptin® every 3 weeks if your doctor considers this will be helpful. You will continue to see your doctor at the center to see what, if any, long-term effects the treatment has on your health.

Oral medication will be given twice daily for 3 days starting the night before Taxotere® to prevent hypersensitivity reaction (allergy). You will also be given drugs to prevent nausea and vomiting as well as extra fluid given by vein in order to prevent kidney damage.

The addition of Herceptin® to combination chemotherapy can have an effect on your heart function. It may decrease the pumping action of your heart. Your heart function will be monitored closely with MUGA scans or echocardiographies before starting the study, after the 3rd, 6th and 8th cycle of chemotherapy and every 4 months until Herceptin® is stopped. A MUGA and echocardiography exam is a test that evaluates if the pumping of your heart is normal. Heart function may be monitored more frequently if the result is not normal. Your doctor can explain the cardiac monitoring in greater detail.

The amount of Herceptin present in your blood may have an effect on the effectiveness of Herceptin. When a Herceptin dose is delayed by more than one week, it can take a long time to get back to the levels in your blood prior to the dose delay. In this situation, you will receive Herceptin as if you were just starting Herceptin for the very first time. Because there will still be some Herceptin in your blood from the initial dosing, the amount of Herceptin in your blood after re-starting the treatment may go higher than the initial levels by up to 20%. This increased level has not been investigated previously in patients. We do not expect this higher level to cause a major increase in the chance you will have side effects.

Recommendations for Herceptin dose adjustments after missed or delayed doses have been issued and your doctor will discuss practical implications with you. If one of your Herceptin doses is missed or delayed by more than one week, your treating physician may recommend that you re-start Herceptin as soon as possible with the same dose as if you were starting Herceptin for the very first time. This means for a weekly dosing to give 4mg/kg initially followed by 2 mg/kg every week or for the 3-weekly dosing 8 mg/kg followed by 6 mg/kg every three weeks.

INVESTIGATIONS DURING THE STUDY

A blood test will be done before the study begins and before each course of chemotherapy to check your blood count and blood chemistry. Each sample of blood will be 2 to 3 teaspoons. These regular blood tests and other examinations will be performed to check that the drugs are not adversely affecting your bone marrow, kidneys, and liver. You will be monitored with blood tests regularly while being treated with chemotherapy.

A physical examination and a number of tests (scans and X-rays), including heart function tests (MUGA test or echocardiography and electrocardiogram “ECG”) will be done before you start the study, during the study and the follow-up period.

A pregnancy test will be done before you receive any chemotherapy if there is a chance that you might become pregnant. If you have had only your uterus removed and are under 55 years of age, a special test to check your hormonal levels will be done in order to help determine your menopausal status. Chemotherapy could affect an unborn child so it is very important that you do not get pregnant while receiving these treatments. Your doctor will talk with you about methods of birth control if you are of childbearing age. If you think that you might be pregnant, call the doctor or nurse whose phone numbers are on the last page of this form.

INVESTIGATIONS DURING FOLLOW UP

The follow-up will take place at the end of the study (one month after the last infusion) as well as every other month.
You will have a physical exam and a complete radiology assessment (this will determine whether your tumor is growing) every 2 months. To evaluate cardiac safety, heart exams (either MUGA or echocardiography) will be added at the end of chemotherapy and every 4 months until Herceptin® discontinuation.

If at any time you develop signs or symptoms that your doctor feels may be related to cancer, the tests may be performed sooner, and additional tests may be ordered.

SIDE EFFECTS

Every treatment can have side effects. The TH regimen has side effects, which your doctor will explain to you. It is important that you know the possible side effects of the treatments given in this study. The following are the side effects of each drug used in this study. These side effects may or may not be more severe when the drugs are taken together. These are the side effects we know about at present. However, since this is a study of new treatments there may be other side effects that we do not know about yet. It is therefore important that you report immediately to your study doctor/ nurse the occurrence of any unusual symptoms.

- With Taxotere®, you may also experience low white blood cell counts which may lead to an increased of risk of developing fever and infection, short lasting mild to moderate nausea and/or vomiting, mouth irritation which may cause you some problems with food intake, diarrhea, fatigue, reversible pins and needle sensation in hands or feet, hair loss, skin reactions, low blood pressure which needs a close monitoring during infusion. Patients experienced all these side effects during previous studies and you may also experience other ones, which are not predictable at the moment. There is a chance of developing shortness of breath or a drop in blood pressure with the use of Taxotere®. Rarely these reactions can be severe or life threatening. The center where you are being treated is equipped to deal with such events in this case. You may be asked to weigh yourself weekly to enable your doctor to assess early on if you are developing any fluid retention which can lead to swelling of limbs or fluid around the lungs or abdomen. The infusion itself may cause temporary local irritation and bruises if the drug is infused using a vein in your arm.

- With Herceptin® you may experience some side effects. Your doctor will carefully monitor your symptoms throughout the study. It is important for you to tell your doctor if you are experiencing any discomforts.

Herceptin® has been safely administered intravenously to patients. Some patients have experienced flu-like symptoms such as chills and a mild brief fever, pain sometimes at tumor sites, diarrhea during or after receiving their first dose of Herceptin®. These symptoms were usually mild or moderate in severity and were treated with Tylenol, Benadryl or, rarely, Demerol. These symptoms occurred less often with later infusions. You may also experience low blood counts, an increased risk of infection, headache, dizziness, rash and loss of appetite.

Infrequently, more severe infusion related or allergic reactions have been reported. The symptoms have included shortness of breath, low blood pressure, wheezing, constriction of the airways that lead to the lungs, rapid heart rate, abnormal fluid in the lungs, reduced oxygen in the blood and breathing difficulties, including adult respiratory distress syndrome. Uncommonly, hypersensitivity or allergic reactions such as hives and swelling in the throat occurred. In rare cases these events were associated with a clinical course resulting in a fatal outcome, particularly in those who already had lung disease and shortness of breath. In the majority of the patients, the onset of the symptoms was associated with the first infusion of Herceptin®. Serious reactions have been treated with supportive therapy.

Some patients who receive Herceptin and chemotherapy develop symptoms of a heart condition called congestive heart failure. Symptoms of congestive heart failure include shortness of breath, swelling (usually of the lower legs) and fatigue. Your doctor will monitor your heart function before starting the study and at regular intervals throughout the study. If you develop symptoms of congestive heart failure during the study, your doctor will treat you and will evaluate whether or not to continue your Herceptin treatments. Although severe heart dysfunction continued in some patients and can be fatal, signs and symptoms of heart failure often improved after standard medical treatment was given.

Herceptin® may persist in the circulation for up to 24 weeks after stopping Herceptin® treatment. The use of anthracyclines during these 24 weeks may possibly be at increased risk of cardiotoxicity. If your physician decides to use anthracyclines as the best treatment to treat your disease after a Herceptin® containing regimen, your cardiac function will be monitored carefully.

- With carboplatin you may experience nausea and vomiting, low blood counts, which may increase your risk of developing an infection, decreased appetite, hair loss, decreased function of your kidneys, thrombocytopenia, and numbness and tingling in fingers and toes.

These side effects may be a minor inconvenience or could be severe, but the physician in charge of you will watch you closely if any occurs and will decide to adjust your chemotherapy doses or to stop the treatment.

In case of fever or bruising after receiving either drug, you must contact doctors in the department.

If you have a fever and/or infection, your doctor will do some blood work and may prescribe an antibiotic (such as ciprofloxacin). If your white blood cells (cells responsible for fighting infection) are low at the time, your doctor may also prescribe a medication (G-CSF) to stimulate the production of your white blood cells. This would be given as a once daily needle injection. You may be asked to learn how to give yourself these injections.

INTRAVENOUS NEEDLES AND BLOOD WORK

Some known risks, although rare, are associated with placing a needle into a vein or under the skin. These include discomfort, the possibility of infection, and may leave a temporary bruise, or swelling.

MANDATORY TESTING ON YOUR TISSUE SAMPLE

Tumor material taken either at time of your prior surgery (ies) or at the present will be sent to a laboratory that Breast Cancer International Research Group (BCIRG) will designate in order to confirm that your cancer has the amplification of the HER2 gene.

ADDITIONAL TESTING ON YOUR TISSUE SAMPLE

We are now asking you for permission to store your tumor sample and use it to measure certain markers in the future. Markers are substances made by breast cancer cells. It has been found that there is a correlation between some markers in certain types of cancers and the treatment response. There will be a number of these measurements which will be made on your tumor material in order to determine a possible correlation with the benefit that you will have from the treatment you receive during this study. The markers that will be tested are: p53, members of the Bcl family (Bcl-2, Bax, Bcl-x and Bag-1), MUC1, MIB1 and tubulin isoforms (particularly II, III, IV and Tau). It is possible that as more information about these research measurements is made available to us during this study, newer markers will also be measured on your tissue sample.

Should you (or your legally authorized representative) not wish the scientists to use your tumor sample, refusing to grant permission for testing of these other markers will not affect either your participation in BCIRG 007 trial or the quality of the care you will receive as a participant in this study in any way. Your tumor sample will be returned to your doctor once the mandatory testing for HER2 has been performed.

The results of the marker testing may not help you directly now, or in the future. The research will not have an effect on your care.

There are no additional tests required for you to undertake as a result of giving us permission to use this tumor tissue. The BCIRG will keep the samples and use the material in future studies to learn more about breast cancer and other medical problems. The samples will be kept for 10 years. The tissue will be used only for research and will not be sold. Some new products could be made because of the results of the research that uses your samples. These products might be sold at some time in the future but you will not be paid. The results of the markers will not be given to you or your doctor during the course of your participation in this study unless specifically requested. This information will not be put in your health record.

You can request at any time that your tissue not be used any longer for research. You need to contact your study doctor and let him know that you do not want us to use your tissue. The tissue will no longer be used for research.

Do you agree to have your tumor sample stored and used to measure the markers currently identified in the study and for markers identified in the future? Please circle your answer.

YES **NO** **Patient Initials: _____**

ADDITIONAL TESTING FOR SERUM SAMPLE

In addition to the tissue sample, we are also asking for your permission to forward an extra sample of blood to the central laboratory prior to you starting the study. We wish to also sample your blood each time you have your tumor assessments (at the end of cycles 3 and 6, once you have finished the chemotherapy, every 2 months and at the time your disease gets worse, if it does, for the first 2 years of follow-up. We wish to use these blood samples to see if we can determine whether the type of cancer you have with the HER2 gene can indicate whether a tumor is coming back prior to its return. In the future, this will be useful in detecting your kind of cancer in patients with breast cancer. This sample will be used only for research and will not be sold. The research may be helpful to other patients in the future. Some new products could be made because of the results of the research that uses your sample. These products might be sold at some time in the future, but you will not be paid.

Should you not wish to provide the scientists with a blood sample at any time, refusing to grant permission for these additional tests will not affect your participation in BCIRG 007 trial or the quality of the care you will receive as a participant in this study in any way.

Do you agree to have an extra sample of blood to be forwarded to the central laboratory at the time mentioned above? Please circle your answer.

YES **NO** **Patient Initials: _____**

ADDITIONAL TESTING FOR BLOOD AND PLASMA SAMPLE

In addition to the tissue and the serum sample, we are also asking for your permission to forward an extra sample of blood and an extra sample of plasma to the central laboratory at certain times throughout the course of this study.

The blood sample will be collected prior to you starting the study abd at the same time than any other blood evaluation. We wish to use the blood sample to identify and characterize human genetic variations as a new risk factor for cardiac dysfunction.

The plasma samples will be collected for the first time prior to you starting the study, then at the end of cycles 3, 6 of your chemotherapy treatment, once you have finished the chemotherapy and then every 4 months during the first 2 years of follow-up and also at any time of clinical evidence of cardiac failure. We wish to use these plasma samples to identify cardiac biochemical markers leading to an early dectection of cardiac dysfunction, before clinical heart failure.

These samples will be used only for research and will not be sold. The research may be helpful to other patients in the future. Some new products could be made because of the results of the research that uses your sample. These products might be sold at some time in the future, but you will not be paid.

Should you not wish to provide the scientists with a blood sample or plasma samples at any time, refusing to grant permission for these additional tests will not affect your participation in BCIRG 007 trial or the quality of the care you will receive as a participant in this study in any way.

Do you agree to have an extra sample of blood to be forwarded to the central laboratory prior to you starting the study? Please circle your answer.

YES **NO** **Patient Initials: _____**

Do you agree to have extra plasma samples to be forwarded to the central laboratory prior to you starting the study, at the end of cycles 3, 6, once you have finished the chemotherapy and every 4 months during the 2 first years of follow-up and at any time of a clinical evidence of cardiac failure?
Please circle your answer.

YES **NO** **Patient Initials: _____**

STANDARD TREATMENTS

Your participation in this study is voluntary. If you decide to take part but later change your mind, you are free to do so and do not have to give any reason, however, you should advise your doctor of your decision so he can tell you the procedure to be followed with your medical condition to be properly evaluated and then to continue medical care. The level of care you receive from your doctor will not be affected.

