A randomized phase III study comparing single-agent docetaxel followed by cyclophosphamide, epirubicin and 5-FU (CEF) to docetaxel with capecitabine followed by cyclophosphamide, epirubicin and capecitabine (CEX) as adjuvant treatment for early breast cancer

_Finnish Breast Cancer Group Protocol No. 01-2003_

Roche protocol number MO17728

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SYNOPSIS OF PROTOCOL FBCSG 01-2003

TITLE A randomized phase III study comparing single-agent docetaxel followed by cyclophosphamide, epirubicin and 5-FU (CEF) to docetaxel with capecitabine followed by cyclophosphamide, epirubicin and capecitabine (CEX) as adjuvant treatment for early breast cancer

SPONSOR The Finnish Breast Cancer Group

INDICATION Female patients with invasive early breast cancer with no distant metastases, who have a > 25% risk of distant recurrence within 5 years from the time of diagnosis.

OBJECTIVES

Primary: To compare the recurrence-free survival of the two treatment arms.

Secondary: To compare

- Adverse event rate using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0
- Overall survival between the two treatment arms.

TRIAL DESIGN

Open-label, two-arm, randomized multi-center phase III trial to compare efficacy and safety of a taxane-anthracycline regimen to a taxane-anthracycline-capecitabine regimen in the adjuvant setting in breast cancer patients with an intermediate-to-high risk of cancer recurrence.

Patients diagnosed with early breast cancer with > 25% risk of distant recurrence within 5 years from the diagnosis will be randomly allocated to one of the following 2 arms (1:1):

A. 3-weekly docetaxel 80 (3 cycles) → 3-weekly CE75F (3 cycles)
B. 3-weekly docetaxel 60 plus capecitabine twice-daily 900 mg/m² days 1-15 (3 cycles) → 3-weekly CE75 + capecitabine twice-daily 900 mg/m² days 1-15 (3 cycles)

Patients will be followed for at least 5 years post-randomization.

Locoregional radiotherapy will be given according
to institutional practice within approximately 3 weeks of completing adjuvant chemotherapy.

All patients with ER and/or PgR positive disease will receive adjuvant endocrine therapy. This will consist of 1 mg p.o. anastrozole (Arimidex®) given for 60 months in women who are post-menopausal prior to chemotherapy (no menstrual periods for > 6 months) or tamoxifen 20 mg for 60 months in women who are pre-menopausal prior to chemotherapy.

NUMBER OF PATIENTS

1,500 patients (750 patients per arm) to be randomized.

RANDOMIZATION

Randomization, stratified by number of positive nodes (≤ 3, > 3), HER-2 status (+ve, -ve) and study center will be made using a central computer-generated randomization system.

TARGET POPULATION

**Inclusion Criteria**

To be eligible for inclusion in the study, each patient must fulfill each of the criteria below.

1. Have provided written informed consent prior to study-specific screening procedures, with the understanding that the patient has the right to withdraw from the study at any time, without prejudice.

2. Be female and ≥ 18 years of age.

3. Have histologically confirmed invasive breast cancer.

4. High risk of breast cancer recurrence (≥ 25% within the first 5 years without adjuvant therapy, > 35% within the first 10 years) with one of the following:
   
   i) Regional node positive disease (pN+; tumor cells or tumor cell clusters < 0.2 mm in diameter are not counted as metastases)

   ii) Pathological N0 and PgR- and tumor size > 20 mm

**Exclusion Criteria**

Patients who fulfill any of the following criteria will be excluded:
1. ≥ 66 years of age.

2. "Special type" histology (mucinous, papillary, medullary, or tubular breast cancer), when pN0.

3. ER, PgR and HER-2 status (via in situ hybridization or immunohistochemistry, see Section 6.4) not determined.

4. Presence of distant metastases.

5. Previous chemotherapy in the neoadjuvant setting.


7. Pregnant or lactating women. Women of childbearing potential (menstruating within 6 months of study entry or with no hysterectomy and age ≤ 55) with either a positive or no pregnancy test at baseline.

8. Women of childbearing potential unless using a reliable and appropriate contraceptive method. (Post-menopausal women must have been amenorrheic for at least 6 months to be considered of non-childbearing potential).

9. More than 12 weeks between breast surgery and date of randomization.

10. Organ allografts with immunosuppressive therapy required.

11. Major surgery (except breast surgery) within 4 weeks prior to study treatment start, or lack of complete recovery from the effects of major surgery.

12. Participation in any investigational drug study within 4 weeks preceding treatment start.

13. Patients with a history of uncontrolled seizures, central nervous system disorders or psychiatric disability judged by the investigator to be clinically significant precluding informed consent or interfering with compliance for oral drug intake.

14. History of another malignancy within the last five years except cured basal cell carcinoma of skin or carcinoma in situ of the uterine cervix.
15. Clinically significant (i.e. active) cardiac disease (e.g. congestive heart failure, symptomatic coronary artery disease and cardiac arrhythmia not well controlled with medication) or myocardial infarction within the last 12 months.

16. Abnormal laboratory values:
   - Hemoglobin $\leq 10.0$ g/dL, neutrophils $< 1.5 \times 10^9$/L, platelet count $< 120 \times 10^9$/L
   - Serum creatinine $> 1.5 \times$ Upper Limit of Normal (ULN)
   - Creatinine clearance (calculated per Cockroft and Gault) $< 50$ mL/min
   - Serum bilirubin $> \text{ULN}$
   - ALAT $> 1.5 \times \text{ULN}$
   - Alkaline phosphatase $> 2.5 \times \text{ULN}$

17. Serious uncontrolled intercurrent infections or other serious uncontrolled concomitant disease.

18. Lack of physical integrity of the upper gastrointestinal tract or those who have clinically significant malabsorption syndrome.

19. Inability to swallow tablets.

20. Life expectancy of less than 3 months.

21. Unwilling or unable to comply with the protocol for the duration of the study.

22. Requirement for concurrent use of the antiviral agent sorivudine or chemically related analogues, such as brivudine.

**STUDY DRUG REGIMENS**

**Arm A:**

- Docetaxel: 80 mg/m² as a 60-minute intravenous (IV) infusion (with appropriate pre-medication), given on day 1 of each 3-week cycle. 3 cycles will be given.
- CEF: given day 1 every 3 weeks. 3 cycles will be given.
  - Cyclophosphamide: 600 mg/m² IV
  - Epirubicin: 75 mg/m² IV
  - 5-Fluorouracil: 600 mg/m² IV
Arm B:
Docetaxel: 60 mg/m² as a 60-minute IV infusion (with appropriate pre-medication), given on day 1 of each 3-week cycle, with
Capecitabine: twice-daily 900 mg/m², given orally days 1-15 of each 3-week cycle. The first dose of each cycle will be administered as the evening dose on day 1 and the last dose of each cycle is scheduled the morning of day 15, followed by a 7-day rest period. 3 cycles of docetaxel / capecitabine will be given.

CEX: every 3 weeks. 3 cycles will be given.
- Cyclophosphamide: 600 mg/m² IV, given day 1
- Epirubicin: 75 mg/m² IV, given day 1
- Capecitabine: twice-daily 900 mg/m², given orally days 1-15 of each 3-week cycle.

Locoregional radiotherapy will be started according to institutional practice within approximately 3 weeks of completing adjuvant chemotherapy.

Upon completion of chemotherapy, all patients who have ER +ve and/or PgR +ve disease will also receive anastrozole or tamoxifen. Anastrozole or tamoxifen should be initiated within 2 months of completing chemotherapy.

- Anastrozole (Arimidex®): 1 mg p.o. given daily for 60 months (if post-menopausal prior to chemotherapy (no menstrual periods for > 6 months)), or
- Tamoxifen: 20 mg given daily for 60 months (if pre-menopausal prior to chemotherapy).

ASSESSMENTS OF:

**EFFICACY**
- **Primary:** recurrence-free survival.
- **Secondary:** overall survival.

**SAFETY**
Adverse events and laboratory tests, graded according to the CTCAE (version 3.0), premature withdrawals, vital signs.

An Independent Safety Monitoring Committee will monitor patient safety throughout the study.
STATISTICAL CONSIDERATIONS

Assuming 5-year recurrence-free survival will improve from 75% to 83%, $\alpha=0.05$, $1-\beta=0.90$, using 2-sided testing about 200 recurrences are needed for the main analysis. Allowing for a 3% annual drop-out rate, approximately 1,500 patients will need to be randomized.

LENGTH OF STUDY

Recruitment should begin January 2004. The recruitment period is expected to be 3.5 years. The planned rate of accrual is 430 patients per year. The planned date for end of recruitment is August 2007. The primary analysis will be performed when 200 events (recurrence or death) have been reached among in the intent to treat population. This is expected to occur about 2 years after the last patient has been enrolled. The planned date for the final study report is mid-2011.
<table>
<thead>
<tr>
<th>Study Week</th>
<th>Study Day</th>
<th>Treatment Cycle</th>
<th>Day of Cycle</th>
<th>Follow-up Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>-1</td>
<td>-1 - 6</td>
<td>1 - 6</td>
<td>(at 1, 3 and 5 years post-randomization)</td>
</tr>
<tr>
<td>-28 to 1</td>
<td>-7 to 1</td>
<td>1 - 126</td>
<td>1 - 127 ± 14</td>
<td></td>
</tr>
</tbody>
</table>

**Screening / Baseline**

- Informed consent (a)
- Demographics, medical history (b)
- Concomitant diseases & treatment
- Cancer/treatment history (c)
- General physical examination/vital signs (d)
- Pregnancy test (if applicable) (e)
- ECG
- Chest CT or X-ray (f)
- Bone Scan (f)
- CT/MRI or ultrasound of abdomen (f)
- Hematology (g)
- Blood chemistry (g)
- Research blood / serum sample (h)
- Study drug compliance
- Adverse events and treatments (i)
- Survival follow-up / additional cancer therapies (j)

**Study Treatment Phase**

- As clinically indicated

**Follow-up Phase**

- As clinically indicated

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30 a) Written informed consent must be obtained before any study-specific screening procedures are performed.

31 b) Includes data of birth and menopausal status.