If you do not wish to participate in this study, there are other treatments available to you. Your doctor will discuss with you other treatment options available to patients with your type of cancer and explain the risks and benefits of these options to you. Right now, the usual treatment is to use any or all of the standard therapies, other drugs and procedures or other investigational drugs. The doctors can provide detailed information about this and the benefits of various treatments available to you. Other therapies, which are optional, may not be curative but may control symptoms. Your refusal to participate in this study will not result in loss of benefit or treatment. You may also choose to have no treatment in which case your tumor will be expected to grow.

POTENTIAL BENEFITS

Participation in this study may be of no personal benefit to you. However, based on the results of this study, it is hoped that in the future, patient care can be improved.

WITHDRAWAL FROM STUDY

In discussion with you, your doctor at the center, either at his/her own initiative or at the request from the sponsor of this study, may withdraw you from the study at any time if it is in your best interests. You may also withdraw from the study at any time if you wish to do so. You will be informed of any significant new findings about the drugs used in the study. This new information may or may not affect your willingness to continue participating in the study.

COSTS

You will not have to pay for the treatment you receive in this study. If you are covered by a private insurance company, you will get some or all your money back, but if you do not have private insurance, the sponsors of this study will cover these costs. In the same way, you will have to pay for the drugs you need for side effects, such as your anti-nausea medications. You will be coming to the cancer center more often than if you were not part of a study. There may be some extra costs, such as parking and meals that you will have to pay.

INJURY CLAUSE

It is important to note that nothing said in this consent form alters your legal rights to recover damages should injury be suffered as a result of participation in the study

If you have any questions regarding a research-related injury or other medical concerns, or any further inquiries concerning the procedures of this study, you should contact:

Doctor name: _____ Telephone number: _____

Study Coordinator name: _____ Telephone number: _____

For information concerning research and your rights as a study participant, you should contact:

Name: _____ Telephone number: _____

Name and phone number of patient representative or ethics committee contact person: _____

Name: _____ Telephone number: _____

CONFIDENTIALITY

The information that we collect, as part of this study, will be shared with other researchers and doctors. However, you will not be identified in any of these reports. Data and materials collected as part of this study, and some information from your medical records as it relates to this study, may need to be sent to the statistical headquarters of BCIRG. Strict confidentiality will be maintained and you will not be identified by name on any of the data and materials submitted, except if required by law.

We will keep all the material we collect for this study in a safe storage area. In the future, other researchers may want to use this material for new studies. Although we will not contact you if this happens, each new study will be reviewed by the relevant agency or organization to make sure that it is ethical. Representatives from the Ethics Committees, the government, Canadian Health Protection Branch or the Food and Drug Administration in the United States or other Regulatory authorities around the world, BCIRG, as well as the sponsor may want to look at your medical record as it relates to this study at the center. This is part of the process of quality control. Each person looking at your records will follow the relevant center's policies and procedures that control these actions.

PATIENT CONSENT

I have been informed of the purpose, procedures and duration of the study (BCIRG 007) with the drug Taxotere® and Herceptin®, or Taxotere®, carboplatin and Herceptin®, of its possible advantages and inconveniences and I agree to participate to this study conducted by Dr..... .

A summary of the information has been given to me.

I know that I am free to refuse to participate and that I can withdraw my consent at any time during the study. I have been given a copy of this consent form to retain.

Name of Patient (Print)	Signature of Patient
	Date
Name of Investigator (Print)	Signature of Investigator:
	Date

APPENDIX 7 – Herceptin® Multi Dose and Single Dose vials

A.Single Dose Vials (SDV) DESCRIPTION

1.1. Formulation, Packaging, Labeling, Preparation and Administration

1.1.1 Formulation

Lyophilized Formulation: Herceptin® will be supplied as a freeze-dried preparation at a content of 150 mg per vial for parenteral administration. Herceptin® is formulated in histidine, trehalose, and polysorbate 20. Each vial is reconstituted with 7. 2 mL of Sterile Water for Injection (SWI), USP, yielding a solution of 21 mg/mL Herceptin®. Reconstituted Herceptin® will be added to 250 mL of 0.9% Sodium Chloride Injection, USP. This formulation does not contain a preservative (once the infusion is prepared it should be administered immediately) and is suitable for single use only. This formulation must be infused within 8 hours after reconstitution.

DO NOT FREEZE HERCEPTIN® THAT HAS BEEN RECONSTITUTED.

1.1.2 Drug Preparation

Appropriate aseptic technique should be used. Each vial of Herceptin® is reconstituted with 7. 2 mL of Sterile Water for Injection (SWI). Herceptin® should be carefully handled during reconstitution. Causing excessive foaming during reconstitution or shaking the reconstituted Herceptin® may result in problems with the amount of Herceptin® that can be withdrawn from the vial.

The following instructions have to be followed:
1) Using a sterile syringe, slowly inject 7.2 ml of sterile water for injections in the vial containing the lyophilised Herceptin®, directing the stream into the lyophilised cake.
2) Swirl vial gently to aid reconstitution. DO NOT SHAKE!

This yields a 7.4 ml solution for single-dose use, containing 21 mg/mL Herceptin®, at a pH of approximately 6.0.
Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The reconstituted Herceptin® results in a colourless to pale yellow transparent solution and should be essentially free of visible particulates.

Determine the volume of the solution required based on a loading dose of 4 mg Herceptin®/kg body weight, or a maintenance dose of either 2 mg Herceptin®/kg body weight during chemotherapy or 6 mg Herceptin®/kg body weight during follow-up period:

$$\textbf{Volume}\ (\text{mL}) = \frac{\textbf{Body weight}\ (\text{kg}) \times \textbf{dose}\ (\textbf{4}\ \text{mg/kg for loading or either}\ \textbf{2}\ \text{or}\ \textbf{6}\ \text{mg/kg for maintenance})}{\textbf{21}\ (\text{mg/mL, concentration of reconstituted solution})}$$

The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 mL of 0.9% sodium chloride. Glucose-containing solution should not be used since this can cause aggregation of the protein. The bag should be gently inverted to mix the solution in order to avoid foaming. Parenteral drug products should be inspected visually for particulates and discoloration prior to administration. Once the infusion is prepared it should be administered immediately. If diluted aseptically, it may be stored for 24 hours when refrigerated at 2°C–8°C.

1.1.3 Dosage and Administration

Herceptin® is administered as a 90-minute intravenous infusion. Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Interruption of the infusion may help control such symptoms. The infusion may be resumed when symptoms abate.
If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30-minute infusion. Emergency equipment must be available.On very rare occasions, patients have experienced the onset of infusion symptoms or pulmonary symptoms more than six hours after the start of the Herceptin® infusion. Patients should be warned of the possibility of such a late onset and should be instructed to contact their physician if these symptoms occur.

Do not administer as an intravenous push or bolus.

1.1.4 Storage Requirements

Vials of Herceptin® are shipped on wet ice at a temperature ranging from 2°C to 8°C (36°F to 46°F), and must be placed in a refrigerator (same temperature range) immediately upon receipt to ensure optimal retention of physical and biochemical integrity. Do not use beyond the expiration date stamped on the vial. Temperature logs must be maintained (in accordance with local pharmacy practice) on the refrigerator to ensure proper storage conditions. Do not use beyond the expiration date stamped on the vial.
DO NOT FREEZE. Herceptin® may be sensitive to shear-induced stress (e.g., agitation or rapid expulsion from a syringe).
DO NOT SHAKE. Vigorous handling of solutions of Herceptin® results in aggregation of the protein and may create cloudy solutions.

After reconstitution with sterile water for injections the reconstituted solution is physically and chemically stable for 48 hours at 2°C – 8°C. Any remaining reconstituted solution should be discarded.

Solutions of Herceptin® for infusion are physically and chemically stable in polyvinylchloride or polyethylene bags containing 0.9% sodium chloride for 24 hours at temperatures not exceeding 30°C.

From a microbiological point of view, the reconstituted solution and Herceptin® infusion solution should be used immediately.

B.Multi-Dose Vial (MDV) DESCRIPTION

1.1 Formulation, Packaging, Labeling, Preparation and Administration

1.1.1 Formulation

Lyophilized Formulation: Herceptin® will be supplied for use as a freeze-dried preparation at a nominal content of 440 mg per vial for parenteral administration. The drug is formulated in histidine, trehalose, and polysorbate 20.

For intravenous (IV) administration, each vial of Herceptin® is reconstituted with 20 mL sterile Bacteriostatic Water for Injection (BWFI), USP (containing 1.1% benzyl alcohol), which is supplied with each vial. The reconstituted solution contains 21 mg/mL Herceptin® and will be added to 250 mL of 0.9% Sodium Chloride Injection, USP. This formulation is designed for multiple uses and must be used within 28 days after reconstitution.

DO NOT FREEZE HERCEPTIN® THAT HAS BEEN RECONSTITUTED.

1.1.2 Drug Preparation

Appropriate aseptic technique should be used. Each vial of Herceptin® is reconstituted with 20 mL of Bacteriostatic Water for Injection, as supplied. Herceptin® should be carefully handled during reconstitution. Causing excessive foaming during reconstitution or shaking the reconstituted Herceptin® may result in problems with the amount of Herceptin® that can be withdrawn from the vial.
The following instructions have to be followed:

1) Using a sterile syringe, slowly inject 20 ml of sterile water for injections in the vial containing the lyophilised Herceptin®, directing the stream into the lyophilised cake.

2) Swirl vial gently to aid reconstitution. DO NOT SHAKE!

This yields a multi-dose solution, containing 21 mg/mL Herceptin®, at a pH of approximately 6.0.
Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The reconstituted Herceptin® results in a colourless to pale yellow transparent solution and should be essentially free of visible particulates.

Determine the volume of the solution required based on a loading dose of 4 mg Herceptin®/kg body weight, or a maintenance dose of either 2 mg Herceptin®/kg body weight during chemotherapy or 6 mg Herceptin®/kg body weight during follow-up:

$$\textbf{Volume}\ (\text{mL}) = \frac{\textbf{Body weight}\ (\text{kg}) \times \textbf{dose}\ (\textbf{4}\ \text{mg/kg for loading or either}\ \textbf{2 or 6}\ \text{mg/kg for maintenance})}{\textbf{21}\ (\text{mg/mL, concentration of reconstituted solution})}$$

The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 mL of 0.9% sodium chloride. Glucose-containing solution should not be used since this can cause aggregation of the protein. The bag should be gently inverted to mix the solution in order to avoid foaming. Parenteral drug products should be inspected visually for particulates and discoloration prior to administration. Once the infusion is prepared it should be administered immediately. If diluted aseptically, it may be stored for 24 hours when refrigerated at 2°C–8°C.

1.1.3 Dosage and Administration

Herceptin® is administered as a 90-minute intravenous infusion. Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Interruption of the infusion may help control such symptoms. The infusion may be resumed when symptoms abate.
If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30-minute infusion. Emergency equipment must be available.
On very rare occasions, patients have experienced the onset of infusion symptoms or pulmonary symptoms more than six hours after the start of the Herceptin® infusion. Patients should be warned of the possibility of such a late onset and should be instructed to contact their physician if these symptoms occur.

Do not administer as an intravenous push or bolus.

1.1.4 Storage Requirements

Vials of Herceptin® are shipped on wet ice at a temperature ranging from 2°C to 8°C (36°F to 46°F), and must be placed in a refrigerator (same temperature range) immediately upon receipt to ensure optimal retention of physical and biochemical integrity. Do not use beyond the expiration date stamped on the vial. Temperature logs must be maintained (in accordance with local pharmacy practice) on the refrigerator to ensure proper storage conditions. Do not use beyond the expiration date stamped on the vial.

DO NOT FREEZE. Herceptin® may be sensitive to shear-induced stress (e.g., agitation or rapid expulsion from a syringe). **DO NOT SHAKE**. Vigorous handling of solutions of Herceptin® results in aggregation of the protein and may create cloudy solutions.

The reconstituted formulation (440 mg vial) with BWFI is designed for multiple uses. Unused drug may be stored for 28 days at 2°C-8°C (36°F-46°F). Discard any remaining multi-dose reconstituted solution after 28 days.
Solutions of Herceptin® for infusion are physically and chemically stable in polyvinylchloride or polyethylene bags containing 0.9% sodium chloride for 24 hours at temperatures not exceeding 30°C.
From a microbiological point of view, the Herceptin® infusion solution should be used immediately. The product is not intended to be stored after dilution.

GENERAL: Dosage and Administration

Herceptin® will be administered in an outpatient setting. Patients in IV infusion the test arm will receive a loading dose of 4 mg/kg Herceptin® at Day 1, followed by weekly administration of 2 mg/kg IV infusion of Herceptin® until three weeks after the last cycle of chemotherapy. Three weeks after the last cycle of chemotherapy, Herceptin® will be administered at a dose of 6 mg/kg by IV infusion every 3 weeks. Do not administer as an IV push or bolus. The initial total dose should be based on the baseline body weight and should not be changed unless the body weight changes by greater than 5 percent. The initial dose of Herceptin® will be administered over a 90-minute-period (see Table 8). If this first dose is well tolerated, subsequent infusion period may be shortened to 30 minutes. If the initial or subsequent doses are not well tolerated, (e.g., the patient experiences fever or chills), subsequent infusions may be shortened only after a dose is well tolerated. Patients must remain under medical supervision for 4-hours 1/2 following completion of the initial 4 mg/kg-loading dose of Herceptin® (see Table 8). If no adverse events occur with the first infusion, the post-infusion observation period for the second infusion may be shortened to 1-hour 1/2. During the follow-up visits Herceptin® will be administered over a 30-minutes infusion period with a post-infusion observation of an 1-hour 1/2 (see Table 8).

APPENDIX 8 – Taxotere ® (Docetaxel) Vials

Implementation Of Taxotere® With New Storage Conditions

Implementation of the Taxotere® with new storage conditions for clinical trials is following the implementation on the Market. First Market supplied is the European Community*, plus Norway and Switzerland.

In these first countries, for Clinical trials, Taxotere® stored between +2°C to +8°C will be replaced by Taxotere® stored between +2°C to + 25 °C. Locally, Taxotere® stored between +2°C to +8°C will be used until inventories are depleted.

Supplies for clinical trials of the Taxotere® with new storage conditions will be implemented progressively, depending on Local Approval, and Market Launch.

For a short period, inventories of Taxotere® stored between +2°C to +8°C and inventories of Taxotere® stored between +2°C to + 25 °C will be available at the same investigational sites. We suggest not to mix premix solution of Taxotere® stored between +2°C to +8°C, and premix solution of Taxotere® stored between +2°C to +25°C. In case it happens, the period for use of the premix and the infusion bags will be the shortest, corresponding to the instructions for use of Taxotere® stored between +2°C to +8°C.

* European Community

Austria
Belgium
Denmark
Finland
France
Germany
Greece
Ireland
Italy
Luxemburg
Portugal
Spain
Sweden
The Netherlands
United Kingdom

APPENDIX 8(A):

PREPARATION GUIDE FOR USE WITH TAXOTERE® CONCENTRATE AND SOLVENT FOR SOLUTION FOR INFUSION FOR TAXOTERE®

Storage Conditions + 2° C and +8 °C

1. Drug substance

- International non-proprietary name : docetaxel
- Code name: RP56976

2. Formulations

TAXOTERE® concentrate for solution for infusion is a clear viscous, yellow to brown-yellow solution containing 40-mg/ml docetaxel (anhydrous) in polysorbate 80. The Solvent for TAXOTERE® is a 13% w/w solution of ethanol in water for injection.

3. Presentation

3.1 TAXOTERE® 80 mg vial:

- The TAXOTERE® 80 mg vial is a 15 ml clear glass vial with a red flip-off cap.
- The labeled dosage strength is 80 mg docetaxel per vial.
- The labeled volume of one vial is 2 ml of a 40 mg/ml solution of docetaxel in polysorbate 80.
- **Practically, TAXOTERE® 80 mg vial contains 2.36 ml of the 40-mg/ml solution of docetaxel equivalent to 94.4 mg docetaxel. This volume has been established and validated during the development of Taxotere® to compensate for liquid loss during preparation of the premix (see section 4) due to foaming, adhesion to the walls of the vial and "dead-volumes". This overfill ensures that there is a minimal extractable premix volume of 8 ml containing 10 mg/ml docetaxel which corresponds to the labeled amount of 80 mg per vial.**

3.2 Solvent for Taxotere® 80 mg vial:

- The Solvent for TAXOTERE® 80 mg vial is a 15 ml clear glass vial with a transparent colorless flip-off cap.
- The Solvent for TAXOTERE®® composition is a 13% w/w solution of ethanol in water for injection
- The theoretical volume of one vial is 6 ml of Solvent for TAXOTERE®.
- **Practically, a solvent for TAXOTERE® 80 mg vial contains 7.33 ml ± 5% of Solvent. This volume has been established and validated based on the practical content of the TAXOTERE® 80 mg vial and ensures a premix concentration of 10-mg/ml docetaxel.**

STORAGE CONDITIONS:

In a refrigerator, protected from bright light.

4. Preparation of the premix solution under aseptic conditions

4.1. Remove the required number of TAXOTERE® 80 mg vials and solvent for TAXOTERE® vials from the refrigerator and allow standing at room temperature for 5 minutes.

4.2. For each TAXOTERE® 80 mg vial, using a syringe fitted with a needle, withdraw **THE ENTIRE CONTENTS** of the corresponding Solvent for TAXOTERE® 80 mg vial (7.33 ml ± 5% for TAXOTERE® 80mg vial) and inject it into the corresponding TAXOTERE® 80 mg vial.

The addition of **THE ENTIRE CONTENTS** of one Solvent for TAXOTERE® 80 mg vial to one TAXOTERE® 80 mg vial ensures a minimal extractable volume of the premix solution of 8 ml.

4.3. Remove the syringe and needle and shake the mixture manually for 15 seconds.

4.4. Allow the premix vial to stand for 5 minutes at room temperature and then check that the solution is homogenous and clear. (Foaming is normal even after 5 minutes due to the presence of polysorbate 80 in the formulation)

The premix solution contains 10-mg/ml docetaxel and should be used immediately to prepare the infusion solution.

5. Preparation of the infusion solution under aseptic conditions

5.1. More than one premix vial may be necessary to obtain the required dose for the patient. Based on the required dose for the patient expressed in mg, use graduated syringes fitted with a needle to withdraw the corresponding premix volume containing 10-mg/ml docetaxel from the appropriate number of premix vials. For example, a dose of 140 mg docetaxel would require 14 ml premix solution.

5.2. Inject the required premix volume into a 250 ml infusion bag or bottle containing either 5% glucose solution or 0.9% sodium chloride solution.

If a dose greater than 200 mg of docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.74-mg/ml docetaxel is not exceeded.

5.3. Mix infusion bag or bottle manually using a rocking motion.

The TAXOTERE® infusion solution should be administered intravenously within the four hours including a one-hour infusion under room temperature and normal lighting conditions.

6. Visual inspection

As with all parenteral products, TAXOTERE® should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If TAXOTERE® premix solution or infusion solution is not clear or appears to have precipitation, the solution should be discarded.

7. Recommendations for the safe handling

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

* U.S.A.

APPENDIX 8(B):

PREPARATION GUIDE FOR USE WITH TAXOTERE® CONCENTRATE AND SOLVENT FOR SOLUTION FOR INFUSION FOR TAXOTERE®

Storage Conditions + 2° C and +25 °C

1. Drug Substance

- International non-proprietary name: docetaxel
- Code name: RP56976

2. Formulations

TAXOTERE® concentrate for solution for infusion is a clear viscous, yellow to brown-yellow solution containing 40-mg/ml docetaxel (anhydrous) in polysorbate 80. The Solvent for TAXOTERE® is a 13% w/w solution of ethanol in water for injection.

3. Presentation

3.1 TAXOTERE® 80 mg vial:

- The TAXOTERE® 80 mg vial is a 15 ml clear glass vial with a red flip-off cap.
- The labeled dosage strength is 80 mg docetaxel per vial.
- The labeled volume of one vial is 2 ml of a 40-mg/ml solution of docetaxel in polysorbate 80.
- **Practically, TAXOTERE® 80 mg vial contains 2.36 ml of the 40-mg/ml solution of docetaxel equivalent to 94.4 mg docetaxel. This volume has been established and validated during the development of Taxotere® to compensate for liquid loss during preparation of the premix (see section 4) due to foaming, adhesion to the walls of the vial and "dead-volumes". This overfill ensures that there is a minimal extractable premix volume of 8 ml containing 10 mg/ml docetaxel which corresponds to the labeled amount of 80 mg per vial.**

3.2 Solvent for Taxotere® 80 mg vial:

- The Solvent for TAXOTERE® 80 mg vial is a 15 ml clear glass vial with a transparent colorless flip-off cap.
- The Solvent for TAXOTERE® composition is a 13% w/w solution of ethanol in water for injection
- The theoretical volume of one vial is 6 ml of Solvent for TAXOTERE®.
- **Practically, a solvent for TAXOTERE® 80 mg vial contains 7.33 ml ± 5% of Solvent. This volume has been established and validated based on the practical content of the TAXOTERE® 80 mg vial and ensures a premix concentration of 10-mg/ml docetaxel.**

STORAGE CONDITIONS:

Vials should be stored between +2°C and +25°C and protected from bright light.

4. Preparation of the premix solution under aseptic conditions

4.1. Remove the required number of TAXOTERE® 80 mg vials and solvent for TAXOTERE® vials from the refrigerator and allow standing at room temperature for 5 minutes.

4.2. For each TAXOTERE® 80 mg vial, using a syringe fitted with a needle, withdraw **THE ENTIRE CONTENTS** of the corresponding Solvent for TAXOTERE® 80 mg vial (7.33 ml ± 5% for TAXOTERE® 80mg vial) and inject it into the corresponding TAXOTERE® 80 mg vial.

The addition of **THE ENTIRE CONTENTS** of one Solvent for TAXOTERE® 80 mg vial to one TAXOTERE® 80 mg vial ensures a minimal extractable volume of the premix solution of 8 ml.

4.3. Remove the syringe and needle and shake the mixture manually for 15 seconds.

4.4. Allow the premix vial to stand for 5 minutes at room temperature and then check that the solution is homogenous and clear. (Foaming is normal even after 5 minutes due to the presence of polysorbate 80 in the formulation)

The premix solution contains 10-mg/ml docetaxel and should be used immediately to prepare the infusion solution. However the chemical and physical stability of the premix solution has been demonstrated for 8 hours when stored either between +2°C and +8°C or at room temperature.

5. Preparation of the infusion solution under aseptic conditions

5.1. More than one premix vial may be necessary to obtain the required dose for the patient. Based on the required dose for the patient expressed in mg, use graduated syringes fitted with a needle to withdraw the corresponding premix volume containing 10-mg/ml docetaxel from the appropriate number of premix vials. For example, a dose of 140 mg docetaxel would require 14 ml premix solution.

5.2. Inject the required premix volume into a 250 ml infusion bag or bottle containing either 5% glucose solution or 0.9% sodium chloride solution.

If a dose greater than 200 mg of docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/ml docetaxel is not exceeded.

5.3. Mix infusion bag or bottle manually using a rocking motion. The TAXOTERE® infusion solution should be used within 4 hours and should be aseptically administered as a 1-hour infusion under room temperature and normal lighting conditions.

The TAXOTERE® infusion solution should be administered intravenously within the four hours including a one hour infusion under room temperature and normal lighting conditions.

6. Visual inspection

As with all parenteral products, TAXOTERE® should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If TAXOTERE® premix solution or infusion solution is not clear or appears to have precipitation, the solution should be discarded.

7. Recommendations for the safe handling

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

POLYSORBATE 80 (TWEEN 80®) CONTAINING DRUGS

VEPESID®	ETOPOSIDE
DEPO-PROVERA®	MEDROXYPROGESTERONE ACETATE
DEPO-PRODASONE® 500 - 250mg	MEDROXYPROGESTERONE
DEXTANCYL®	DEXAMETHASONE
DIPROSTENE®	BETAMETHASONE
HYDROCORTANCYL®	PREDNISOLONE (ACETATE)
HYDROCORTANCYL (Roussel)®	HYDROCORTISONE (ACETATE)
CORTISONE (Roussel)® 25, 125 mg	CORTISONE (ACETATE)
ALTIM®	CORTIVASOL
TEDAROL® 50 mg	TRIAMCINOLONE
KENACORT - retard®	TRIAMCINOLONE
ARISTOPAN®	TRIAMCINOLONE
DURACILLIN A.S.®	PENICILLINE
LIBRIUM®	CHLORODIAZEPOXIDE
E. FEROL®	VITAMINE E
CORBIONAX®	AMIODARONE
ACTILYSE® 20, 50 mg	T.P.A. (Activateur tissulaire du plasminogene)
DECAPEPTYL®	TRIPTORELINE
ORTHOCLONE OKT3®	
TERPONE®	ESSENCES TERPENIQUES
VACCIN GENHEVAC B® (Pasteur)	

APPENDIX 9 – SERIOUS ADVERSE EVENT REPORT FORM

BCIRG

Study Number BCIRG ____

Page 1 of 3

SERIOUS ADVERSE EVENT(S) REPORT FORM

Report Type
☐ Initial
☐ *Follow up

Investigator Number | Patient Number | Country | Visit number: Cycle ☐ Follow up ☐

Patient Initials | day | month | year — Date of Birth | Age | Sex | Height (cm) | Weight (kg)

Serious Reaction Onset Date day | month | year

Description of Reaction and Duration

Did Event Abate After Stopping Drug?
☐ No
☐ Yes
☐ Not Applicable

Did Event Reappear After Reintroduction?
☐ No
☐ Yes
☐ Not Applicable

Relevant Lab Data

Medication used to treat the event

Study Medication(s)

	Product Name	Dose / Unit	Route	First Administration Date	Last Administration Date
1.				day month year	day month year
2.				day month year	day month year
3.				day month year	day month year

	Indication	Batch / Lot Number
1.		
2.		
3.		