32 c) Includes histological type, histological grade, number of axillary metastases, hormonal status (i.e. estrogen/progesterone receptor status), TNM classification, HER-2 status, Ki-67 (optional), date of diagnosis, type of surgery, tissue block number/code.
d) Includes a clinical examination, WHO performance status (see Appendix 1), height (baseline only), weight, pulse rate and blood pressure.

e) Pregnancy test is required during screen/baseline for all women of childbearing potential (menstruating women or women with menstruation within 6 months of study entry). S-FSH will be measured if patient’s age is < 55 years and a hysterectomy has been done to confirm post-menopausal status.

f) All staging studies including physical exam, CT, chest X-ray, and bone scan must show no evidence of metastatic disease, including suspicious lymphadenopathy or skin nodules on physical exam. Staging studies are mandatory if ≥ pN4+. All other staging studies are at the treating physician’s discretion. Any other staging test (e.g., CT scans, MRI studies, ultrasound of abdomen, PET scans) must be negative for metastatic disease.

g) Hematology (blood cell counts including the neutrophil count) and serum chemistries (serum creatinine, total bilirubin, ALAT, alkaline phosphatase) will be sampled within 7 days prior to the first chemotherapy cycle and within 3 days prior to the start of subsequent chemotherapy cycles. Results must be available and reviewed by investigator before starting treatment.

h) Participation is optional. One serum sample will be divided into two aliquots and one whole blood sample (5 mL citrate) will be taken. Post-study samples will be required at approximately 1, 3 and 5 years post-randomization.

i) Adverse events are monitored continuously during study treatment and for 28 days after the last intake/infusion of study drug.

j) Survival and additional cancer therapies documented for all patients until recurrence or for a minimum of 5 years following randomization. All patients should have visits at approximately 1, 3 and 5 years post-randomization.
### GLOSSARY OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>5-FU</td>
<td>5-fluorouracil</td>
</tr>
<tr>
<td>5-FUH₂</td>
<td>dihydro-5-fluorouracil</td>
</tr>
<tr>
<td>5'-DFCR</td>
<td>5'-deoxy-5-fluorocytidine</td>
</tr>
<tr>
<td>5'-DFUR</td>
<td>5'-deoxy-5-fluorouridine</td>
</tr>
<tr>
<td>ALAT (SGPT)</td>
<td>alanine aminotransferase</td>
</tr>
<tr>
<td></td>
<td>serum glutamic pyruvic transaminase</td>
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<tr>
<td>ASAT (SGOT)</td>
<td>asparagine aminotransferase</td>
</tr>
<tr>
<td></td>
<td>serum glutamic oxaloacetic transaminase</td>
</tr>
<tr>
<td>AUC</td>
<td>area under the plasma concentration-time curve</td>
</tr>
<tr>
<td>Cₓmax</td>
<td>maximum plasma concentration</td>
</tr>
<tr>
<td>CMF</td>
<td>cyclophosphamide, methotrexate and 5-fluorouracil</td>
</tr>
<tr>
<td>CT</td>
<td>computer tomography</td>
</tr>
<tr>
<td>CTCAE</td>
<td>Common Terminology Criteria for Adverse Events</td>
</tr>
<tr>
<td>CRF</td>
<td>case report form(s)</td>
</tr>
<tr>
<td>DPD</td>
<td>dihydropyrimidine dehydrogenase</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
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<tr>
<td>ESF</td>
<td>eligibility screening form</td>
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<tr>
<td>FBAL</td>
<td>(alpha-fluoro-beta-alanine)</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
</tr>
<tr>
<td>Q3W</td>
<td>every 3 weeks</td>
</tr>
<tr>
<td>Tₓmax</td>
<td>time to maximum concentration</td>
</tr>
<tr>
<td>TP</td>
<td>thymidine phosphorylase</td>
</tr>
<tr>
<td>ULN</td>
<td>upper limit of normal</td>
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<td>vs</td>
<td>versus</td>
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1. BACKGROUND AND RATIONALE

1.1 Disease Background – Breast Cancer

Breast cancer is the most common form of malignancy occurring in women around the world. In 1999, more than 795,000 new cases (21% of all cancer sites) were diagnosed and 314,000 breast cancer deaths (14.1%) occurred\(^1\). In the European Community, an estimated 135,000 new cases per year (24% of all cancers cases) and 58,000 recorded deaths per year (18% of all cancer deaths) will be reported\(^2\). In Finland 3,746 women are estimated to have breast cancer diagnosed in 2003, and 844 women died of breast cancer in 1999\(^3\). If current breast cancer rates stay constant, a female born today has a 1 in 8 chance of developing breast cancer sometime during her life.

Surgery is the main modality of local treatment for breast cancer. Surgery and/or radiotherapy can control local-regional disease in the majority of patients. However, approximately one-third of the patients will ultimately die due to distant recurrence of disease. The use of radiation therapy and/or systemic therapy following surgery (referred to as adjuvant therapy) is based on the rationale that subclinical tumor remaining following surgery may cause a recurrence at a later date. If some of these remaining tumor cells can be killed by adjuvant therapy, the time to disease progression, and thus overall survival, may be lengthened. More optimistically, if the remaining tumor cells can be eliminated, a cure is conceivable. Adjuvant therapy was firmly established as effective in the treatment of breast cancer when the results of a meta-analysis of data collected worldwide were presented in 1995\(^4\).

The primary focus of research today is improvement of existing adjuvant regimens by incorporating new, more effective drugs and optimizing the dose and schedule of administration.

1.2 Adjuvant Treatment Of Breast Cancer

Two types of systemic adjuvant therapy have been used increasingly over the last 20 years to successfully reduce the rate of breast cancer recurrence and death. Adjuvant chemotherapy involves a combination of cytotoxic anti-cancer drugs; adjuvant hormonal therapy deprives cancer cells of the hormone estrogen which some breast cancer cells need to grow. These therapeutic modalities are complementary and are often used in combination.

The ‘Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) meta-analysis summarized results of randomized trials beginning before 1990; that compared different chemotherapy regimens in otherwise similar patient groups. In 47 trials comparing combination chemotherapy to no chemotherapy, a significant reduction in mortality occurred in patients receiving chemotherapy irrespective of nodal status (negative vs positive), estrogen receptor (ER) status (ER-rich vs ER-unknown, or ER-poor), and whether or not tamoxifen (TAM) was given\(^5\). For women < 50 years of age at randomization, overall survival (OS) improved from...
1.2.1 Anthracycline-based adjuvant chemotherapy of breast cancer

Although the first results on the efficacy of adjuvant chemotherapy were derived from studies on the CMF combination (cyclophosphamide, methotrexate and 5-fluorouracil), there has been a shift towards use of anthracyclines during the past decade. The largest direct comparison of anthracycline-based vs CMF chemotherapy was carried out by the United States (US) Intergroup (trial INT0102)\(^5\). In this trial, 2,691 node negative patients were randomized to receive six cycles of either cyclophosphamide/doxorubicin/5-fluorouracil (CAF) or CMF, with a second randomization to 5 years of tamoxifen or no tamoxifen. At 5 years, CAF was marginally superior to CMF for both disease-free survival (DFS) (86% vs 84%, \(p = 0.03\)) and overall survival (92% vs 91%, \(p = 0.03\)), independent of tamoxifen use. In node-positive disease, several studies have demonstrated superiority for anthracycline containing regimens over CMF, while others have not \(^7\)-\(^10\). Nevertheless, the Oxford Overviews of 1995 and 2000 demonstrate a significant advantage for anthracyclines over CMF in terms of both DFS and OS \(^5\),\(^11\). The 1995 EBCTCG meta-analysis, which compared 11 anthracycline vs CMF chemotherapy trials that began in 1976 through 1989 reported 5-year recurrence-free and OS differences of 57% vs 54% (\(p = 0.006\)) and 72% vs 69% (\(p = 0.02\)), for anthracycline-containing polychemotherapy vs CMF, respectively\(^5\). The results of the 2000 overview confirm a significant advantage for anthracycline polychemotherapy over CMF in the order of 3-4% absolute survival gain\(^11\).

1.2.2 Taxane based adjuvant chemotherapy of breast cancer

The addition of paclitaxel (P) to the adjuvant treatment has been investigated in the Cancer and Leukemia Group-B (CALGB) 9344 trial (4 cycles of adriamycin and cyclophosphamide (AC) vs 4 cycles of AC followed by 4 cycles of P at 175 mg/m\(^2\) (AC/P)). The hazard reductions from adding paclitaxel to AC were 17% for recurrence (adjusted Wald \(X^2\) \(p = 0.0023\); unadjusted Wilcoxon \(p = 0.0011\)) and 18% for death (adjusted \(p = 0.0064\); unadjusted \(p = 0.0098\)). At 5 years, DFS was 65% and 70%, and OS was 77% and 80% after AC alone or AC plus P, respectively. The effects of adding paclitaxel were not significantly different in subsets defined by the protocol, but in an unplanned subset analysis, the hazard ratio of AC plus paclitaxel vs AC alone was 0.72 (95% confidence interval, 0.59 to 0.86) for those with estrogen receptor-negative tumors and only 0.91 (95%
confidence interval, 0.78 to 1.07) for patients with estrogen receptor-positive
tumors, almost all of whom received adjuvant tamoxifen. The additional toxicity
from adding four cycles of paclitaxel was generally modest[12].

Although these results are provocative, the most recent results from the NSABP
B28 trial (4 cycles of AC vs 4 cycles of AC then 4 cycles of P 225 mg/m²,
n = 3,060) support the findings of CALGB 9344 showing a similar improvement in
disease-free survival in favor of the paclitaxel arm[13]. The MD Anderson trial (8
cycles of cyclophosphamide/adriamycin/5-FU (FAC) vs 4 cycles of P then 4
cycles of FAC, n = 524) showed no statistical advantage for the addition of
taxanes to date, although results are preliminary[14, 15].

The role of adjuvant docetaxel has so far been preliminary, reported from a
planned interim analysis of a trial comparing docetaxel with adriamycin and
cyclophosphamide (TAC) (75/50/500 mg/m² Q3W x 6 cycles) with FAC
(500/50/500 mg/m² Q3W x 6 cycles) in node-positive breast cancer patients with
33 months median follow-up (range 0-49 months). This study randomized 1,491
patients with prospective stratification by nodes (1+ to 3+, vs 4+). Patients with
ER+ and/or PR+ (HR+) tumors received tamoxifen for 5 years after
chemotherapy. Cox analysis for DFS showed a relative risk ratio for TAC/FAC of
0.64 (0.50, 0.81; p = 0.0002) and for overall survival 0.71 (0.50, 1.00; p = 0.049).
TAC/FAC disease-free survival risk ratio was 0.68 (0.54, 0.86; p = 0.02) in HR+
patients, 0.62 (0.44, 0.86, p = 0.005) in HR- patients[16].

1.2.3 Tamoxifen adjuvant therapy in breast cancer

The EBCTCG meta-analysis of tamoxifen vs no tamoxifen trials supports the
benefit of tamoxifen independent of the added use of chemotherapy in both
younger (< 50 years) and older women with hormone receptor positive breast
cancer, based on data from 37,000 women enrolled in 55 trials, with an average
follow-up of ten years[17]. ER status was positive in 18,000, negative in 8,000,
and unknown in approximately 12,000 women.

The use of tamoxifen was associated with a highly significant decrease in both
recurrence and death among women with hormone receptor positive or unknown
disease, and there was a significant trend of increased benefit with longer
duration of therapy. There was no significant effect for women with hormone
receptor negative disease, so these women were removed from analysis of
estimated benefit. Overall, with five years of tamoxifen, the relative risk reduction
was 47% (2p < 0.00001) for recurrence, and 26% (2p < 0.00001) for death. The
greatest benefit in mortality was observed in node positive disease, (n = 2,210,
92% ER+) with a relative risk reduction of 43% for recurrence and 28% for death
with 5 years of tamoxifen. This is equivalent to an absolute 10-year survival
improvement of 10.9% (from 50.5% for no hormonal therapy, to 61.4%;
2p < 0.00001). For 1 and 2 years of tamoxifen use, the absolute 10-year survival benefits were less pronounced (4.5% and 7.2%, respectively).

Although a debate exists as to whether more than 5 years of adjuvant tamoxifen provides additional protective benefit against breast cancer recurrence or death, 5 years is considered the current standard duration of therapy.

1.3 Capecitabine Background

1.3.1 Activation pathway and mechanism of action

Capecitabine is administered as a non-cytotoxic systemic prodrug of 5’-deoxy-5-fluorouridine (5’-DFUR)\(^{[18]}\). After administration, it is extensively absorbed unchanged from the gastrointestinal tract, and is sequentially converted to the cytotoxic moiety, 5-FU in a series of metabolic steps\(^{[19]}\). First, capecitabine is metabolized primarily in the liver by the 60 kDa carboxylesterase to 5’-deoxy-5-fluorocytidine (5’-DFCR). 5’-DFCR is then converted to 5’-DFUR by cytidine deaminase, which is principally located in the liver and tumor tissues. Metabolism of 5’-DFUR to 5-FU is performed by the tumor-associated angiogenic factor, thymidine phosphorylase (TP). 5-FU is generated preferentially at the tumor site through the exploitation of the higher concentrations of thymidine phosphorylase found in tumor tissues as compared to normal tissues (Figure 1).