NOTE: Report SAE within 24 hours to BCIRG Safety Manager
* Please provide only/all new information on the event

Draft: May 25, 2001

BCIRG

Page 2 of 3

Study Number BCIRG ___

SERIOUS ADVERSE EVENT(S) REPORT FORM

Patient Number ___

Serious Adverse Event(s) Only	Seriousness Criteria 1. Died 2. Life-threatening 3. Hospitalization 4. Disability 5. Congenital anomaly 6. Other medical conditions	Grade * (1-4)	Onset Date Stop Date	Outcome 1. Recovered/Resolved 2. Recovering/Resolving 3. Not recovered/Not resolved 4. Fatal 5. Unknown	Action Taken Study Medication 0: None 1: Discontinued 2: Interrupted 3: Dose Reduced 4: Dose Frequency Changed 5: Dose Reduced and Dose Frequency Changed			Relation to Study Medication 1: Not Related 2: Related			Other Most Likely Cause 1. Underlying/Concomitant illness 2. Possibly associated with concomitant drugs 3. Directly related to study procedures 4. Other known or suspected cause, please specify 5. None
					Taxotere	Platinum Salt	Herceptin	Taxotere	Platinum Salt	Herceptin	
			day month year day month year ☐ Ongoing								
			day month year day month year ☐ Ongoing								
			day month year day month year ☐ Ongoing								
			day month year day month year ☐ Ongoing								
			day month year day month year ☐ Ongoing								
			day month year day month year ☐ Ongoing								

* If NCI version 2.0 grade is not applicable, code severity as: 1=Mild, 2=Moderate, 3=Severe, 4=Life Threatening .

BCIRG

Page 3 of 3

Study Number BCIRG ____ Patient Number ____

SERIOUS ADVERSE EVENT(S) REPORT FORM

Relevant Medical History ☐ Check if None

Medical Term	Ongoing	Comments
	☐ No ☐ Yes	
	☐ No ☐ Yes	
	☐ No ☐ Yes	
	☐ No ☐ Yes	

Concomitant Medication ☐ Check if None

Medication / Dose	Start Date	Stop Date	Indication	* Causal Relationship Yes or No
	day month year	day month year or ☐ Ongoing		
	day month year	day month year or ☐ Ongoing		
	day month year	day month year or ☐ Ongoing		
	day month year	day month year or ☐ Ongoing		
	day month year	day month year or ☐ Ongoing		

*Is there a reasonable possibility that the adverse event is associated with the concomitant medication?

In case of Death

Date of Death

day month year

Was an autopsy performed?

☐ No ☐ Yes ☐ Planned

Cause of Death

1. Disease for which patient was enrolled ☐ Yes ☐ No
2. Other pre-existing condition(s) ☐ Yes ☐ No
3. Serious adverse event ☐ Yes ☐ No
4. Unknown ☐ Yes ☐ No

Reporter or Investigator Information

Name _____

Address _____

Report Sent to Local Authorities

☐ Yes ☐ No

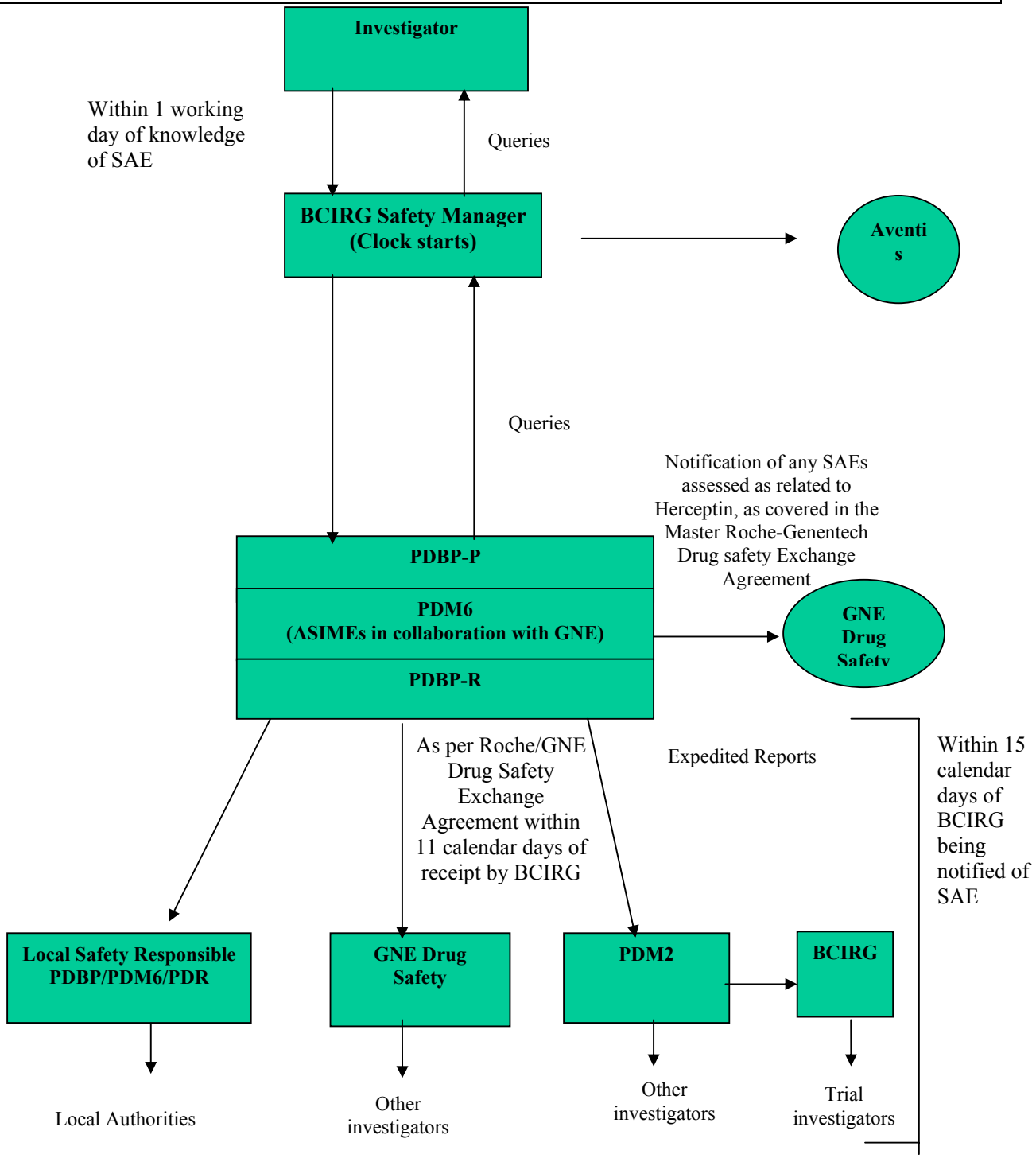
day month year

Investigator Signature: _____

day month year

Draft: May 25, 2001

Appendix 9A - FLOW CHART OF SERIOUS ADVERSE EVENT REPORTING


Investigator
Within 1 working day of knowledge of SAE
Queries
BCIRG Safety Manager (Clock starts)
Aventis
Queries
Notification of any SAEs assessed as related to Herceptin, as covered in the Master Roche-Genentech Drug safety Exchange Agreement
PDBP-P
PDM6 (ASIMEs in collaboration with GNE)
PDBP-R
GNE Drug Safety
As per Roche/GNE Drug Safety Exchange Agreement within 11 calendar days of receipt by BCIRG
Expedited Reports
Within 15 calendar days of BCIRG being notified of SAE
Local Safety Responsible PDBP/PDM6/PDR
GNE Drug Safety
PDM2
BCIRG
Local Authorities
Other investigators
Other investigators
Trial investigators

APPENDIX 10 – PER CENT OF NORMAL BONE MARROW IRRADIATED USING STANDARD RADIATION PORTS

	MARROW VOLUME AT RISK
Skull (not including mandible)	12%
Upper limb girdle (unilateral) (humeral head, scapulae, clavicle)	4%
Sternum	2%
Ribs (all)	8%
Ribs (hemithorax)	4%
Cervical vertebrae (all)	3%
Thoracic vertebrae (all)	14%
Lumbar vertebrae (all)	11%
Sacrum	14%
Pelvis (including both innominates and both femoral heads and necks)	26%
Mantle (approximate)	25%
Upper para aortic nodes (approximate)	11%
Inverted Y (approximate)	45%

* Based on Ellis RE: *Phys Med Biol* 5:255, 1961

APPENDIX 11 - HEMATOLOGY NORMAL LABORATORY VALUES

BCIRG 007 (WO 16437)
HEMATOLOGY NORMAL LABORATORY VALUES

Test	Lower limit	Upper limit	Units
Hemoglobin	12.00 (F)	15.60 (F)	g/dL
Platelets	150.00	400.00	10^9/L
White Blood Cells	4.00	10.00	10^9/L
Neutrophils	2.00	6.00	10^9/L
Lymphocytes	2.00	4.00	10^9/L
Monocytes	0.20	0.95	10^9/L
Eosinophils	0.04	0.60	10^9/L
Basophils	0.01	0.05	10^9/L
Atypical lymphocytes	< 0		

The table above is to inform you of the standard normal ranges which will be used to analyse hematological parameters for the study. The standard values have been taken from NCI Common Toxicity Criteria (Version 2.0) and Clinical Decisions for Lab Tests by B.E. Statland, published by Medical Economics Books, 1987 when not defined in the NCI Common Toxicity Criteria.

APPENDIX 12 – NCI Common Toxicity Criteria, Version 2.0

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
ALLERGY/IMMUNOLOGY					
Allergic reaction/ hypersensitivity (including drug fever)	none	transient rash, drug fever < 38°C (<100.4°F)	urticaria, drug fever ≥ 38°C (≥100.4°F), and/or asymptomatic bronchospasm	symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedem a	anaphylaxis
Note: Isolated urticaria, in the absence of other manifestations of an allergic or hypersensitivity reaction, is graded in the DERMATOLOGY/SKIN category.					
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	none	mild, not requiring treatment	moderate, requiring treatment	-	-
Autoimmune reaction	none	serologic or other evidence of autoimmune reaction but patient is asymptomatic (e.g., vitiligo), all organ function is normal and no treatment is required	evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism), requiring treatment other than immunosuppressiv e drugs	reversible autoimmune reaction involving function of a major organ or other adverse event (e.g., transient colitis or anemia), requiring short-term immunosuppressiv e treatment	autoimmune reaction causing major grade 4 organ dysfunction; progressive and irreversible reaction; long-term administration of high-dose immuno-suppressive therapy required
Also consider Hypothyroidism, Colitis, Hemoglobin, Hemolysis.					
Serum sickness	none	-	-	present	-
Urticaria is graded in the DERMATOLOGY/SKIN category if it occurs as an isolated symptom. If it occurs with other manifestations of allergic or hypersensitivity reaction, grade as Allergic reaction/hypersensitivity above.					
Vasculitis	none	mild, not requiring treatment	symptomatic, requiring medication	requiring steroids	ischemic changes or requiring amputation
Allergy/Immunology-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
AUDITORY/HEARING					
Conductive hearing loss is graded as Middle ear/hearing in the AUDITORY/HEARING category.					
Earache is graded in the PAIN category.					
External auditory canal	normal	external otitis with erythema or dry desquamation	external otitis with moist desquamation	external otitis with discharge, mastoiditis	necrosis of the canal soft tissue or bone
Note: Changes associated with radiation to external ear (pinnae) are graded under Radiation dermatitis in the DERMATOLOGY/SKIN category.					

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Inner ear/hearing	normal	hearing loss on audiometry only	tinnitus or hearing loss, not requiring hearing aid or treatment	tinnitus or hearing loss, correctable with hearing aid or treatment	severe unilateral or bilateral hearing loss (deafness), not correctable
Middle ear/hearing	normal	serous otitis without subjective decrease in hearing	serous otitis or infection requiring medical intervention; subjective decrease in hearing; rupture of tympanic membrane with discharge	otitis with discharge, mastoiditis or conductive hearing loss	necrosis of the canal soft tissue or bone
Auditory/Hearing-Other (Specify, _____)	normal	mild	moderate	severe	life-threatening or disabling
BLOOD/BONE MARROW					
Bone marrow cellularity	normal for age	mildly hypocellular or 25% reduction from normal cellularity for age	moderately hypocellular or >25 - ≤ 50% reduction from normal cellularity for age or >2 but <4 weeks to recovery of normal bone marrow cellularity	severely hypocellular or >50 - ≤ 75% reduction in cellularity for age or 4 - 6 weeks to recovery of normal bone marrow cellularity	aplasia or >6 weeks to recovery of normal bone marrow cellularity
Normal ranges:					
children (≤ 18 years)	90% cellularity average				
younger adults (19-59)	60-70% cellularity average				
older adults (≥ 60 years)	50% cellularity average				
Note: Grade Bone marrow cellularity only for changes related to treatment not disease.					
CD4 count	WNL	< LLN - 500/mm^3	200 - < 500/mm^3	50 - < 200/mm^3	< 50/mm^3
Haptoglobin	normal	decreased	-	absent	-
Hemoglobin (Hgb)	WNL	< LLN - 10.0 g/dL < LLN - 100 g/L < LLN - 6.2 mmol/L	8.0 - < 10.0 g/dL 80 - < 100 g/L 4.9 - < 6.2 mmol/L	6.5 - < 8.0 g/dL 65 - 80 g/L 4.0 - < 4.9 mmol/L	< 6.5 g/dL < 65 g/L < 4.0 mmol/L
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies or bone marrow infiltrative/ myelophthisic processes	WNL	10 - <25% decrease from pretreatment	25 - <50% decrease from pretreatment	50 - <75% decrease from pretreatment	≥75% decrease from pretreatment

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis, other)	none	only laboratory evidence of hemolysis [e.g., direct antiglobulin test (DAT, Coombs') schistocytes]	evidence of red cell destruction and ≥ 2gm decrease in hemoglobin, no transfusion	requiring transfusion and/or medical intervention (e.g., steroids)	catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)
Also consider Haptoglobin, Hemoglobin.					
Leukocytes (total WBC)	WNL	< LLN - 3.0 x 10^9 /L < LLN - 3000/mm^3	≥2.0 - < 3.0 x 10^9 /L ≥2000 - < 3000/mm^3	≥1.0 - < 2.0 x 10^9 /L ≥1000 - < 2000/mm^3	< 1.0 x 10^9 /L < 1000/mm^3
For BMT studies:	WNL	≥2.0 - <3.0 X 10^9/L ≥2000 - <3000/mm^3	≥1.0 - <2.0 x 10^9 /L ≥1000 - <2000/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	<0.5 x 10^9 /L <500/mm^3
Note: The following criteria using age, race and sex normal values may be used for pediatric studies if the protocol so specifies.					
		≥75 - <100% LLN	*≥50 - <75% LLN*	*≥25 - 50% LLN*	*<25% LLN*
Lymphopenia	WNL	<LLN - 1.0 x 10^9 /L <LLN - 1000/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	<0.5 x 10^9 /L <500/mm^3	-
Note: The following criteria using age, race, and sex normal values may be used for pediatric studies if the protocol so specifies.					
		≥75-<100%LLN	*≥50-<75%LLN*	*≥25-<50%LLN*	*<25%LLN*
Neutrophils/granulocytes (ANC/AGC)	WNL	≥1.5 - <2.0 x 10^9 /L ≥1500 - <2000/mm^3	≥1.0 - <1.5 x 10^9 /L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	< 0.5 x 10^9 /L < 500/mm^3
For BMT:	WNL	≥1.0 - <1.5 x 10^9 /L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	≥0.1 - <0.5 x 10^9 /L ≥100 - <500/mm^3	<0.1 x 10^9 /L <100/mm^3
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies or bone marrow infiltrative/ myelophthisic process	WNL	10 - <25% decrease from baseline	25 - <50% decrease from baseline	50 - <75% decrease from baseline	≥75% decrease from baseline
Platelets	WNL	< LLN - <75.0 x 10^9 /L < LLN - 75000/mm^3	≥50.0 - < 75.0 x 10^9 /L ≥50000 - < 75000/mm^3	≥10.0 - < 50.0 x 10^9 /L ≥10000 - < 50000/mm^3	< 10.0 x 10^9 /L < 10000/mm^3
For BMT:	WNL	≥50.0 - <75.0 x 10^9 /L ≥50000 - <75000/mm^3	≥20.0 - <50.0 x 10^9 /L ≥20000 - <50000/mm^3	≥10.0 - <20.0 x 10^9 /L ≥10000 - <20000/mm^3	<10.0 x 10^9 /L <10000/mm^3
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies or bone marrow infiltrative/ myelophthisic process	WNL	10 - <25% decrease from baseline	25 - <50% decrease from baseline	50 - <75% decrease from baseline	≥75% decrease from baseline

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Transfusion: Platelets	none	-	-	yes	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)
For BMT:	none	1 platelet transfusion in 24 hours	2 platelet transfusions in 24 hours	≥3 platelet transfusions in 24 hours	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)
Also consider Platelets.					
Transfusion: pRBCs	none	-	-	Yes	-
For BMT:	none	≤2 u pRBC (≤*15mL/kg*) in 24 hours elective or planned	3 u pRBC (>*15* ≤*30mL/kg*) in 24 hours elective or planned	≥4 u pRBC (>*30mL/kg*) in 24 hours	hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin
Also consider Hemoglobin.					
Blood/Bone Marrow-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
CARDIOVASCULAR (ARRHYTHMIA)					
Conduction abnormality/ Atrioventricular heart block	none	asymptomatic, not requiring treatment (e.g., Mobitz type I second-degree AV block, Wenckebach)	symptomatic, but not requiring treatment	symptomatic and requiring treatment (e.g., Mobitz type II second-degree AV block, third-degree AV block)	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Nodal/junctional arrhythmia/dysrhythmia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Palpitations	none	present	-	-	-

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Note: Grade palpitations only in the absence of a documented arrhythmia.					
Prolonged QTc interval (QTc > 0.48 seconds)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus bradycardia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus tachycardia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment of underlying cause	-
Supraventricular arrhythmias (SVT/atrial fibrillation/ flutter)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Syncope (fainting) is graded in the NEUROLOGY category.					
Vasovagal episode	none	-	present without loss of consciousness	present with loss of consciousness	-
Ventricular arrhythmia (PVCs/bigeminy/trigeminy/ ventricular tachycardia)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Cardiovascular/ Arrhythmia-Other (Specify, _____)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic, and requiring treatment of underlying cause	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
CARDIOVASCULAR (GENERAL)					
Acute vascular leak syndrome	absent	-	symptomatic, but not requiring fluid support	respiratory compromise or requiring fluids	life-threatening; requiring pressor support and/or ventilatory support
Cardiac-ischemia/infarction	none	non-specific T-wave flattening or changes	asymptomatic, ST- and T- wave changes suggesting ischemia	angina without evidence of infarction	acute myocardial infarction
Cardiac left ventricular function	normal	asymptomatic decline of resting ejection fraction of ≥ 10% but < 20% of baseline value; shortening fraction ≥ 24% but < 30%	asymptomatic but resting ejection fraction below LLN for laboratory or decline of resting ejection fraction ≥ 20% of baseline value; < 24% shortening fraction	CHF responsive to treatment	severe or refractory CHF or requiring intubation

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
CNS cerebrovascular ischemia is graded in the NEUROLOGY category.					
Cardiac troponin I (cTnI)	normal	-	-	levels consistent with unstable angina as defined by the manufacturer	levels consistent with myocardial infarction as defined by the manufacturer
Cardiac troponin T (cTnT)	normal	≥ 0.03 - < 0.05 ng/mL	≥ 0.05 - < 0.1 ng/mL	≥ 0.1 - < 0.2 ng/mL	≥ 0.2 ng/mL
Edema	none	asymptomatic, not requiring therapy	symptomatic, requiring therapy	symptomatic edema limiting function and unresponsive to therapy or requiring drug discontinuation	anasarca (severe generalized edema)
Hypertension	none	asymptomatic, transient increase by >20 mmHg (diastolic) or to > 150/100* if previously WNL; not requiring treatment	recurrent or persistent or symptomatic increase by > 20 mmHg (diastolic) or to > 150/100* if previously WNL; not requiring treatment	requiring therapy or more intensive therapy than previously	hypertensive crisis
**Note: For pediatric patients, use age and sex appropriate normal values > 95th percentile ULN.*					
Hypotension	none	changes, but not requiring therapy (including transient orthostatic hypotension)	requiring brief fluid replacement or other therapy but not hospitalization; no physiologic consequences	requiring therapy and sustained medical attention, but resolves without persisting physiologic consequences	shock (associated with acidemia and impairing vital organ function due to tissue hypoperfusion)
Also consider Syncope (fainting).					
Note: Angina or MI is graded as Cardiac- ischemia/infarction in the CARDIOVASCULAR (GENERAL) category.					
For pediatric patients, systolic BP 65 mmHg or less in infants up to 1 year old and 70 mmHg or less in children older than 1 year of age, use two successive or three measurements in 24 hours.					
Myocarditis	none	-	-	CHF responsive to treatment	severe or refractory CHF
Operative injury of vein/artery	none	primary suture repair for injury, but not requiring transfusion	primary suture repair for injury, requiring transfusion	vascular occlusion requiring surgery or bypass for injury	myocardial infarction; resection of organ (e.g., bowel, limb)
Pericardial effusion/ pericarditis	none	asymptomatic effusion, not requiring treatment	pericarditis (rub, ECG changes, and/or chest pain)	With physiologic consequences	tamponade (drainage or pericardial window required)
Peripheral arterial ischemia	none	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., amputation)
Phlebitis (superficial)	none	-	present	-	-
Note: Injection site reaction is graded in the DERMATOLOGY/SKIN category.					

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					
Syncope (fainting) is graded in the NEUROLOGY category.					
Thrombosis/embolism	none	-	deep vein thrombosis, not requiring anticoagulant	deep vein thrombosis, requiring anticoagulant therapy	embolic event including pulmonary embolism
Vein/artery operative injury is graded as Operative injury of vein/artery in the CARDIOVASCULAR (GENERAL) category.					
Visceral arterial ischemia (non-myocardial)	none	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., resection of ileum)
Cardiovascular/ General-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
COAGULATION					
Note: See the HEMORRHAGE category for grading the severity of bleeding events.					
DIC (disseminated intravascular coagulation)	absent	-	-	laboratory findings present with no bleeding	laboratory findings and bleeding
Also grade Platelets.					
Note: Must have increased fibrin split products or D-dimer in order to grade as DIC.					
Fibrinogen	WNL	≥0.75 - <1.0 x LLN	≥0.5 - <0.75 x LLN	≥0.25 - <0.5 x LLN	<0.25 x LLN
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies:	WNL	<20% decrease from pretreatment value or LLN	≥20 - <40% decrease from pretreatment value or LLN	≥40 - <70% decrease from pretreatment value or LLN	<50 mg%
Partial thromboplastin time (PTT)	WNL	> ULN - ≤ 1.5 x ULN	> 1.5 - ≤ 2 x ULN	>2 x ULN	-
Phelbitis is graded in the CARDIOVASCULAR (GENERAL) category.					
Prothrombin time (PT)	WNL	> ULN - ≤ 1.5 x ULN	> 1.5 - ≤ 2 x ULN	>2 x ULN	-
Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTP or hemolytic uremic syndrome/HUS)	absent	-	-	laboratory findings present without clinical consequences	laboratory findings and clinical consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure) requiring therapeutic intervention

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
For BMT:	-	evidence of RBC destruction (schistocytosis) without clinical consequences	evidence of RBC destruction with elevated creatinine (≤3 x ULN)	evidence of RBC destruction with creatinine (>3 x ULN) not requiring dialysis	evidence of RBC destruction with renal failure requiring dialysis and/or encephalopathy
Also consider Hemoglobin (Hgb), Platelets, Creatinine.					
Note: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments).					
Coagulation-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
CONSTITUTIONAL SYMPTOMS					
Fatigue (lethargy, malaise, asthenia)	none	increased fatigue over baseline, but not altering normal activities	moderate (e.g., decrease in performance status by 1 ECOG level or 20% Karnofsky or *Lansky*) or causing difficulty performing some activities	severe (e.g., decrease in performance status by ≥2 ECOG levels or 40% Karnofsky or *Lansky*) or loss of ability to perform some activities	bedridden or disabling
Note: See Appendix III for performance status scales.					
Fever (in the absence of neutropenia, where neutropenia is defined as AGC < 1.0 x 10^9/L)	none	38.0 - 39.0°C (100.4 - 102.2°F)	39.1 - 40.0°C (102.3 - 104.0°F)	> 40.0°C (>104.0°F) for < 24hrs	> 40.0°C (>104.0°F) for > 24hrs
Also consider Allergic reaction/hypersensitivity.					
Note: The temperature measurements listed above are oral or tympanic.					
Hot flashes/flushes are graded in the ENDOCRINE category.					
Rigors, chills	none	mild, requiring symptomatic treatment (e.g., blanket) or non-narcotic medication	severe and/or prolonged, requiring narcotic medication	not responsive to narcotic medication	-
Sweating (diaphoresis)	normal	mild and occasional	frequent or drenching	-	-
Weight gain	< 5%	5 - <10%	10 - <20%	≥ 20%	-
Also consider Ascites, Edema, Pleural effusion.					
Weight gain - veno-occlusive disease (VOD)					
Note: The following criteria is to be used ONLY for weight gain associated with Veno-Occlusive Disease.					
	<2%	≥2 - <5%	≥5 - <10%	≥10% or as ascities	≥10% or fluid retention resulting in pulmonary failure
Weight loss	< 5%	5 - <10%	10 - <20%	≥20%	-
Also consider Vomiting, Dehydration, Diarrhea.					
Constitutional Symptoms-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
DERMATOLOGY/SKIN					
Alopecia	normal	mild hair loss	pronounced hair loss	-	-