Figure 1 Metabolism of capecitabine
The exchange of hydrogen by fluorine in the position five of the naturally occurring pyrimidine ring, uracil, is responsible for the cytotoxic activity of 5-FU. Cell death is induced mainly by:

- inhibition of the key enzyme of thymidine synthesis, thymidylate synthase, after metabolism to 5-fluoro-2'-deoxyuridine-5'-monophosphate (5-FdUMP)
- incorporation as a false pyrimidine base in RNA after metabolism to 5-fluorouridine-5'-triphosphate (5-FUTP)
- incorporation as a false pyrimidine base in DNA after metabolism to 5-fluoro-2'-deoxyuridine-5'-triphosphate (5-FdUTP).

5-FU is catabolised (via dihydropyrimidine dehydrogenase (DPD)) to dihydro-5-fluorouracil (5-FUH₂), 5-fluoro-ureidopropionic acid (FUPA) and alpha-fluoro-beta-alanine (FBAL), none of which have anti-proliferative activity.

The preferential activation of capecitabine to 5-FU in tumor, as compared to normal tissue, was demonstrated in a study in patients with colorectal cancer. After administration of capecitabine, concentrations of 5-FU in primary colorectal tumors were significantly higher than in adjacent healthy tissue (mean ratio primary tumor:healthy tissue of 3.2 (p=0.002), and in plasma (mean ratio primary tumor:plasma of 21.4)\(^{29}\). In contrast, after administration of intravenous 5-FU, tumor:healthy tissue and tumor:plasma 5-FU concentration ratios were estimated to be close to unity\(^{21}\). While conversion of capecitabine to 5-FU was observed in healthy tissue, it was less extensive than in tumor tissue.

### 1.3.2 Clinical pharmacokinetics

The clinical pharmacokinetics of capecitabine have been extensively investigated\(^ {18, 22-37}\). A summary is provided below.

#### 1.3.2.1 Absorption

Following oral administration after food intake, capecitabine passes unchanged through the intestinal wall. Absorption is rapid (T\(_{\text{max}}\) ranging from 0.3-3 hours) and extensive, approaching 100%\(^ {34, 35}\). Mean maximum concentration values (C\(_{\text{max}}\)) of 2.7-4.0 µg/mL capecitabine were reached approximately 2 hours after oral administration\(^ {35}\).

#### 1.3.2.2 Metabolism

Capecitabine is converted via a three-step enzymatic pathway to 5-FU, as described in Section 1.3.1 (Figure 1). Following oral intake, the time taken to reach peak plasma concentrations of the metabolites of capecitabine, 5'-DFCR, 5'-DFUR and 5-FU, is approximately 2 hours. Concentrations decline exponentially with half-lives (t\(_{1/2}\)) of 0.6-0.8 hours\(^ {34}\). FBAL reaches peak plasma concentration 3-4 hours after administration of capecitabine\(^ {36}\). Low plasma concentrations of 5-FU are observed after administration of capecitabine. After 2 weeks of treatment with capecitabine twice-daily 1250 mg/m\(^2\) (total daily dose 2500 mg/m\(^2\)), systemic exposure (AUC) to 5-FU was approximately 12 times lower than systemic exposure to 5'-DFUR\(^ {22}\).
1.3.2.3 **Plasma protein binding**

The plasma protein binding of capecitabine is relatively low (54%) and is not concentration dependent. Plasma protein binding for the three metabolites 5'-DFCR, 5'-DFUR and 5-FU was 10%, 60% and 10%, respectively\[^{35}\].

1.3.2.4 **Elimination**

In a pharmacokinetic study of radiolabeled capecitabine\[^{34}\], approximately 96% of the capecitabine dose was recovered in the urine. FBAL was the major metabolite excreted in urine (57% of the total percentage excreted).

A large proportion (84%) of the dose was recovered within 12 hours of administration. Fecal excretion during the same period was minimal (2.6%). The mean elimination half-life of capecitabine is short, ranging from 0.6-0.9 hours\[^{36}\]. Elimination half-lives for 5'-DFCR, 5'-DFUR, 5-FU and 5-FUH₂ are also short, whereas the half-life for FBAL ranges from 2.6-11.5 hours.

1.3.2.5 **Time dependency**

As expected from the short half-lives (< 1 hour), there is no indication that capecitabine, 5'-DFCR or 5'-DFUR accumulate in plasma after chronic dosing every 12 hours\[^{22}\]. Plasma concentrations of 5-FU prior to drug dosing on day 14 are undetectable. The AUC of 5-FU increased by 10-60% during multiple dosing, but plasma concentrations of 5-FU declined to undetectable concentrations within 12 hours of the previous dose.

1.3.2.6 **Hepatic impairment**

Capecitabine (1250 mg/m² as a single dose) has been evaluated in patients with mild to moderate hepatic dysfunction caused by liver metastases\[^{30}\]. No significant differences in the pharmacokinetic parameters of the main metabolites (5'-DFUR, 5-FU and FBAL) were seen in this group compared to patients with normal hepatic function. Caution should be exercised, however, when administering capecitabine to patients with mild to moderate hepatic dysfunction caused by liver metastases, although no *a priori* dose adjustment is recommended.

1.3.2.7 **Renal impairment**

Based on a pharmacokinetic study in patients with cancer and mild to severe renal impairment treated with capecitabine 1250 mg/m² (monotherapy), there is no evidence for an effect of creatinine clearance on the pharmacokinetics of intact drug and 5-FU. However, creatinine clearance was found to influence the systemic exposure to 5'-DFUR (35% increase in AUC when creatinine clearance decreases by 50%) and to FBAL (114% increase in AUC when creatinine clearance decreases by 50%)\[^{38}\]. 5'-DFUR is the direct precursor of 5-FU and FBAL is a metabolite without antiproliferative activity.

From the study performed in patients with varying degrees of renal impairment, as well as safety data from capecitabine clinical trials\[^{56}\], the following principles for drug administration were derived.
- As patients with severe renal impairment at baseline (calculated creatinine clearance < 30 mL/min) had a high rate of grade 3-4 and serious adverse events and shorter treatment duration, capecitabine is contraindicated in this population.

- As patients with moderate renal impairment at baseline (calculated creatinine clearance 30-50 mL/min) had a greater overall incidence of treatment-related grade 3-4 and serious adverse events relative to patients with normal renal function, the starting dose of capecitabine in this population should be reduced to 75% of the standard starting dose.

- As patients with mild renal impairment at baseline (calculated creatinine clearance 51-80 mL/min) experienced slightly more serious adverse events and withdrawals due to adverse events than patients with normal renal function, careful monitoring during capecitabine treatment is advised, with no adjustment being made for the standard starting dose.

It should be noted that the creatinine clearance values for all the analyses were calculated according to the Cockroft and Gault formula (see Appendix 2) by employing actual body weights. There is no evidence of a direct nephrotoxic effect of capecitabine. Thus, if the calculated creatinine clearance during treatment decreases to a value of 30-50 mL/min (due to an increase in serum creatinine or decrease in body weight), this change is not, by itself, a reason for a dose reduction. Dose reductions during treatment should be based on adverse events.

1.3.2.8 Effect of age and gender on pharmacokinetics

The population pharmacokinetic analysis demonstrated that gender had no clinically relevant effect on the pharmacokinetics of capecitabine or its metabolites\(^{27}\). Similarly, age had no influence on the pharmacokinetics of 5'-DFUR or 5-FU. The AUC of FBAL increased with age, an effect probably caused by a change in renal function in the elderly.

1.3.2.9 Effect of co-administration of capecitabine and docetaxel on pharmacokinetics

The phase I study SO15304 investigated the combination of capecitabine given on days 1 to 14 together with docetaxel given on day 1 of each three-week cycle with appropriate co-medication. A total of 33 patients were treated in two dose escalation phases. Initially the dose of docetaxel was increased (75, 85 and 100 mg/m\(^2\)) in combination with a fixed dose of capecitabine (twice-daily 825 mg/m\(^2\)). Subsequently the dose of capecitabine was increased (twice-daily 1000 mg/m\(^2\) and twice-daily 1250 mg/m\(^2\)) in combination with a fixed dose of docetaxel defined as tolerable in the first stage (75 mg/m\(^2\)). The effect of docetaxel on the pharmacokinetics of capecitabine and its metabolites was investigated by comparing the results obtained when capecitabine was given alone (without docetaxel on day 14), with the results obtained when capecitabine was given concomitantly with docetaxel (on day 1). Pharmacokinetic parameters estimated
after doses of twice-daily 825, 1000 and 1250 mg/m² of capecitabine were used for this comparison. Conclusions from this study included:

- capecitabine had no effect on the pharmacokinetics of docetaxel,
- administration of docetaxel (75, 85 or 100 mg/m²) had no effect on the pharmacokinetics of the main metabolites 5'-DFUR and FBAL,
- administration of docetaxel (75, 85 or 100 mg/m²) appears not to have an effect on capecitabine and 5'-DFCR.

For 5-FU, there was a possible PK interaction due to docetaxel, with a higher C_max and AUC being noted at day 14, than at day 1. When doses of capecitabine > 500 mg/m² are given alone, the plasma concentration of 5-FU increases from 10 to 60% by day 14. Thus, the observed effect on 5-FU in this study (i.e. an increase in the C_max and AUC by day 14) may be due either to the previously described 5-FU pharmacokinetics or due to a pharmacokinetic interaction with docetaxel[35].

In the open-label, multi-center, multi-national, randomized phase III study (SO14999) described further in Section 1.5.3, patients were randomized to receive either capecitabine twice-daily 1250 mg/m² days 1-14 (2500 mg/m²/day) in combination with docetaxel 75 mg/m² given on day 1 Q3W or docetaxel monotherapy (100 mg/m² given on day 1 Q3W). Sixteen patients receiving both capcitabine and docetaxel were supposed to have specimens drawn at study treatment days 14 and 77[37]. The intention of the analysis of this subgroup of patients was to examine for potential effects of long-term co-administration of the two agents on the pharmacokinetic parameters of capecitabine, 5'-DFCR, 5'-DFUR, 5-FU, FBAL and docetaxel. Due to dose reductions or early withdrawals, only 5 patients had specimens drawn at both planned time points. As a consequence, although no major or clinically relevant differences in the pharmacokinetics of capcitabine between the first and fourth cycle were observed, the results of the comparison were inconclusive because of the small number of patients studied.

1.4 Docetaxel Background

Docetaxel (Taxotere®) is a member of the taxane class of anticancer therapeutics. First synthesized in 1986, it has undergone clinical evaluation in a number of cancer indications following promising preclinical evidence of activity. In the treatment of metastatic breast cancer, at the most frequently studied dose of 100 mg/m² given on day 1 every 3 weeks, response rates of 54-68% have been reported in phase II studies in the first-line metastatic setting[38, 39], and of 53-58% in phase II studies in the second-line metastatic setting[40-42]. In 392 patients previously treated with anthracyclines for metastatic breast cancer, docetaxel at 100 mg/m² Q3W was compared in a randomized fashion with mitomycin 12 mg/m² Q6W and vinblastine 6 mg/m² Q3W[43]. A significantly higher response rate (30% vs 12%), was observed for docetaxel. In addition, time to progression (median 19 and 11 weeks, respectively) and overall survival (median 11.4 and 8.7 months, respectively) were significantly longer with...
In a second study, 326 patients previously treated with alkylating agents for metastatic breast cancer were randomized to receive docetaxel at the 100 mg/m² dose vs doxorubicin 75 mg/m² Q3W\(^{[44]}\). Again, docetaxel proved superior in this setting for response rate (48% vs 33%), time to progression (median 26 vs 21 weeks) and overall survival (median 15 months vs 14 months). Docetaxel has been approved in Europe and the USA for use in the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy.

The dose-limiting toxicity of docetaxel is neutropenia, which is usually of short duration. At 100 mg/m² every 3 weeks, grade 4 neutropenia is seen in 75.4% of patients, however stem cell support is not normally required. Other toxicities (all grades) include anemia (90.4%), alopecia (75.8%), asthenia (61.2%), neuropathy (49.3%), fluid retention (peripheral edema, pleural effusions or ascites) (47%), stomatitis (41.7%), nausea/vomiting (38.8 and 22.3%, respectively), and diarrhea (38.7%)\(^{[45]}\).

Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions characterized by hypotension and/or bronchospasm, or generalized rash/erythema occurred in 2.2% of 92 patients with metastatic breast cancer premedicated with 3-day corticosteroids\(^{[45]}\). Severe fluid retention occurs more frequently after a cumulative dose of docetaxel of 800 mg/m². In 92 patients premedicated with a 3-day course of corticosteroids, severe fluid retention was noted in 6.5% of patients\(^{[45]}\). Because of the risk of hypersensitivity reactions and fluid retention, premedication with corticosteroids is recommended.

### 1.5 Capecitabine and Docetaxel Combination Therapy

#### 1.5.1 Preclinical data

The combination of capecitabine and docetaxel in a human xenograft model led to efficacy that was more than additive\(^{[46]}\). The mechanism is thought to be related to the upregulation of thymidine phosphorylase (TP) expression by docetaxel. However, in some cell lines where TP expression is not induced, the combination of capecitabine and docetaxel is still synergistic, indicating that other mechanisms may also be involved in this process\(^{[47]}\).

#### 1.5.2 Phase I study

In the phase I study SO15304 (Section 1.2.2.9), minimal toxicity, other than the expected neutropenia, was observed at the 75 mg/m² docetaxel / twice-daily 1250 mg/m² capecitabine dose level; this combination was chosen for further exploration in the phase III setting\(^{[48]}\).

#### 1.5.3 Phase III study

An open-label, multi-center, multinational, randomized phase III study (SO14999) was conducted to compare the safety and efficacy profiles of capecitabine (intermittent regimen) in combination with docetaxel vs docetaxel monotherapy for the treatment of locally advanced and/or metastatic breast cancer resistant to,
or recurring after an anthracycline-containing therapy, or relapsing during or recurring within two years of completing an anthracycline-containing adjuvant therapy. Prior treatment with a docetaxel-containing regimen either in the adjuvant or advanced disease setting was not allowed, although previous treatment with paclitaxel was. Stratification was based on previous paclitaxel treatment.

A total of 511 patients with metastatic breast cancer were randomized to 3-week treatment cycles of either capecitabine twice-daily 1250 mg/m² given on days 1–14 (for a total daily dose of 2500 mg/m²/day), plus docetaxel 75 mg/m² on day 1 (n = 255), or docetaxel monotherapy at 100 mg/m² on day 1 (n = 256). Patients who responded (complete or partial response) or had stable disease at the end of 2 cycles of treatment were allowed to continue to receive treatment until disease progression. No other anticancer treatment was to be given until disease progression. Patients with documentation of progressive disease (PD) were to discontinue study therapy at that time.

The combination regimen of capecitabine and docetaxel resulted in significantly superior overall survival (hazard ratio = 0.775 [23% decrease in risk of death], median 14.5 vs 11.5 months), time to disease progression (median 6.1 vs 4.2 months), and objective tumor response rate (42% vs 30%, all randomized patients; 47% vs 28% per-protocol population) compared with docetaxel monotherapy. There was a higher incidence of gastrointestinal side effects and hand-foot syndrome in the combination arm, but myalgia, arthralgia, and grade 3/4 neutropenia were less frequently observed than with docetaxel alone[37].

1.6 Rationale for Performing the Study

Despite the significant reduction in breast cancer relapse and mortality achieved with adjuvant polychemotherapy and endocrine therapy, recurrences still occur in many breast cancer patients, even following anthracycline- and taxane-containing chemotherapy regimens.

The Finnish Breast Cancer Study Group has performed a randomized study (FinHER) comparing 3 cycles of docetaxel followed by 3 cycles of 5-FU/epirubicin/cyclophosphamide (FEC) to 8 weekly cycles of vinorelbine followed by 3 cycles of FEC. In a second randomization, HER-2 positive patients were randomized to either 8 weekly infusions of Herceptin or no additional therapy during the docetaxel or vinorelbine treatment. No efficacy data are currently available from this study. However, based on excessive toxicity from docetaxel at the initial dose of 100 mg/m² the dose was subsequently reduced to 80 mg/m². Based on the experiences by FBCSG with docetaxel (80 mg/m²) followed by 3 cycles of FEC, this regimen has been chosen as the standard treatment arm for the current study. In the experimental arm capecitabine is substituted for 5-FU in the FEC regimen or added to docetaxel.

1.6.1 Rational for capecitabine

The oral fluoropyrimidine capecitabine was rationally designed to mimic continuous infusion 5-FU and to generate 5-FU preferentially in tumor tissue.
This tumor selectivity is achieved through exploitation of the significantly higher activity of thymidine phosphorylase (TP) in many human tumor tissues compared with healthy tissue. Clinical studies have shown that single-agent capecitabine is an active and tolerable treatment in metastatic breast cancer that has progressed during or following anthracycline and taxane therapy, achieving response rates of 20% to 29% and a median survival in excess of 1 year. 

This activity in heavily-pretreated patients provided the rationale for investigating capecitabine earlier in the disease course and in combination with other cytotoxic agents. In addition, capecitabine is an attractive agent for incorporation into combination regimens because of the low incidence of myelosuppression. Consequently, a number of studies have investigated capecitabine in combination with cytotoxic agents with differing mechanisms of action and safety profiles. Preclinical studies in human cancer xenograft models demonstrated that administration of docetaxel or paclitaxel results in further upregulation of TP in tumor tissue. This has been confirmed in women with primary breast cancer who were treated with preoperative docetaxel. Co-administration of capecitabine and with docetaxel or paclitaxel in xenograft models resulted in synergistic antitumor activity, whereas taxanes in combination with either 5-FU or uracil plus tegafur demonstrated only additive efficacy.

1.6.2 Rationale for the combination of capecitabine and docetaxel

A recent international phase III trial (SO14999) investigated the efficacy and tolerability of capecitabine/docetaxel combination therapy compared with single-agent docetaxel in anthracycline-pretreated patients with metastatic breast cancer. A total of 511 patients with metastatic breast cancer were randomized to 21-day treatment cycles of either capecitabine (1250 mg/m² twice-daily) days 1-14, plus docetaxel (75 mg/m²) day 1 (n = 255), or single-agent docetaxel (100 mg/m²) day 1 (n = 256) with 21-day treatment cycles. After a minimum follow-up of 15 months, the combination regimen resulted in significantly superior efficacy, including time to disease progression (hazard ratio = 0.652, p = 0.0001, median 6.1 vs 4.2 months) overall survival (hazard ratio = 0.775, p = 0.0126, median 14.5 vs 11.5 months), and objective tumor response rate (42% vs 30%, p = 0.006) compared with single-agent docetaxel.

A total of 454 patients from 15 countries completed quality of life questionnaires (224 in the combination arm; 230 in the single-agent arm). The EORTC QLQ-C30 global health score was preselected as the primary parameter for statistical testing in the quality of life analysis, with a comparison of the treatment arms at day 127 prespecified in the protocol. No significant differences could be found. There was a trend towards less deterioration of global health score in the combination arm over time.

The significantly superior time-to-disease progression, overall survival and objective response rate achieved with the addition of capecitabine to docetaxel (75 mg/m²) compared with single-agent docetaxel (100 mg/m²), along with a
manageable toxicity profile, indicate that this combination provides clear benefit in patients with breast cancer. Because improvement in median overall survival with chemotherapy in metastatic breast cancer is a rare achievement, the docetaxel/capecitabine combination should be studied as adjuvant therapy to determine whether the disease-free survival and overall survival of primary breast cancer patients can be improved.

1.6.3 Adverse events of capecitabine and docetaxel

The incidence of treatment-related adverse events was similar in the combination and single-agent arms (98% vs 94%, respectively). Patients receiving the combination regimen experienced a higher incidence of gastrointestinal adverse events and hand-foot syndrome whereas patients receiving docetaxel alone experienced a higher incidence of neutropenic fever, arthralgia, and pyrexia. The percentage of patients experiencing grade 3 treatment-related adverse events was higher in the combination therapy group (71% vs 49% in the single-agent docetaxel arm), but there was a lower incidence of grade 4 treatment-related adverse events with combination therapy (25% vs 30%). In both treatment groups the overall incidence of grade 3 or 4 adverse events was highest in the first treatment cycle (38% in the combination group, 40% in the single-agent group). In the second cycle more patients experienced grade 3 or 4 adverse events in the combination arm, due primarily to grade 3 hand-foot syndrome (combination arm: 2% in weeks 1-3, 13% in weeks 4-6) and neutropenic fever (combination arm: 6% in weeks 1-3, 5% in weeks 4-6; single-agent arm: 10% in weeks 1-3, 5% in weeks 4-6). In all other cycles the incidence of grade 3/4 adverse events was similar in the two groups. A summary of the safety profile is provided in the tables below:

Table 1: Summary of Treatment-Related Adverse Events for Capecitabine

<table>
<thead>
<tr>
<th>Safety Parameter</th>
<th>Capecitabine/Docetaxel (N = 251) n (%)</th>
<th>Docetaxel (N = 255) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomatitis*</td>
<td>167 (67)</td>
<td>109 (43)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>102 (41)</td>
<td>107 (42)</td>
</tr>
<tr>
<td>Hand-and-Foot Syndrome*</td>
<td>159 (63)</td>
<td>20 (8)</td>
</tr>
<tr>
<td>Face Edema</td>
<td>8 (3)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Eyelid Edema</td>
<td>2 (1)</td>
<td>1 (&lt; 1)</td>
</tr>
<tr>
<td>Neutropenic Sepsis</td>
<td>6 (2)</td>
<td>10 (4)</td>
</tr>
<tr>
<td>Upper Respiratory Tract</td>
<td>5 (2)</td>
<td>10 (4)</td>
</tr>
<tr>
<td>Nail Bed Infection Nos</td>
<td>3 (3)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Localized Infection</td>
<td>1 (&lt; 1)</td>
<td>1 (&lt; 1)</td>
</tr>
<tr>
<td>Edema Lower Limb</td>
<td>34 (14)</td>
<td>31 (12)</td>
</tr>
<tr>
<td>Edema Peripheral</td>
<td>9 (4)</td>
<td>14 (5)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>31 (12)</td>
<td>25 (10)</td>
</tr>
<tr>
<td>Conjunctivitis Nos</td>
<td>10 (4)</td>
<td>9 (4)</td>
</tr>
</tbody>
</table>
### Table 2: Summary of Treatment-Related Grade 3/4 Adverse Events for Capecitabine

<table>
<thead>
<tr>
<th>Safety Parameter</th>
<th>Capecitabine/Docetaxel (N = 251) n (%)</th>
<th>Docetaxel (N = 255) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-Related Grade 4 AEs (Life-Threatening)</td>
<td>62 (25)</td>
<td>78 (31)</td>
</tr>
<tr>
<td>Treatment-Related Grade 3 AEs (Severe)</td>
<td>178 (71)</td>
<td>125 (49)</td>
</tr>
</tbody>
</table>