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Bruising (in absence of grade 3 or 4 thrombocytopenia)	none	localized or in dependent area	generalized	-	-
Note: Bruising resulting from grade 3 or 4 thrombocytopenia is graded as Petechiae/purpura and Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia in the HEMORRHAGE category, not in the DERMATOLOGY/SKIN category.					
Dermatitis, focal (associated with high-dose chemotherapy and bone marrow transplant)	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include spontaneous bleeding not induced by minor trauma or abrasion
Dry skin	normal	controlled with emollients	not controlled with emollients	-	-
Erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	absent	-	scattered, but not generalized eruption	severe or requiring IV fluids (e.g., generalized rash or painful stomatitis)	life-threatening (e.g., exfoliative or ulcerating dermatitis or requiring enteral or parenteral nutritional support)
Flushing	absent	present	-	-	-
Hand-foot skin reaction	none	skin changes or dermatitis without pain (e.g., erythema, peeling)	skin changes with pain, not interfering with function	skin changes with pain, interfering with function	-
Injection site reaction	none	pain or itching or erythema	pain or swelling, with inflammation or phlebitis	ulceration or necrosis that is severe or prolonged, or requiring surgery	-
Nail changes	normal	discoloration or ridging (koilonychia) or pitting	partial or complete loss of nail(s) or pain in nailbeds	-	-
Petechiae is graded in the HEMORRHAGE category.					
Photosensitivity	none	painless erythema	painful erythema	erythema with desquamation	-
Pigmentation changes (e.g., vitiligo)	none	localized pigmentation changes	generalized pigmentation changes	-	-
Pruritus	none	mild or localized, relieved spontaneously or by local measures	intense or widespread, relieved spontaneously or by systemic measures	intense or widespread and poorly controlled despite treatment	-
Purpura is graded in the HEMORRHAGE category.					

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Radiation dermatitis	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion
Note: Pain associated with radiation dermatitis is graded separately in the PAIN category as Pain due to radiation.					
Radiation recall reaction (reaction following chemotherapy in the absence of additional radiation therapy that occurs in a previous radiation port)	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion
Rash/desquamation	none	macular or papular eruption or erythema without associated symptoms	macular or papular eruption or erythema with pruritus or other associated symptoms covering <50% of body surface or localized desquamation or other lesions covering <50% of body surface area	symptomatic generalized erythroderma or macular, papular or vesicular eruption or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis
For BMT:	none	macular or papular eruption or erythema covering <25% of body surface area without associated symptoms	macular or papular eruption or erythema with pruritis or other associated symptoms covering ≥25 - <50% of body surface or localized desquamation or other lesions covering ≥25 - <50% of body surface area	symptomatic generalized erythroderma or symptomatic macular, papular or vesicular eruption, with bullous formation, or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis or bullous formation
Also consider Allergic reaction/hypersensitivity.					
Note: Erythema multiforme (Stevens-Johnson syndrome) is graded separately as Erythema multiforme.					
Urticaria (hives, welts, wheals)	none	requiring no medication	requiring PO or topical treatment or IV medication or steroids for <24 hours	requiring IV medication or steroids for ≥24 hours	-
Wound- infectious	none	cellulitis	superficial infection	infection requiring IV antibiotics	necrotizing fascitis

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Wound- non-infectious	none	incisional separation	incisional hernia	fascial disruption without evisceration	fascial disruption with evisceration
Dermatology/Skin-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
ENDOCRINE					
Cushingoid appearance (e.g., moon face with or without buffalo hump, centripetal obesity, cutaneous striae)	absent	-	present	-	-
Also consider Hyperglycemia, Hypokalemia.					
Feminization of male	absent	-	-	present	-
Gynecomastia	none	mild	pronounced or painful	pronounced or painful and requiring surgery	-
Hot flashes/flushes	none	mild or no more than 1 per day	moderate and greater than 1 per day	-	-
Hypothyroidism	absent	asymptomatic,TSH elevated, no therapy given	symptomatic or thyroid replacement treatment given	patient hospitalized for manifestations of hypothyroidism	myxedema coma
Masculinization of female	absent	-	-	present	-
SIADH (syndrome of inappropriate antidiuretic hormone)	absent	-	-	present	-
Endocrine-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
GASTROINTESTINAL					
Amylase is graded in the METABOLIC/LABORATORY category.					
Anorexia	none	loss of appetite	oral intake significantly decreased	requiring IV fluids	requiring feeding tube or parenteral nutrition
Ascites (non-malignant)	none	asymptomatic	symptomatic, requiring diuretics	symptomatic, requiring therapeutic paracentesis	life-threatening physiologic consequences
Colitis	none	-	abdominal pain with mucus and/or blood in stool	abdominal pain, fever, change in bowel habits with ileus or peritoneal signs, and radiographic or biopsy documentation	perforation or requiring surgery or toxic megacolon
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Melena/GI bleeding, Rectal bleeding/hematochezia, Hypotension.					

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Constipation	none	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Dehydration	none	dry mucous membranes and/or diminished skin turgor	requiring IV fluid replacement (brief)	requiring IV fluid replacement (sustained)	physiologic consequences requiring intensive care; hemodynamic collapse
Also consider Hypotension, Diarrhea, Vomiting, Stomatitis/pharyngitis (oral/pharyngeal mucositis).					
Diarrhea Patients without colostomy:	none	increase of < 4 stools/day over pre-treatment	increase of 4-6 stools/day, or nocturnal stools	increase of ≥7 stools/day or incontinence; or need for parenteral support for dehydration	physiologic consequences requiring intensive care; or hemodynamic collapse
Patients with a colostomy:	none	mild increase in loose, watery colostomy output compared with pretreatment	moderate increase in loose, watery colostomy output compared with pretreatment, but not interfering with normal activity	severe increase in loose, watery colostomy output compared with pretreatment, interfering with normal activity	physiologic consequences, requiring intensive care; or hemodynamic collapse
For BMT	none	>500 - ≤1000mL of diarrhea/day	>1000 - ≤1500mL of diarrhea/day	>1500mL of diarrhea/day	severe abdominal pain with or without ileus
For Pediatric BMT:		*>5 - ≤10 mL/kg of diarrhea/day*	*>10 - ≤15 mL/kg of diarrhea/day*	*>15 mL/kg of diarrhea/day*	-
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Pain, Dehydration, Hypotension.					
Duodenal ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	uncontrolled by outpatient medical management; requiring hospitalization	perforation or bleeding, requiring emergency surgery
Dyspepsia/heartburn	none	mild	moderate	severe	-
Dysphagia, esophagitis, odynophagia (painful swallowing)	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring IV hydration	complete obstruction (cannot swallow saliva) requiring enteral or parenteral nutritional support, or perforation
Note: If adverse event is radiation-related, grade <u>either</u> under Dysphagia- esophageal related to radiation <u>or</u> Dysphagia- pharyngeal related to radiation.					
Dysphagia- <u>esophageal</u> related to radiation	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft or liquid diet	dysphagia requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Also consider Pain due to radiation, Mucositis due to radiation.					
Note: Fistula is graded separately as Fistula- esophageal.					
Dysphagia - pharyngeal related to radiation	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation
Also consider Pain due to radiation, Mucositis due to radiation.					
Note: Fistula is graded separately as Fistula- pharyngeal.					
Fistula- esophageal	none	-	-	present	requiring surgery
Fistula- intestinal	none	-	-	present	requiring surgery
Fistula- pharyngeal	none	-	-	present	requiring surgery
Fistula- rectal/anal	none	-	-	present	requiring surgery
Flatulence	none	mild	moderate	-	-
Gastric ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	bleeding without perforation, uncontrolled by outpatient medical management; requiring hospitalization or surgery	perforation or bleeding, requiring emergency surgery
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					
Gastritis	none	-	requiring medical management or non-surgical treatment	uncontrolled by out-patient medical management; requiring hospitalization or surgery	life-threatening bleeding, requiring emergency surgery
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					
Hematemesis is graded in the HEMORRHAGE category.					
Hematochezia is graded in the HEMORRHAGE category as Rectal bleeding/hematochezia.					
Ileus (or neuroconstipation)	none	-	intermittent, not requiring intervention	requiring non-surgical intervention	requiring surgery
Mouth dryness	normal	mild	moderate	-	-
Mucositis					
Note: Mucositis not due to radiation is graded in the GASTROINTESTINAL category for specific sites: Colitis, Esophagitis, Gastritis, Stomatitis/pharyngitis (oral/pharyngeal mucositis), and Typhlitis; or the RENAL/GENITOURINARY category for Vaginititis.					
Radiation-related mucositis is graded as Mucositis due to radiation.					
Mucositis due to radiation	none	erythema of the mucosa	patchy pseudomembranous reaction (patches generally ≤ 1.5 cm in diameter and non-contiguous)	confluent pseudomembranous reaction (contiguous patches generally > 1.5 cm in diameter)	necrosis or deep ulceration; may include bleeding not induced by minor trauma or abrasion
Also consider Pain due to radiation.					

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Note: Grade radiation mucositis of the larynx here.					
Dysphagia related to radiation is also graded as <u>either</u> Dysphagia- esophageal related to radiation <u>or</u> Dysphagia- pharyngeal related to radiation, depending on the site of treatment.					
Nausea	none	able to eat	oral intake significantly decreased	no significant intake, requiring IV fluids	-
Pancreatitis	none	-	-	abdominal pain with pancreatic enzyme elevation	complicated by shock (acute circulatory failure)
Also consider Hypotension.					
Note: Amylase are graded in the METABOLIC/LABORATORY category.					
Pharyngitis is graded in the GASTROINTESTINAL category as Stomatitis/pharyngitis (oral/pharyngeal mucositis).					
Proctitis	none	increased stool frequency, occasional blood-streaked stools, or rectal discomfort (including hemorrhoids), not requiring medication	increased stool frequency, bleeding, mucus discharge, or rectal discomfort requiring medication; anal fissure	increased stool frequency/diarrhea, requiring parenteral support; rectal bleeding, requiring transfusion; or persistent mucus discharge, necessitating pads	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, and Pain due to radiation.					
Note: Fistula is graded separately as Fistula- rectal/anal.					
Proctitis occurring more than 90 days after the start of radiation therapy is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme. (See Appendix IV)					
Salivary gland changes	none	slightly thickened saliva/may have slightly altered taste (e.g., metallic); additional fluids may be required	thick, ropy, sticky saliva; markedly altered taste; alteration in diet required	-	acute salivary gland necrosis
Sense of smell	normal	slightly altered	markedly altered	-	-
Stomatitis/pharyngitis (oral/pharyngeal mucositis)	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema, or ulcers, but can eat or swallow	painful erythema, edema, or ulcers requiring IV hydration	severe ulceration or requires parenteral or enteral nutritional support or prophylatic intubation
For BMT:	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema or ulcers but can swallow	painful erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral (or enteral) nutritional support	severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia
Note: Radiation-related mucositis is graded as Mucositis due to radiation.					
Taste disturbance (dysgeusia)	normal	slightly altered	markedly altered	-	-

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Typhlitis (inflammation of the cecum)	none	-	-	abdominal pain, diarrhea, fever, and radiographic or biopsy documentation	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Hypotension, Febrile/neutropenia.					
Vomiting	none	1 episode in 24 hours over pretreatment	2-5 episodes in 24 hours over pretreatment	≥6 episodes in 24 hours over pretreatment; or need for IV fluids	Requiring parenteral nutrition; or physiologic consequences requiring intensive care; hemodynamic collapse
Also consider Dehydration.					
Weight gain is graded in the CONSTITUTIONAL SYMPTOMS category.					
Weight loss is graded in the CONSTITUTIONAL SYMPTOMS category.					
Gastrointestinal-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
HEMORRHAGE					
Note: Transfusion in this section refers to pRBC infusion. For <u>any</u> bleeding with grade 3 or 4 platelets (< 50,000), <u>always</u> grade Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia. Also consider platelets, transfusion: pRBCS, and Transfusion: platelets in addition to grading severity by grading the site or type of bleeding. If the site or type of Hemorrhage/bleeding is listed, also use the grading that incorporates the site of bleeding: CNS Hemorrhage/bleeding, Hematuria, Hematemesis, Hemoptysis, Hemorrhage/bleeding with surgery, Melena/lower GI bleeding, Petechiae/purpura (Hemorrhage/bleeding into skin), Rectal bleeding/hematochezia, Vaginal bleeding. If the platelet count is ≥50,000 and the site or type of bleeding is listed, grade the specific site. If the site or type is <u>not</u> listed and the platelet count is ≥50,000, grade Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia and specify the site or type in the OTHER category.					
Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia	none	mild without transfusion		requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Also consider Platelets, Hemoglobin, Transfusion: platelets, Transfusion: pRBCs, site or type of bleeding. If the site is not listed, grade as Hemorrhage-Other (Specify site, _____).					
Note: This adverse event must be graded for any bleeding with grade 3 or 4 thrombocytopenia.					
Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia	none	mild without transfusion		requiring transfusion	catastrophic bleeding requiring major non-elective intervention
Also consider Platelets, Hemoglobin, Transfusion: platelets, Transfusion:pRBCs, Hemorrhage – Other (Specify site, _____).					
Note: Bleeding in the absence of grade 3 or 4 thrombocytopenia is graded here only if the specific site or type of bleeding is not listed elsewhere in the HEMORRHAGE category. Also grade as Other in the HEMORRHAGE category.					