**Frequent (> 10%) Treatment-Related Grade 3/4 AEs**

- Hand-Foot Syndrome: 61 (24) vs. 3 (1)
- Stomatitis: 44 (18) vs. 12 (5)
- Neutropenic Fever: 40 (16) vs. 53 (21)
- Neutropenia*: 39 (16) vs. 37 (15)
- Diarrhea: 35 (14) vs. 15 (6)
- Related Deaths on Study: ** (2) vs. 1 (< 1)
- Related SAEs: 79 (31) vs. 84 (33)
- Patients Withdrawn Due to AEs: 66 (26) vs. 49 (19)
- Patients Withdrawn Due to Treatment-Related AEs: 62 (25) vs. 45 (18)
- Hospitalization for Treatment-Related AEs: 72 (29) vs. 67 (26)

*leading to medical intervention

**patient 20018/2003 died 29 days after last study drug administration.

### Table 3: Most Common Grade 3/4 Clinically Hematologic Abnormalities for Capecitabine

<table>
<thead>
<tr>
<th>Safety Parameter</th>
<th>Capecitabine/Docetaxel (N = 251) n (%)</th>
<th>Docetaxel (N = 255) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia/Granulocytopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>171 (68.1)</td>
<td>195 (76.5)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>122 (48.6)</td>
<td>169 (66.3)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>152 (60.6)</td>
<td>190 (74.5)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>59 (23.5)</td>
<td>84 (32.9)</td>
</tr>
</tbody>
</table>

* collapsed or sponsor-defined term as described in Clinical Study Report SO14999.
Table 4: Most Common Grade 3/4 Blood Chemistry Abnormalities for Capecitabine

<table>
<thead>
<tr>
<th>Safety Parameter</th>
<th>Capecitabine/Docetaxel (N = 251) n (%)</th>
<th>Docetaxel (N = 255) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>23 (9.6)</td>
<td>14 (5.9)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>6 (2.8)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>7 (2.8)</td>
<td>6 (2.8)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>3 (1.2)</td>
<td>3 (1.6)</td>
</tr>
</tbody>
</table>

Approximately two-thirds of patients (65%) in the combination arm required dose reduction of capecitabine alone (4%), docetaxel alone (10%), or both drugs (51%) for adverse events. In the single-agent docetaxel group, 36% of patients required dose reduction. Dose reduction was effective in reducing the recurrence of grade 3/4 treatment-related adverse events in both treatment arms, as shown in the table below.

Table 5: Percentage of Patients with Treatment-Related Adverse Events with Capecitabine Cycles of the Starting Dose (100%), and after Dose Reductions to 75% or 50% of the Starting Dose

<table>
<thead>
<tr>
<th>Combination Therapy Capecitabine/Docetaxel</th>
<th>Single-Agent Arm Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>No. of patients</td>
</tr>
<tr>
<td>100% dose</td>
<td>100% dose</td>
</tr>
<tr>
<td>75% dose</td>
<td>75% dose</td>
</tr>
<tr>
<td>50% dose</td>
<td>50% dose</td>
</tr>
</tbody>
</table>

| 251 | 255 | 251 | 255 |
| 156 | 87  | 156 | 87  |
| 52  | 18  | 52  | 18  |
| 677 | 986 | 618 | 344 |
| 238 | 43  | 238 | 43  |


<table>
<thead>
<tr>
<th>treatment cycles</th>
<th>17</th>
<th>32</th>
<th>49</th>
<th>33</th>
<th>37</th>
<th>33</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0 (none)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>15</td>
<td>21</td>
<td>19</td>
<td>19</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>Grade 2</td>
<td>37</td>
<td>33</td>
<td>22</td>
<td>27</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>Grade 3</td>
<td>23</td>
<td>11</td>
<td>9</td>
<td>12</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Grade 4</td>
<td>8</td>
<td>3</td>
<td>1</td>
<td>9</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

1.6.4 Rationale for the dose of capecitabine in combination with docetaxel

The incidence of grade 3/4 adverse events was greatest during the first two cycles of therapy. In retrospective analyses, it was determined that dose reductions implemented early in therapy (first two cycles) were effective in reducing the incidence of grade 2, 3, and 4 adverse events by cycle (including diarrhea, hand-foot syndrome, stomatitis, and neutropenic fever) and in reducing the recurrence of grade 3/4 treatment-related adverse events. The dose received in each cycle was recorded as a percentage of the planned dose, which was defined using the first dose in cycle 1. In the combination arm the median delivered dose of capecitabine during the course of the study was 77% of the planned dose and the corresponding value for docetaxel was 87%.

The impact of dose reductions on efficacy (time to disease progression or death) was assessed via a Cox proportional hazard regression model, where the time to the first dose reduction (to 75% or 50% of the starting dose) was included in the model as a time dependent covariate. For the combination therapy arm, this retrospective analysis did not show any evidence that dose modification had a negative impact on efficacy. The hazard ratio of 0.84 (dose reduction vs no dose reduction, p=0.43) indicated that time to disease progression was not compromised in patients requiring dose reduction for management of side effects.

All SO14999 patients randomized to the combination therapy arm started with doses of twice-daily 1250 mg/m² capecitabine and 75 mg/m² docetaxel. Given the dose reductions and discontinuations described above, the median dose of capecitabine actually delivered to the patients on this arm during the course of the study was 77% of the planned dose; the corresponding value for docetaxel was 87%[36]. Thus, for this study, patients will receive twice-daily 900 mg/m² of capecitabine and 60 mg/m² of docetaxel in the combination treatment arm.

1.6.5 Rationale for the CEX combination

As the FEC combination is widely used in Europe, the EORTC performed a study on this regimen with capecitabine substituted for 5-FU. Escalated doses of capecitabine were combined with fixed doses of epirubicin (100 mg/m²) and cyclophosphamide (600 mg/m²) as the primary treatment for large operable or locally advanced/inflammatory breast cancer. The regimen given every 21 days is referred as CEX[69]. The defined dose levels of capecitabine were twice-daily.
A maximum of six cycles of therapy was planned. An initial cohort of 3 patients had to be treated at each dose level, with a minimum of four cycles in total to be completed by these 3 patients before including new patients at the next dose level. Dose escalation to the next dose level was allowed when no dose-limiting toxicity (DLT) for 3 patients or no more than one DLT for 6 patients was registered. If ≥ 2 patients developed a DLT, the maximum tolerated dose was reached, and the previous dose was defined as the recommended dose for phase II studies. DLT was defined as (1) febrile neutropenia with absolute neutrophil count (ANC) < 1.0 x 10^9/L and a single oral temperature > 38.5°C; (2) grade 4 neutropenia lasting > 7 days; (3) grade 4 thrombocytopenia; (4) grade 3-4 non-haematological toxicity other than inadequately prevented vomiting; and (5) discontinuation of capecitabine for more than eight doses due to toxicity (other than a grade 3 or 4 non-haematological toxicity already counted as a DLT).

A total of 23 patients were enrolled in the study. A total of 117 cycles were delivered. The median delivered number of cycles was 6 (range 1-6), and the median time on study was 18 weeks (range 3-24 weeks). All the planned dose levels were evaluated. The number of patients entered at dose levels 1, 2, 3 and 4 were 3, 3, 15 and 2, respectively.

No DLTs occurred at dose levels 1, 2 and 3. At dose level 4, 2 out of 2 patients presented DLTs. At dose level 4, no additional patients were entered and dose level 3 was considered as a possible recommended dose for phase II studies. A total of 15 patients were entered, and 80 cycles were delivered at this dose level. During the entire treatment period, a total of 32 DLTs were encountered. DLTs that occurred more than once were grade 3 febrile neutropenia, fatigue, PPE, nausea, stomatitis and hypocalcaemia. Grade 3 PPE was reported only at dose level 3.

Capecitabine treatment had to be interrupted in 12 patients (52%) and in 16 cycles (14%). The vast majority of treatment interruptions occurred at dose level 3 (7 patients or 47% of patients at this dose level; 12 cycles or 15% of cycles given at this level). The median duration of treatment interruption was 4.5 days (range 0.5-14 days), and the median number of cycles interrupted per patient was 2 (range 1-3). Capecitabine treatment dose reductions were required in 4 patients (27%) and nine cycles (11%) at dose level 3. Overall, at dose level 3, 8 patients (53%) and 21 cycles (26%) required a capecitabine treatment modification (interruption and/or reduction). The most common reasons for capecitabine treatment modification at dose level 3 were nausea/vomiting (n = 5), mucositis (n = 2), diarrhea (n = 2) and PPE (n = 2). Epirubicin was reduced by 25% in 5 patients and 17 cycles; cyclophosphamide was reduced by the same amount in 4 patients and 16 cycles. All the dose reductions were performed at dose level 3. Treatment delay (5 patients; seven cycles) was exclusively required at dose level 3.
Only 47% of the patients treated at dose level 3 received 90% or more of the
planned capecitabine dose intensity. The high rate of capecitabine treatment
modification at dose level 3 led to a median relative dose intensity of 85.7%. The
median delivered dose intensity was slightly higher at dose level 2 than at dose
levels 3 and 4. Reasons for stopping study treatment were treatment completion
(18 patients, 78%), excessive toxicity (3 patients) and patient’s request
(2 patients). Nineteen patients (83%) achieved an objective response.

Based on the study the recommended dose of capecitabine for further studies is
twice-daily 900 mg/m² days 1-15 followed by a one-week break, with a cycle
length of 21 days.

1.6.6  Rationale for anastrozole in postmenopausal patients

Recent early results indicate that aromatase inhibitors might further improve
results on tamoxifen in the adjuvant setting. In addition side effects of long-term
use might decrease (endometrial cancer, thromboembolic disorders). In a
randomized study enrolling 9366 post-menopausal patients with invasive
operable breast cancer who had completed primary therapy and were eligible to
receive adjuvant hormonal therapy, tamoxifen was compared to anastrozole
alone and the combination of anastrozole plus tamoxifen for 5 years. Median
follow-up was 33.3 months. Eighty-four percent of the patients were known to be
hormone-receptor-positive. Disease-free survival at 3 years was 89.4% on
anastrozole and 87.4% on tamoxifen (hazard ratio 0.83 [95% CI 0.71-0.96],
p = 0.013). Results with the combination were not significantly different from
those with tamoxifen alone (87.2%, 1.02 [0.89-1.18], p = 0.8). The improvement
in DFS with anastrozole was seen in the subgroup of hormone-receptor-positive
patients, but not the receptor-negative patients. Incidence of contralateral breast
cancer was significantly lower with anastrozole than with tamoxifen (odds ratio
0.42 [0.22-0.79], p = 0.007). Anastrozole was significantly better tolerated than
tamoxifen with respect to endometrial cancer (p = 0.02), vaginal bleeding and
discharge (p < 0.0001 for both), cerebrovascular events (p = 0.0006), venous
thromboembolic events (p = 0.0006), and hot flushes (p < 0.0001). Tamoxifen
was significantly better tolerated than anastrozole with respect to
musculoskeletal disorders and fractures (p < 0.0001 for both)[70].

1.6.7  Rationale for patient selection

Although it seems that all patients benefit from adjuvant systemic therapy in
terms of relative risk reduction, the absolute risk reduction in good risk patients is
moderate. In these cases the possible adverse events of systemic therapy have
to be weighed against the anticipated benefits. Thus patient selection in this trial
is risk adapted. Based on a large database on Finnish breast cancer patients
with a more than 25% risk of breast cancer recurrence have been identified
based on certain risk factors to be included in the study[71].
2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to compare the recurrence-free survival of docetaxel followed by CEF compared to docetaxel with capecitabine followed by CEX in the adjuvant treatment of patients with early stage breast cancer.

2.2 Secondary Objectives

Secondary objectives include the evaluation and comparison between the two treatment arms of:

- Safety profile, using the CTCAE (version 3.0)
- Overall survival

3. STUDY DESIGN AND DURATION

3.1 Overview of Study Design and Dosing Regimen

This is an open-label, two-arm, multi-center, randomized phase III study of docetaxel followed by CEF vs docetaxel with capecitabine followed by CEX in the adjuvant treatment of patients with early stage breast cancer. Three cycles of docetaxel (with or without capecitabine) will be followed by three cycles of CEX or CEF, respectively. Patients will be subsequently followed for 5 years.

3.2 Number of Patients/Assignment to Treatment Arms

Approximately 1,500 patients will be enrolled in this study. Patients will be randomized (stratified by number of positive nodes (≤ 3, > 3), HER-2 status (+ve, -ve) and study center) between the two treatment arms in a 1:1 ratio.

The HER-2 status will be reported during the randomization procedure (see Section 6.4).

Randomization will be made using a central computer-generated randomization system through the HUS Department of Oncology:

<table>
<thead>
<tr>
<th>Contact phone numbers:</th>
<th>(09) 471 753 84</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>050 427 1362</td>
</tr>
<tr>
<td></td>
<td>(09) 471 732 08</td>
</tr>
<tr>
<td>Study code name:</td>
<td>FinXX</td>
</tr>
<tr>
<td>Required information:</td>
<td>Patient’s name and an identity code based on the date of birth</td>
</tr>
<tr>
<td></td>
<td>Study site</td>
</tr>
<tr>
<td></td>
<td>The number of metastatic regional lymph nodes</td>
</tr>
</tbody>
</table>
Her-2 status

Patient numbers will be chronologically assigned at time of study randomization. All patient numbers across the study will be unique.

3.3 Centers

This is a multi-center Finnish-Scandinavian study with 10 to 25 centers planning to participate.

3.4 Treatment Duration

3.4.1 Study treatment phase

Patients will receive 3 cycles (9 weeks) of docetaxel followed by 3 cycles (9 weeks) of CEF or 3 cycles (9 weeks) of docetaxel with capecitabine followed by 3 cycles (9 weeks) of CEX.

Locoregional radiotherapy will be given according to institutional practice within approximately 3 weeks of completing adjuvant chemotherapy.

Within 2 months of completing chemotherapy, all patients with ER and/or PgR positive disease will receive adjuvant endocrine therapy. This will consist of 1 mg p.o. anastrozole (Arimidex®) given for 60 months in women who are post-menopausal prior to chemotherapy (no menstrual periods for > 6 months) and tamoxifen 20 mg for 60 months in women who are pre-menopausal prior to chemotherapy.

3.4.2 Discontinuation of therapy

Patients are expected to complete study treatment unless they experience disease recurrence, intolerable toxicity or patient withdrawal of consent. Patients experiencing disease recurrence (metastatic disease, local relapse or new breast cancer primary) must be taken off treatment at time of recurrence.

4. STUDY POPULATION

4.1 Target Population

The intended population for this study is female patients with invasive early breast cancer with no distant metastases, who have a > 25% risk of distant recurrence within 5 years from the time of diagnosis.

Under no circumstances are patients who enroll in this study and who have completed treatment as specified, permitted to be re-randomized to this study and enrolled for a second course of treatment.

4.2 Inclusion Criteria

To be eligible for inclusion in the study, each patient must fulfill each of the criteria below.
1. Have provided written informed consent prior to study-specific screening procedures, with the understanding that the patient has the right to withdraw from the study at any time, without prejudice.

2. Be female and ≥ 18 years of age.

3. Have histologically confirmed invasive breast cancer.

4. High risk of breast cancer recurrence (≥ 25% within the first 5 years without adjuvant therapy; > 35% within the first 10 years) with one of the following:
   i. Regional node positive disease (pN+; tumor cells or tumor cell clusters < 0.2 mm in diameter are not counted as metastases)
   ii. Pathological N0, and PgR-, and tumor size > 20 mm

4.3 Exclusion Criteria

Patients who fulfill any of the following criteria will be excluded:

1. > 66 years of age.

2. "Special type" histology (mucinous, papillary, medullary, or tubular breast cancer), when pN0.

3. ER, PgR and HER-2 status (via in situ hybridization or immunohistochemistry, see Section 6.4) not determined.

4. Presence of distant metastases.

5. Previous chemotherapy in the neoadjuvant setting.

6. Non-ambulatory or WHO performance status > 1 (see Appendix 1).

7. Pregnant or lactating women. Women of childbearing potential (menstruating within 6 months of study entry or with no hysterectomy and age ≤ 55) with either a positive or no pregnancy test at baseline.

8. Women of childbearing potential unless using a reliable and appropriate contraceptive method. (Post-menopausal women must have been amenorrheic for at least 6 months to be considered of non-childbearing potential).

9. More than 12 weeks between breast surgery and date of randomization.

10. Organ allografts with requirement for immunosuppressive therapy.

11. Major surgery (except breast surgery) within 4 weeks prior to study treatment start, or lack of complete recovery from the effects of major surgery.

12. Participation in any investigational drug study within 4 weeks preceding treatment start.

13. Patients with a history of uncontrolled seizures, central nervous system disorders or psychiatric disability judged by the investigator to be clinically
significant precluding informed consent or interfering with compliance for oral drug intake.

14. History of another malignancy within the last five years except cured basal cell carcinoma of skin or carcinoma in situ of the uterine cervix.

15. Clinically significant (i.e. active) cardiac disease (e.g. congestive heart failure, symptomatic coronary artery disease and cardiac arrhythmia not well controlled with medication) or myocardial infarction within the last 12 months.

16. Abnormal laboratory values:
   - Hemoglobin < 10.0 g/dL, neutrophils < 1.5 x 10^9/L, platelet count < 120 x 10^9/L
   - Serum creatinine > 1.5 x Upper Limit of Normal (ULN)
   - Creatinine clearance (calculated per Cockroft and Gault, see Appendix 2) < 50 mL/min
   - Serum bilirubin > ULN
   - ALAT > 1.5 x ULN
   - Alkaline phosphatase > 2.5 x ULN

17. Serious uncontrolled intercurrent infections or other serious uncontrolled concomitant disease.

18. Lack of physical integrity of the upper gastrointestinal tract or those who have clinically significant malabsorption syndrome.

19. Inability to swallow tablets.

20. Life expectancy of less than 3 months.

21. Unwilling or unable to comply with the protocol for the duration of the study.

22. Requirement for concurrent use of the antiviral agent sorivudine or chemically related analogues, such as brivudine.

5. **Concomitant Medication and Treatment**

At study initiation, patients should continue with their concomitant medications, as directed by their physician.

All concomitant medication must be recorded on the baseline Case Report Form (CRF). Additionally, any cancer therapeutic or surgical procedure performed during the study period should be recorded in the hospital case records including the date, indication, description of the procedure(s) and any clinical findings.

Patients should not routinely receive prophylactic antibiotics during the study.
5.1 Palliative And Supportive Care

Palliative and supportive care for disease-related symptoms will be offered as needed to all patients in this study.

5.2 Hematopoietic Growth Factors

Hematopoietic growth factors may be used to treat symptomatic neutropenia but should not be used prophylactically.

5.3 Other Supportive Measures

The use of drugs with laxative properties should be avoided. Use of vitamin B6 pyridoxine (50-150 mg twice-daily) is permitted for symptomatic or secondary prophylactic treatment of hand-foot syndrome.

5.4 Oral Coumarin-Derived Anticoagulants

Patients receiving concomitant capecitabine or 5-FU and oral coumarin-derived anticoagulants should have their anticoagulant response (INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose accordingly. Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking capecitabine concomitantly with coumarin-derived anticoagulants such as warfarin and phenprocoumon. A PK interaction has been observed. The use of low molecular weight heparin instead of coumarin is at the discretion of the Investigator.

5.5 Phenytoin

Increased phenytoin plasma concentrations have been reported during concomitant use of capecitabine with phenytoin. Formal drug-drug interaction studies with phenytoin have not been conducted. Patients taking phenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations and associated clinical symptoms.

5.6 Allopurinol

Interactions with allopurinol have been observed for 5-FU; with possible decreased efficacy of 5-FU. Concomitant use of allopurinol with capecitabine should be avoided.

5.7 Antivirals and Antiprotozoals

Capecitabine or 5-FU should not be administered together with the antiviral drug sorivudine or its chemically related analogues, such as brivudine. A clinically significant drug-drug interaction between sorivudine and 5-FU, resulting from the inhibition of DPD by sorivudine, has been described in the literature. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal. Metronidazole increased the toxicity of fluorouracil in patients with colorectal cancer, apparently by reducing the clearance of the antineoplastic. As it has been described in the literature, caution should be exercised.
5.8 Gastrointestinal Drugs

Pretreatment with cimetidine for 4 weeks led to increased plasma concentrations of fluorouracil following intravenous and oral administration in six patients. The effect was probably due to a combination of hepatic enzyme inhibition and reduced hepatic blood flow. No such effect was seen following single doses of cimetidine in five patients or pretreatment for just one week in six. Care is required in patients taking both drugs simultaneously.

5.9 Other Anticancer Therapies

The use of other cytotoxic agents, investigational drugs, breast cancer active or passive immunotherapy or hormonal therapy (other than that specified by the protocol) is not allowed during the study. Patients requiring radiotherapy during study to other body sites than the breast and the regional lymphatics will be considered to have had relapsed and should come off study before receipt of radiotherapy. The adjuvant use of trastuzumab (Herceptin®) is allowed provided that breast cancer is HER2-positive. HER2-positivity is recommended to be confirmed by FISH or CISH analysis for the presence of erbB2 gene amplification, but strong membranous staining (+++) in 80% or more of cancer cells in immunohistochemistry is also considered acceptable.

6. STUDY EVALUATIONS

6.1 Screening Examination and Eligibility Screening Form

Written informed consent must be obtained before any study-specific screening procedures are performed. Study-specific screening procedures do not include staging examinations or laboratory investigations carried out as institutional praxis.

Patients will be screened for eligibility to enter the study, based on the eligibility criteria detailed in Section 4.

It is recommended that patients who are considered for study entry, but who fail to meet the eligibility requirements, should also have an Eligibility Screening Form (ESF) completed with the reason for lack of eligibility given, since this provides information on the selection of the trial population. These completed ESFs should be kept at the investigational site.

Patient numbers will be assigned by the central randomization center as patients are enrolled in the study.

The screening procedure may be done in two stages. The first group of assessments can be done at any time within 4 weeks prior to treatment start (day –28 to day 1). The second group must be done within 7 days prior to treatment start. If the assessments are undertaken on day 1, the investigator must have reviewed the results prior to study drug administration. Refer to the Schedule of Assessments and Procedures.
6.2 Demographic Data

Demographic data includes data of birth and menopausal status.

6.3 Medical History

Medical history includes previous and concomitant diseases and concomitant medications.

6.4 Cancer / Treatment History

The assessment of cancer / treatment history includes:

- Histological type, histological grade, number of axillary metastases
- Hormonal status (i.e. estrogen/progesterone receptor status), TNM classification, HER-2 status, Ki-67 (optional)
- Date of diagnosis, type of surgery, tissue block number/code

HER-2 status can be tested using either the in situ hybridization method or immunohistochemistry. HER-2 positivity is confirmed with immunohistochemistry when at least 80% of the cells are stained (corresponding to 3rd degree staining).