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
CNS hemorrhage/bleeding	none	-	-	bleeding noted on CT or other scan with no clinical consequences	hemorrhagic stroke or hemorrhagic vascular event (CVA) with neurologic signs and symptoms
Epistaxis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematemesis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematuria (in the absence of vaginal bleeding)	none	microscopic only	intermittent gross bleeding, no clots	persistent gross bleeding or clots; may require catheterization or instrumentation, or transfusion	open surgery or necrosis or deep bladder ulceration
Hemoptysis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hemorrhage/bleeding associated with surgery	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Note: Expected blood loss at the time of surgery is not graded as a toxicity.					
Melena/GI bleeding	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	none	rare petechiae of skin	petechiae or purpura in dependent areas of skin	generalized petechiae or purpura of skin or petechiae of any mucosal site	-

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Rectal bleeding/ hematochezia	none	mild without transfusion or medication	persistent, requiring medication (e.g., steroid suppositories) and/or break from radiation treatment	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Vaginal bleeding	none	spotting, requiring < 2 pads per day	requiring ≥ 2 pads per day, but not requiring transfusion	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hemorrhage-Other (Specify site, _____)	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
HEPATIC					
Alkaline phosphatase	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Bilirubin	WNL	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
Bilirubin- graft versus host disease (GVHD)					
Note: The following criteria are used only for bilirubin associated with graft versus host disease.					
	normal	≥2 - <3 mg/100 ml	≥3 - <6 mg/100 ml	≥6 - <15 mg/100 ml	≥15 mg/100 ml
GGT (γ - Glutamyl transpeptidase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Hepatic enlargement	absent	-	-	present	-
Note: Grade Hepatic enlargement only for treatment related adverse event including Veno-Occlusive Disease					
Hypoalbuminemia	WNL	<LLN - 3 g/dl	≥2 - <3 g/dl	<2 g/dl	-
Liver dysfunction/failure (clinical)	normal	-	-	asterixis	encephalopathy or coma
Portal vein flow	normal	-	decreased portal vein flow	reversal/retrograde portal vein flow	-
SGOT (AST) (serum glutamic oxaloacetic transaminase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
SGPT (ALT) (serum glutamic pyruvic transaminase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Hepatic-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
INFECTION/FEBRILE NEUTROPENIA					
Catheter-related infection	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment or hospitalization	life-threatening sepsis (e.g., septic shock)

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection)	none	-	-	Present	Life-threatening sepsis (e.g., septic shock)
(ANC < 1.0 x 10^9/L, fever ≥38.5°C)					
Also consider Neutrophils Note: Hypothermia instead of fever may be associated with neutropenia and is graded here.					
Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia	none	-	-	present	life-threatening sepsis (e.g., septic shock)
(ANC < 1.0 x 10^9/L)					
Note: Hypothermia instead of fever may be associated with neutropenia and is graded here. In the absence of documented infection with grade 3 or 4 neutropenia with fever is graded as Febrile neutropenia.					
Infection with unknown ANC	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Note: This adverse event criterion is used in the rare case when ANC is unknown.					
Infection without neutropenia Also consider Neutrophils	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment, or hospitalization	life-threatening sepsis (e.g., septic shock)
Infection/Febrile Neutropenia-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
Wound-infectious is graded in the DERMATOLOGY/SKIN category.					
LYMPHATICS					
Lymphatics	normal	mild lymphedema	moderate lymphedema requiring compression; lymphocyst	severe lymphedema limiting function; lymphocyst requiring surgery	severe lymphedema limiting function with ulceration
Lymphatics-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
METABOLIC/LABORATORY					
Acidosis (metabolic or respiratory)	normal	pH < normal, but ≥7.3	-	pH < 7.3	pH < 7.3 with life-threatening physiologic consequences
Alkalosis (metabolic or respiratory)	normal	pH > normal, but ≤7.5	-	pH > 7.5	pH > 7.5 with life-threatening physiologic consequences
Amylase Bicarbonate	WNL WNL	> ULN - 1.5 x ULN < LLN - 16 mEq/dl	> 1.5 - 2.0 x ULN 11 - 15 mEq/dl	> 2.0 - 5.0 x ULN 8 - 10 mEq/dl	>5.0 x ULN < 8 mEq/dl

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
CPK (creatine phosphokinase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5 x ULN	> 5 - 10 x ULN	> 10 x ULN
Hypercalcemia	WNL	> ULN - 11.5 mg/dl > ULN - 2.9 mmol/L	>11.5 - 12.5 mg/dl > 2.9 - 3.1 mmol/L	>12.5 - 13.5 mg/dl > 3.1 - 3.4 mmol/L	> 13.5 mg/dl > 3.4 mmol/L
Hypercholesterolemia	WNL	> ULN - 300 mg/dl > ULN - 7.75 mmol/L	> 300 - 400 mg/dl > 7.75 - 10.34 mmol/L	> 400 - 500 mg/dl >10.34 - 12.92 mmol/L	> 500 mg/dl > 12.92 mmol/L
Hyperglycemia	WNL	> ULN - 160 mg/dl > ULN - 8.9 mmol/L	> 160 - 250 mg/dl > 8.9 - 13.9 mmol/L	> 250 - 500 mg/dl > 13.9 - 27.8 mmol/L	> 500 mg/dl > 27.8 mmol/L or ketoacidosis
Hyperkalemia	WNL	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Hypermagnesemia	WNL	> ULN - 3.0 mg/dl > ULN - 1.23 mmol/L	-	> 3.0 - 8.0 mg/dl > 1.23 - 3.30 mmol/L	> 8.0 mg/dl > 3.30 mmol/L
Hypernatremia	WNL	> ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Hypertriglyceridemia	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10 x ULN	> 10 x ULN
Hyperuricemia	WNL	> ULN - ≤ 10 mg/dl ≤ 0.59 mmol/L without physiologic consequences	-	> ULN - ≤ 10 mg/dl ≤ 0.59 mmol/L with physiologic consequences	> 10 mg/dl > 0.59 mmol/L
Also consider Tumor lysis syndrome, Renal failure, Creatinine,Hyperkalemia.					
Hypocalcemia	WNL	<LLN - 8.0 mg/dl <LLN - 2.0 mmol/L	7.0 - < 8.0 mg/dl 1.75 - < 2.0 mmol/L	6.0 - < 7.0 mg/dl 1.5 - < 1.75 mmol/L	<6.0 mg/dl < 1.5 mmol/L
Hypoglycemia	WNL	<LLN - 55 mg/dl <LLN - 3.0 mmol/L	40 - < 55 mg/dl 2.2 - < 3.0 mmol/L	30 - < 40 mg/dl 1.7 - < 2.2 mmol/L	< 30 mg/dl < 1.7 mmol/L
Hypokalemia	WNL	<LLN - 3.0 mmol/L	-	2.5 - <3.0 mmol/L	<2.5 mmol/L
Hypomagnesemia	WNL	<LLN - 1.2 mg/dl <LLN - 0.5 mmol/L	0.9 - <1.2 mg/dl 0.4 - < 0.5 mmol/L	0.7 - < 0.9 mg/dl 0.3 - < 0.4 mmol/L	< 0.7 mg/dl < 0.3 mmol/L
Hyponatremia	WNL	<LLN - 130 mmol/L	-	120 - <130 mmol/L	<120 mmol/L
Hypophosphatemia	WNL	<LLN -2.5 mg/dl <LLN - 0.8 mmol/L	≥2.0 - <2.5 mg/dl ≥0.6 - <0.8 mmol/L	≥1.0 - <2.0 mg/dl ≥0.3 - <0.6 mmol/L	< 1.0 mg/dl <0.3 mmol/L
Hypothyroidism is graded in the ENDOCRINE category.					
Lipase	WNL	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Metabolic/Laboratory-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
MUSCULOSKELETAL					
Arthralgia is graded in the PAIN category.					
Arthritis	none	mild pain with inflammation, erythema or joint swelling but not interfering with function	moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with activities of daily living	severe pain with inflammation, erythema, or joint swelling and interfering with activities of daily living	disabling

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Muscle weakness (not due to neuropathy)	normal	asymptomatic with weakness on physical exam	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	bedridden or disabling
Myalgia [tenderness or pain in muscles] is graded in the PAIN category.					
Myositis (inflammation/damage of muscle)	none	mild pain, not interfering with function	pain interfering with function, but not interfering with activities of daily living	pain interfering with function and interfering with activities of daily living	bedridden or disabling
Also consider CPK.					
Note: Myositis implies muscle damage (i.e., elevated CPK).					
Osteonecrosis (avascular necrosis)	none	asymptomatic and detected by imaging only	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	symptomatic; or disabling
Musculoskeletal-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
NEUROLOGY					
Aphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
Arachnoiditis/meningismus/ radiculitis	absent	mild pain not interfering with function	moderate pain interfering with function, but not interfering with activities of daily living	severe pain interfering with activities of daily living	unable to function or perform activities of daily living; bedridden; paraplegia
Also consider Headache, Vomiting, Fever.					
Ataxia (incoordination)	normal	asymptomatic but abnormal on physical exam, and not interfering with function	mild symptoms interfering with function, but not interfering with activities of daily living	moderate symptoms interfering with activities of daily living	bedridden or disabling
CNS cerebrovascular ischemia	none	-	-	transient ischemic event or attack (TIA)	permanent event (e.g., cerebral vascular accident)
CNS hemorrhage/bleeding is graded in the HEMORRHAGE category.					
Cognitive disturbance/ learning problems	*none*	*cognitive disability; not interfering with work/school performance; preservation of intelligence*	*cognitive disability; interfering with work/school performance; decline of 1 SD (Standard Deviation) or loss of developmental milestones*	*cognitive disability; resulting in significant impairment of work/school performance; cognitive decline > 2 SD*	*inability to work/frank mental retardation*

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Confusion	normal	confusion or disorientation or attention deficit of brief duration; resolves spontaneously with no sequelae	confusion or disorientation or attention deficit interfering with function, but not interfering with activities of daily living	confusion or delirium interfering with activities of daily living	harmful to others or self; requiring hospitalization
Cranial neuropathy is graded in the NEUROLOGY category as Neuropathy-cranial.					
Delusions	normal	-	-	present	toxic psychosis
Depressed level of consciousness	normal	somnolence or sedation not interfering with function	somnolence or sedation interfering with function, but not interfering with activities of daily living	obtundation or stupor; difficult to arouse; interfering with activities of daily living	coma
Note: Syncope (fainting) is graded in the NEUROLOGY category.					
Dizziness/lightheadedness	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling
Dysphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
Extrapyramidal/ involuntary movement/ restlessness	none	mild involuntary movements not interfering with function	moderate involuntary movements interfering with function, but not interfering with activities of daily living	severe involuntary movements or torticollis interfering with activities of daily living	bedridden or disabling
Hallucinations	normal	-	-	present	toxic psychosis
Headache is graded in the PAIN category.					
Insomnia	normal	occasional difficulty sleeping not interfering with function	difficulty sleeping interfering with function, but not interfering with activities of daily living	frequent difficulty sleeping, interfering with activities of daily living	-
Note: This toxicity is graded when insomnia is related to treatment. If pain or other symptoms interfere with sleep do NOT grade as insomnia.					
Irritability *(children <3 years of age)*	*normal*	*mild; easily consolable*	*moderate; requiring increased attention*	*severe; inconsolable*	-