If the HER-2 status has been tested with both the in situ hybridization method and with immunohistochemistry, only the in situ hybridization result will be reported. The HER-2 status testing method will be reported during the randomization procedure (see Section 3.2).

6.5 General Physical Examination And Vital Signs

The general physical examination and assessment of vital signs includes:

- Clinical examination
- WHO Performance Status (see Appendix 1)
- Height (baseline only)
- Weight
- Pulse rate
- Blood pressure

6.6 Pregnancy Test

Pregnancy tests will be done as applicable, and are required in women who are pre-menopausal or of childbearing potential, and in post-menopausal women who have been amenorrheic for less than 6 months.

S-FSH will be measured if the patient's age is < 55 years and a hysterectomy has been done to confirm the post-menopausal status.

6.7 Staging Examinations

Staging examinations are mandatory only when ≥ pN4+. These examinations include:

- chest CT or X-ray,
- bone scan
- CT, MRI or ultrasound of abdomen
At time of study entry, all staging studies must show no evidence of metastatic disease, including suspicious lymphadenopathy or skin nodules on physical exam. Staging studies are mandatory in patients who have 4 or more positive axillary nodes (pN4+ or greater). All other staging studies are at the treating physician’s discretion. Any other staging test (e.g., CT scans, MRI studies, ultrasound of abdomen, PET scans) must be negative for metastatic disease.

6.8 Laboratory Assessments

Normal ranges for the study laboratory parameters must be supplied to the Clinical Trial Monitor before the study starts.

During the Study Treatment Phase, all routine laboratory tests during treatment must be performed within 3 days prior to the start of a new chemotherapy cycle and reviewed by the investigator at the scheduled study visit before administration of study medications. When grade 3 or 4 laboratory abnormalities occur, the pertinent tests should be regularly repeated until resolution to less than or equal to baseline. The results are to be entered into the CRF. The following laboratory tests are to be done:

- Hematology (blood cell counts including the neutrophil count)
- Serum chemistries (serum creatinine, total bilirubin, ALAT, alkaline phosphatase)

6.9 Assessment of Research Blood / Serum Sample (Optional)

One serum sample, that will be divided into two aliquots and one whole blood sample (5 mL citrate) will be taken at time of screening, at time of final visit and at follow up visits 1, 3 and 5 years post-randomization.

6.10. Assessment of Quality of Life (Optional)

Quality of life (QOL) will be assessed using the FACT-B instrument. QOL will be assessed at baseline prior to starting the study treatment, after the T/TX part of chemotherapy, after the CEF/CEX part of chemotherapy, and at the 12-month follow-up visit.

7. STUDY MEDICATION

7.1 Dose and Schedule of Study Medications

Table 6 - Study Medication Regimens

<table>
<thead>
<tr>
<th>Arm</th>
<th>Drug</th>
<th>Dose</th>
<th>Treatment Days*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Docetaxel</td>
<td>80 mg/m² via 60-minute IV infusion</td>
<td>Day 1 Q3W for 3 cycles</td>
</tr>
<tr>
<td>Followed by</td>
<td>Docetaxel</td>
<td>Capecitabine</td>
<td>CEX</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------</td>
<td>--------------</td>
<td>-----</td>
</tr>
<tr>
<td>CEF</td>
<td>600 mg/m² via IV</td>
<td>900 mg/m² twice-daily (one dose in the morning and one in the evening)</td>
<td>cyclophosphamide: 600 mg/m² via IV</td>
</tr>
<tr>
<td></td>
<td>epirubicin: 75 mg/m² via IV</td>
<td>for a total daily dose of 1800 mg/m²</td>
<td>Day 1 Q3W for 3 cycles</td>
</tr>
</tbody>
</table>

* the first capecitabine dose of each cycle will be administered as the evening dose on day 1 and the last dose of each cycle is scheduled the morning of day 15, followed by a 7-day rest period.

Upon completion of chemotherapy, all patients who have ER +ve and/or PgR +ve disease will also receive anastrozole or tamoxifen (depending on the patient’s menstrual status). Anastrozole or tamoxifen should be initiated within 2 months of completing chemotherapy.

**Table 7: Endocrine Therapy**

If post-menopausal prior to chemotherapy (no menstrual periods for > 6 months):
- Anastrozole (Arimidex) 1 mg p.o. Daily for 60 months
- Tamoxifen 20 mg Daily for 60 months

If pre-menopausal prior to chemotherapy:
- Anastrozole 1 mg p.o. Daily for 60 months
- Tamoxifen 20 mg Daily for 60 months

Locoregional radiotherapy will be given according to institutional practice, and will be started within approximately 3 weeks of completing adjuvant chemotherapy.

### 7.1.1 Arm A dosing regimen

**Docetaxel** will be given at 80 mg/m² as a 60-minute intravenous infusion, on day 1 of each 3-week cycle. Three cycles in total will be given. The dose to be administered should be equal to the calculated dose of 80 mg/m² x the body surface area.
The docetaxel package insert states that all patients ought to be pretreated with oral corticosteroids to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. The recommended premedication is dexamethasone given as follows:\cite{45}:

- 7.5 to 8 mg dose of dexamethasone the night prior to each docetaxel administration,
- 7.5 to 8 mg dose in the morning, one hour prior to the docetaxel administration,
- Subsequent 7.5 to 8 mg dose in the evening of the day of docetaxel administration,
- 7.5 to 8 mg dose in the morning and evening of the day after docetaxel administration,
- Final 7.5 to 8 mg dose two mornings after the docetaxel administration.

Antihistamines have not been shown to be useful in controlling fluid retention due to docetaxel administration\cite{45}.

**CEF:**

CEF will be administered on day 1 of every 3-week cycle. Three cycles in total will be given. Regimen consists of:

- cyclophosphamide: 600 mg/m\textsuperscript{2} via IV
- epirubicin: 75 mg/m\textsuperscript{2} via IV
- 5-FU: 600 mg/m\textsuperscript{2} via IV

### 7.1.2 Arm B dosing regimen

**Capecitabine** will be taken as twice-daily 900 mg/m\textsuperscript{2} oral doses (total daily dose of 1800 mg/m\textsuperscript{2}) morning and evening in 3-week cycles consisting of 2 weeks of capecitabine treatment followed by 1 week without capecitabine treatment. The first dose of each cycle will be administered as the evening dose on day 1 and the last dose of each cycle is scheduled the morning of day 15, followed by a 7-day rest period. This provides for a total of 28 single doses per cycle over 15 calendar days. The morning and evening dose should be given approximately 12 hours apart, and taken within 30 minutes after the ingestion of food with approximately 200 mL of water, ideally after the breakfast and evening meal. Therefore, a patient with a body surface area of 1.70 m\textsuperscript{2} would be administered a total daily dose of 3000 mg. The patient would receive three 500 mg tablets in the morning and three 500 mg tablets in the evening. Every 3 weeks the patient will be given a sufficient supply of study medication to accommodate one cycle of capecitabine treatment.

**Docetaxel** will be given at 60 mg/m\textsuperscript{2} as a 60-minute intravenous infusion, on day 1 of each 3-week cycle. The dose to be administered should be equal to the calculated dose of 60 mg/m\textsuperscript{2} x body surface area.

The same instructions outlined above in Arm A should be followed with regard to the premedication of patients with corticosteroids prior to the administration of docetaxel.
CEX:

CEX will be administered on day 1 of every 3-week cycle. Three cycles in total will be given. Regimen consists of:

- cyclophosphamide: 600 mg/m² via IV
- epirubicin: 75 mg/m² via IV
- capecitabine: 900 mg/m² orally twice-daily, days 1-15 (the first dose of each cycle will be administered as the evening dose on day 1 and the last dose of each cycle is scheduled the morning of day 15, followed by a 7-day rest period).

7.1.3 Anastrozole (Arimidex®)

Upon completion of chemotherapy, all patients who have ER +ve and/or PgR +ve disease and who are post-menopausal prior to chemotherapy (no menstrual periods for > 6 months) will also receive anastrozole.

Based on concerns regarding an increased risk of deep vein thrombosis and substantially reduced efficacy of chemotherapy, anastrozole should not be given concurrently with chemotherapy[72]. Anastrozole, however, should be initiated within 2 months of completing chemotherapy at a dose of 1 mg p.o., given daily for 60 months.

Anastrozole can be given concurrently with radiotherapy, as this is not associated with an increased risk of adverse effects or antagonistic anti-cancer effects.

7.1.4 Tamoxifen

Upon completion of chemotherapy, all patients who have ER +ve and/or PgR +ve disease and who are pre-menopausal prior to chemotherapy will also receive tamoxifen.

Based on concerns regarding an increased risk of deep vein thrombosis and substantially reduced efficacy of chemotherapy, tamoxifen should not be given concurrently with chemotherapy[72]. Tamoxifen, however, should be initiated within 2 months of completing chemotherapy at a dose of 20 mg p.o., given daily for 60 months.

Tamoxifen can be given concurrently with radiotherapy, as this is not associated with an increased risk of adverse effects or antagonistic anti-cancer effects.

7.1.5 General instructions for chemotherapy dosing

Specific Instructions for Capecitabine Dosing

In order to identify the appropriate daily dose of capecitabine for the patient, perform the following steps:

- Determine the BSA:
- Measure the patient's actual height and weight,
- Derive the Body Surface Area using the nomogram found in Appendix 3.
• Look up the specific dose:

Based on the derived BSA, find the dose to be taken for that BSA by looking it up in the capecitabine dosing table in Appendix 4 (for combination with docetaxel and for CEX).

(DO NOT multiply BSA x the total daily dose: THIS IS AN ERROR).

General Instructions for both Capecitabine and Docetaxel Dosing

Though the weight of the patient may change throughout the study, the surface area will be assumed to stay close to that measured at baseline (i.e. no dose adjustments for changes in body weight will be done). Dose reductions during treatment should be based on adverse events.

7.1.6 Preparation and administration of study medications

Capecitabine (Xeloda®, Hoffmann-La Roche) will be supplied as film-coated 500 mg tablets. The tablets will be packed in polyethylene bottles containing 120 tablets. The tablets are not scored and should not be split. Capecitabine must be stored in a locked facility in a dry place, at room temperature and out of reach of children. Capecitabine will be labeled according to the local law requirements.

Docetaxel (Taxotere®, Aventis) is obtainable commercially in vials of 80 mg (2.0 mL) and 20 mg (0.5 mL) and supplied with solvent. Once reconstituted with the solvent, the docetaxel premix solution has a concentration of 10 mg/mL. This should be further diluted with either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 to 0.9 mg/mL, prior to administration. Docetaxel is compatible with commonly available administration sets including PVC sets. Docetaxel should be supplied from the site’s commercial supplies.

7.2 Compliance with Study Medication

7.2.1 Docetaxel (Arms A and B)

The clinic administration records will be employed to monitor compliance with docetaxel.

7.2.2 Capecitabine (Arm B)

7.2.2.1 Accountability of study medication supply

The investigator or research nurse should verify compliance at every visit.

For each study treatment cycle, study staff should:

1) discuss the number of capecitabine tablets taken each day by the patient over the previous cycle,

2) record this information in the CRF

3) count the tablets of each strength returned by the patient,
4) enter the number of returned tablets in the CRF section for recording capecitabine tablets dispensed and returned,

5) determine if the patient took all planned study medication for the preceding cycle,

6) document and reconcile any discrepancy between the medication returned and the medication that the patient actually took on for that cycle.

A pre-printed drug dispensing log is provided by Roche. It must be kept current and should contain the following information:

1. Identification of the patient to whom the drug was dispensed,
2. Batch numbers of the drug that was dispensed,
3. Date(s) and quantity of the drug dispensed to the patient,
4. Date(s) and quantity of the drug returned by the patient.

The inventory must be available for inspection by the Clinical Trial Monitor. All unused capecitabine medication and empty or partially empty medication bottles must be returned by the patients to the investigator at every other visit for drug compliance assessment and by the investigator to Roche at the end of the study.

All capecitabine medication supplies (empty or partially empty containers, as well as unused medication) must be available for inspection, at every other monitoring visit.

When requested in writing to Roche, unused drug supplies may be destroyed by the investigator provided such disposition does not expose humans to risks from the drug. Records shall be maintained by the investigator of any such alternative disposition of the test drug. These records must show the identification and quantity of each unit disposed of, the method of destruction (taking into account the requirements of the local law), and the person who disposed of the test substance. Such records shall be submitted to Roche.

8. SAFETY INSTRUCTIONS AND GUIDANCE

8.1 Adverse Events and Laboratory Abnormalities

8.1.1 Clinical adverse events

An adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product. Pre-existing conditions that worsen during a study are to be reported as adverse events.

All clinical adverse events (AEs) encountered during the study treatment and up to 28 days after last study drug administration will be reported on the AE pages.
of the CRF. Data recorded in the CRF for each adverse event will include a description of the adverse event, cycle of onset and severity. Additional data is required for serious adverse events (see Appendix 7).

The intensity of clinical adverse events will be graded according to the CTCAE grading system (version 3.0) in the toxicity categories that have recommended gradings. Clinical adverse events that do not have recommended gradings will be graded according to the following intensity four point scale: mild, moderate, severe or life-threatening. Definition of the grades can be found below.

### Table 8 - The Intensity of Adverse Events: Definition of Grades

<table>
<thead>
<tr>
<th>Mild or Grade 1</th>
<th>discomfort noticed but no disruption of normal daily activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate or Grade 2</td>
<td>discomfort sufficient to reduce or affect daily activity</td>
</tr>
<tr>
<td>Severe or Grade 3</td>
<td>inability to work or perform normal daily activity</td>
</tr>
<tr>
<td>Life Threatening or Grade 4</td>
<td>represents an immediate threat to life</td>
</tr>
</tbody>
</table>

#### 8.1.2 Laboratory test abnormalities

Laboratory test results required by the protocol will be recorded on the laboratory results pages of the CRF.

#### 8.2 Handling of Safety Parameters

**8.2.1 Serious Adverse Events**

Serious Adverse Events

Any clinical adverse event or abnormal laboratory test value that is **serious, unexpected and thought to be related to study treatment** must be reported by the investigator to Roche and the Principal Investigator (Heikki Joensuu, M.D., Department of Oncology, Helsinki University Central Hospital, Haartmaninkatu 4, FIN-00029 Helsinki, Finland; Tel. +358-9-471 73208, Fax +358-9-471 74202) within one working day of occurrence (expedited reporting) according to the requirement of the national and European authorities. **Excluded** from the requirement of expedited reporting are the following expected events, although serious (Grade 3 or 4):

- febrile neutropenia with or without sepsis,
- grade 3 infections
- stomatitis (grade 3 or 4),
- diarrhea (grade 3)
- nausea (grade 3),
- hand-foot syndrome (grade 3)
-fatigue (grade 3 or 4)
-myalgia (grade 3)
-grade 3 and 4 blood cell counts
- other grade 3 laboratory values

These events (except for grade 3 or 4 blood cell counts, which occur in most patients and are considered as an integral part of effective therapy) will be reported directly to the Principal Investigator (Heikki Joensuu, M.D., Department of Oncology, Helsinki University Central Hospital, Haartmaninkatu 4, FIN-00029 Helsinki, Finland; Tel. +358-9-471 73208, Fax +358-9-471 74202).

However, in case of unexpected outcome of these events, the reaction should be reported expedited to Roche. Reportable adverse events should be reported according to national and European regulations, preferable using the CIOMS form.

Serious adverse events will be reported during the study treatment, and for up to 28 days after the last intake of study drug.

The definition and reporting requirements of ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 will be adhered to. Complete information can be found in Appendix 7 of the protocol.

**8.2.2 Treatment and follow-up of adverse events**

Adverse events, especially those for which the relationship to study medication is not “unrelated”, should be followed up (even after the patient has completed her study treatment) until they have returned to baseline status. If a clear explanation is established it should be recorded on the CRF. Adverse events and treatments will be recorded throughout study treatment and for 28 days after the last intake of study drug. Unrelated, mild or moderate events must be followed for 28 days after the last study drug administration. Severe, life-threatening or related events must be followed until resolution or stabilization, the patient’s death, the start of a new cancer therapy or the relationship is re-assessed.

**8.2.3 Follow-up of abnormal laboratory test values**

In the event of unexplained abnormal laboratory test values, the tests should be repeated and followed up until they have returned to baseline and/or an adequate explanation of the abnormality is found.

**8.2.4 Vital signs and other assessments**

Any symptomatic treatment for abnormal vital signs (weight and WHO performance status) should be clearly recorded in the CRF.
8.2.5 Pregnancy

A female patient must be instructed to stop taking capecitabine and docetaxel and immediately inform the investigator if she becomes pregnant during the study. The investigator should counsel the patient, discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. The investigator should report all pregnancies within 24 hours to Roche and the principal investigator, using the form for Serious Adverse Events. Pregnancies occurring up to 90 days after the completion of capecitabine must also be reported to the investigator.

8.3 Dose Modification for Toxicity

8.3.1 Special notes regarding dose modifications for toxicity

- Dose reductions should follow the guidelines found below and the instructions outlined in Table 9. Dosing tables corresponding to capecitabine dose reductions may be found in Appendix 4 (in combination with docetaxel and with CEX).

- For any adverse event apparent at baseline, the dose modifications will apply according to the corresponding shift in toxicity grade, if the investigator feels it is appropriate. For example, if a patient has grade 1 asthenia at baseline that increases to grade 2 during treatment this will be considered a shift of 1 grade and treated as a grade 1 toxicity for dose modification purposes.

- For toxicities that are considered by the investigator unlikely to develop into serious or life-threatening events (e.g. alopecia, altered taste etc.), treatment will be continued at the same dose without reduction or interruption. In addition, no dose reductions or interruptions will be required for anemia (non-hemolytic) as it can be satisfactorily managed by transfusions.

- If any grade 1 toxicity or any grade of alopecia occurs, treatment will be continued at the original dose without interruption.

- Capecitabine treatment interruptions are regarded as lost treatment days and the planned treatment schedule for future cycles should be maintained (see Appendix 5). Missed doses due to treatment interruptions should not be replaced.

- If toxicity requires a dosing delay or interruption for more than three weeks, the patient will be withdrawn from the study for toxicity reasons. In such cases (if this occurs during treatment with capecitabine/docetaxel or docetaxel) the remaining chemotherapy cycles should be replaced by an equal number of cycles of CEX or CEF75 depending on the group (CEX in the TX arm and CEF in the T arm), respectively, unless contraindicated.
• Where several toxicities with different grades or severity occur at the same
time, the dose modifications applied should be the greatest reduction
applicable.

• When, at the beginning of a treatment cycle, any intended chemotherapeutic
agent is delayed, all agents should be delayed. Treatment should only be
restarted when the requirements for restarting both docetaxel and
capcitabine are met or when docetaxel has to be discontinued but the
requirements for restarting capcitabine alone are met.

• If the calculated creatinine clearance decreases during treatment to a value of
\(< 50\) mL/min (due to an increase in serum creatinine or decrease in body
weight), this change is not, by itself, a reason for a dose reduction. Dose
reductions during treatment should be based on adverse events.

• CEF and CEX are started at the full doses even when dose reductions have
been made during T/TX-therapy. Exception: When the dose of capcitabine
has been reduced due to the hand-foot syndrome or diarrhoea, CEX may be
started at the reduced capcitabine dose level.

In Table 9, general guidelines for dose modifications for toxicity are described.
However, these instructions do not apply to neutropenia or other specific
toxicities for which instructions may be found throughout this protocol.

If, in the opinion of the investigator, a toxicity is considered to be due solely to
one drug (e.g. hand-foot syndrome, neuropathy, fluid retention, liver toxicity,
diarrhoea), the dose of the other drug does not require modification.

8.3.2 Non-hematologic toxicity

Table 9 Chemotherapy Dose Modification Schedule

<table>
<thead>
<tr>
<th>Toxicity CTCAE grades</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st appearance of any toxicity</td>
<td>Toxicity occurring during the 15 days of capcitabine treatment: interrupt capcitabine treatment until resolved to grade 0-1. Treatment may be resumed during the cycle at 80% of the capcitabine dose. Doses of capcitabine missed during a treatment cycle are not to be replaced. Prophylaxis for toxicities should be implemented where possible.</td>
<td>Chemistry-related toxicity persisting at the time the next treatment is due: delay treatment until resolved to grade 0-1, then continue all chemotherapeutic agents at 80% of the original doses.</td>
<td>Discontinue chemotherapy unless treating physician considers it to be in the best interest of the patient. Continue with chemotherapy at 80% of the original doses.</td>
</tr>
<tr>
<td>Upon resolution to grade 0-1, subsequent treatment cycles should be continued at the original chemotherapeutic doses.</td>
<td>Upon resolution to grade 0-1, subsequent treatment cycles should be continued at 80% of the original chemotherapeutic doses.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Toxicity CTCAE grades

<table>
<thead>
<tr>
<th></th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd appearance</td>
<td>Toxicity occurring during the 15 days of capecitabine treatment: interrupt capecitabine treatment until resolved to grade 0-1. Treatment may be resumed during the cycle at 60% of original capecitabine dose. Doses of capecitabine missed during a treatment cycle are not to be replaced. Prophylaxis for toxicities should be implemented where possible. Chemotherapy-related toxicity persisting at the time the next treatment is due: delay treatment until resolved to grade 0-1. For patients developing 2&lt;sup&gt;nd&lt;/sup&gt; occurrence of grade 2 toxicity at any time during the treatment cycle, upon resolution to grade 0-1, subsequent treatment cycles should be continued at 80% of the original chemotherapy doses. Prophylaxis for toxicities should be implemented where possible.</td>
<td>Discontinue treatment, consider continuing with CEF/CEF depending on the allocation group.</td>
<td>Discontinue treatment, consider continuing with CEF/CEX depending on the allocation group.</td>
</tr>
<tr>
<td>of any toxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd appearance</td>
<td>Reduce dose to 60% from the starting dose.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>of any toxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4&lt;sup&gt;th&lt;/sup&gt; appearance of any toxicity</td>
<td>Discontinue chemotherapy.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* *Common Terminology Criteria for Adverse Events (v 3.0) (see Appendix 6).*

### 8.3.3 Special instructions regarding treatment of toxicity

#### 8.3.3.1 Neutropenia

Capecitabine is not expected to worsen or unduly prolong the episode of neutropenia / granulocytopenia. However, administration of capecitabine should be interrupted if grade 4 neutropenia develops. The next treatment cycle can only start once the neutrophil / granulocyte count has recovered to grade 1.
The next chemotherapy cycle (docetaxel or docetaxel with capecitabine) should only be re-administered when the neutrophil count is $\geq 1.5 \times 10^9$/L and platelets $\geq 120 \times 10^9$/L. CEF / CEX can, at the discretion of the treating physician, be