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Leukoencephalopathy associated radiological findings	*none*	*mild increase in SAS (subarachnoid space) and/or mild ventriculomegaly; and/or small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or < 1/3 of susceptible areas of cerebrum*	*moderate increase in SAS; and/or moderate ventriculomegaly; and/or focal T2 hyperintensities extending into centrum ovale; or involving 1/3 to 2/3 of susceptible areas of cerebrum*	*severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT); focal white matter necrosis (cystic)*	*severe increase in SAS; severe ventriculomegaly; diffuse low attenuation with calcification (CT); diffuse white matter necrosis (MRI)*
Memory loss	normal	memory loss not interfering with function	memory loss interfering with function, but not interfering with activities of daily living	memory loss interfering with activities of daily living	amnesia
Mood alteration-anxiety agitation	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Mood alteration-depression	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Mood alteration-euphoria	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	danger to self
Neuropathic pain is graded in the PAIN category.					
Neuropathy- cranial	absent	-	present, not interfering with activities of daily living	present, interfering with activities of daily living	life-threatening, disabling
Neuropathy- motor	normal	subjective weakness but no objective findings	mild objective weakness interfering with function, but not interfering with activities of daily living	objective weakness interfering with activities of daily living	paralysis

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Neuropathy-sensory	normal	loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	objective sensory loss or paresthesia (including tingling), interfering with function, but not interfering with activities of daily living	sensory loss or paresthesia interfering with activities of daily living	permanent sensory loss that interferes with function
Nystagmus	absent	present	-	-	-
Also consider Vision-double vision.					
Personality/behavioral	normal	change, but not disruptive to patient or family	disruptive to patient or family	disruptive to patient and family; requiring mental health intervention	harmful to others or self; requiring hospitalization
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	normal	asymptomatic with abnormality on physical examination	symptomatic or interfering with function but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling; paralysis
Seizure(s)	none	-	seizure(s) self-limited and consciousness is preserved	seizure(s) in which consciousness is altered	seizures of any type which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)
Speech impairment (e.g., dysphasia or aphasia)	normal	-	awareness of receptive or expressive dysphasia, not impairing ability to communicate	receptive or expressive dysphasia, impairing ability to communicate	inability to communicate
Syncope (fainting)	absent	-	-	present	-
Also consider CARDIOVASCULAR (ARRHYTHMIA), Vasovagal episode, CNS cerebrovascular ischemia.					
Tremor	none	mild and brief or intermittent but not interfering with function	moderate tremor interfering with function, but not interfering with activities of daily living	severe tremor interfering with activities of daily living	-
Vertigo	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling
Neurology-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
OCULAR/VISUAL					

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Cataract	none	asymptomatic	symptomatic, partial visual loss	symptomatic, visual loss requiring treatment or interfering with function	-
Conjunctivitis	none	abnormal ophthalmologic changes, but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Dry eye	normal	mild, not requiring treatment	moderate or requiring artificial tears	-	-
Glaucoma	none	increase in intraocular pressure but no visual loss	increase in intraocular pressure with retinal changes	visual impairment	unilateral or bilateral loss of vision (blindness)
Keratitis (corneal inflammation/ corneal ulceration)	none	abnormal ophthalmologic changes but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	unilateral or bilateral loss of vision (blindness)
Tearing (watery eyes)	none	mild: not interfering with function	moderate: interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	-
Vision- blurred vision	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- double vision (diplopia)	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- flashing lights/floaters	normal	mild, not interfering with function	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Vision- night blindness (nyctalopia)	normal	abnormal electro-retinography but asymptomatic	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- photophobia	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Ocular/Visual-Other (Specify, _____)	normal	mild	moderate	severe	unilateral or bilateral loss of vision (blindness)
PAIN					
Abdominal pain or cramping	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Arthralgia (joint pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Arthritis (joint pain with clinical signs of inflammation) is graded in the MUSCULOSKELETAL category.					
Bone pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Chest pain (non-cardiac and non-pleuritic)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Dysmenorrhea	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Dyspareunia	none	mild pain not interfering with function	moderate pain interfering with sexual activity	severe pain preventing sexual activity	-
Dysuria is graded in the RENAL/GENITOURINARY category.					
Earache (otalgia)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Headache	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Hepatic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Myalgia (muscle pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pain due to radiation	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pelvic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Pleuritic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Rectal or perirectal pain (proctalgia)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor pain (onset or exacerbation of tumor pain due to treatment)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor flair is graded in the SYNDROME category.					
Pain-Other (Specify, _____)	none	mild	moderate	severe	disabling
PULMONARY					
Adult Respiratory Distress Syndrome (ARDS)	absent	-	-	-	present
Apnea	none	-	-	present	requiring intubation
Carbon monoxide diffusion capacity (DL_{CO})	≥ 90% of pretreatment or normal value	≥75 - <90% of pretreatment or normal value	≥50 - <75% of pretreatment or normal value	≥25 - <50% of pretreatment or normal value	< 25% of pretreatment or normal value
Cough	absent	mild, relieved by non-prescription medication	requiring narcotic antitussive	severe cough or coughing spasms, poorly controlled or unresponsive to treatment	-
Dyspnea (shortness of breath)	normal	-	dyspnea on exertion	dyspnea at normal level of activity	dyspnea at rest or requiring ventilator support
FEV_1	≥ 90% of pretreatment or normal value	≥75 - <90% of pretreatment or normal value	≥50 - <75% of pretreatment or normal value	≥25 - <50% of pretreatment or normal value	< 25% of pretreatment or normal value
Hiccoughs (hiccups, singultus)	none	mild, not requiring treatment	moderate, requiring treatment	severe, prolonged, and refractory to treatment	-
Hypoxia	normal	-	decreased O_2 saturation with exercise	decreased O_2 saturation at rest, requiring supplemental oxygen	decreased O_2 saturation, requiring pressure support (CPAP) or assisted ventilation

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Pleural effusion (non-malignant)	none	asymptomatic and not requiring treatment	symptomatic, requiring diuretics	symptomatic, requiring O_2 or therapeutic thoracentesis	life-threatening (e.g., requiring intubation)
Pleuritic pain is graded in the PAIN category.					
Pneumonitis/pulmonary infiltrates	none	radiographic changes but asymptomatic or symptoms not requiring steroids	radiographic changes and requiring steroids or diuretics	radiographic changes and requiring oxygen	radiographic changes and requiring assisted ventilation
Pneumothorax	none	no intervention required	chest tube required	sclerosis or surgery required	life-threatening
Pulmonary embolism is graded as Thrombosis/embolism in the CARDIOVASCULAR (GENERAL) category.					
Pulmonary fibrosis	none	radiographic changes, but asymptomatic or symptoms not requiring steroids	requiring steroids or diuretics	requiring oxygen	requiring assisted ventilation
Note: Radiation-related pulmonary fibrosis is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme- Lung. (See Appendix IV)					
Voice changes/stridor/larynx (e.g., hoarseness, loss of voice, laryngitis)	normal	mild or intermittent hoarseness	persistent hoarseness, but able to vocalize; may have mild to moderate edema	whispered speech, not able to vocalize; may have marked edema	marked dyspnea/stridor requiring tracheostomy or intubation
Note: Cough from radiation is graded as cough in the PULMONARY category.					
Radiation-related hemoptysis from larynx/pharynx is graded as Grade 4 Mucositis due to radiation in the GASTROINTESTINAL category. Radiation-related hemoptysis from the thoracic cavity is graded as Grade 4 Hemoptysis in the HEMORRHAGE category.					
Pulmonary-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
RENAL/GENITOURINARY					
Bladder spasms	absent	mild symptoms, not requiring intervention	symptoms requiring antispasmotic	severe symptoms requiring narcotic	-
Creatinine	WNL	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Note: Adjust to age-appropriate levels for pediatric patients.					
Dysuria (painful urination)	none	mild symptoms requiring no intervention	symptoms relieved with therapy	symptoms not relieved despite therapy	-
Fistula or GU fistula (e.g., vaginal, vesicovaginal)	none	-	-	requiring intervention	requiring surgery
Hemoglobinuria	-	present	-	-	-
Hematuria (in the absence of vaginal bleeding) is graded in the HEMORRHAGE category.					
Incontinence	none	with coughing, sneezing, etc.	spontaneous, some control	no control (in the absence of fistula)	-

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Operative injury to bladder and/or ureter	none	-	injury of bladder with primary repair	sepsis, fistula, or obstruction requiring secondary surgery; loss of one kidney; injury requiring anastomosis or re-implantation	septic obstruction of both kidneys or vesicovaginal fistula requiring diversion
Proteinuria	normal or < 0.15 g/24 hours	1+ or 0.15 - 1.0 g/24 hours	2+ to 3+ or 1.0 - 3.5 g/24 hours	4+ or > 3.5 g/24 hours	nephrotic syndrome
Note: If there is an inconsistency between absolute value and dip stick reading, use the absolute value for grading.					
Renal failure	none	-	-	requiring dialysis, but reversible	requiring dialysis and irreversible
Ureteral obstruction	none	unilateral, not requiring surgery	-	bilateral, not requiring surgery	stent, nephrostomy tube, or surgery
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	none	asymptomatic, not requiring treatment	mild, reversible and manageable with oral replacement	reversible but requiring IV replacement	irreversible, requiring continued replacement
Also consider Acidosis, Bicarbonate, Hypocalcemia, Hypophosphatemia.					
Urinary frequency/urgency	normal	increase in frequency or nocturia up to 2 x normal	increase > 2 x normal but < hourly	hourly or more with urgency, or requiring catheter	-
Urinary retention	normal	hesitancy or dribbling, but no significant residual urine; retention occurring during the immediate postoperative period	hesitancy requiring medication or occasional in/out catheterization (<4 x per week), or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for < 6 weeks	requiring frequent in/out catheterization (≥ 4 x per week) or urological intervention (e.g., TURP, suprapubic tube, urethrotomy)	bladder rupture
Urine color change (not related to other dietary or physiologic cause e.g., bilirubin, concentrated urine, hematuria)	normal	asymptomatic, change in urine color	-	-	-
Vaginal bleeding is graded in the HEMORRHAGE category.					
Vaginitis (not due to infection)	none	mild, not requiring treatment	moderate, relieved with treatment	severe, not relieved with treatment, or ulceration not requiring surgery	ulceration requiring surgery
Renal/Genitourinary-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
SECONDARY MALIGNANCY					

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Secondary Malignancy-Other (Specify type, _____) excludes metastatic tumors	none	-	-	-	present
SEXUAL/REPRODUCTIVE FUNCTION					
Dyspareunia is graded in the PAIN category.					
Dysmenorrhea is graded in the PAIN category.					
Erectile impotence	normal	mild (erections impaired but satisfactory)	moderate (erections impaired, unsatisfactory for intercourse)	no erections	-
Female sterility	normal	-	-	sterile	-
Femininization of male is graded in the ENDOCRINE category.					
Irregular menses (change from baseline)	normal	occasionally irregular or lengthened interval, but continuing menstrual cycles	very irregular, but continuing menstrual cycles	persistent amenorrhea	-
Libido	normal	decrease in interest	severe loss of interest	-	-
Male infertility	-	-	Oligospermia (low sperm count)	Azoospermia (no sperm)	-
Masculinization of female is graded in the ENDOCRINE category.					
Vaginal dryness	normal	mild	requiring treatment and/or interfering with sexual function, dyspareunia	-	-
Sexual/Reproductive Function-Other (Specify, _____)	none	mild	moderate	severe	disabling
SYNDROMES (not included in previous categories)					
Acute vascular leak syndrome is graded in the CARDIOVASCULAR (GENERAL) category.					
ARDS (Adult Respiratory Distress Syndrome) is graded in the PULMONARY category.					
Autoimmune reactions are graded in the ALLERGY/IMMUNOLOGY category.					
DIC (disseminated intravascular coagulation) is graded in the COAGULATION category.					
Fanconi's syndrome is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.					
Renal tubular acidosis is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.					
Stevens-Johnson syndrome (erythema multiforme) is graded in the DERMATOLOGY/SKIN category.					
SIADH (syndrome of inappropriate antidiuretic hormone) is graded in the ENDOCRINE category.					
Thrombotic microangiopathy (e.g., thromboitic thrombocytopenic purpura/TTP or hemolytic uremic syndrom/HUS) is graded in the COAGULATION category.					
Tumor flare	none	mild pain not interfering with function	moderate pain; pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain; pain or analgesics interfering with function and interfering with activities of daily living	Disabling

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Also consider Hypercalcemia.					
Note: Tumor flare is characterized by a constellation of symptoms and signs in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances.					
Tumor lysis syndrome	absent	-	-	present	-
Also consider Hyperkalemia, Creatinine.					
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) is graded in the RENAL/GENITOURINARY category.					
Syndromes-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling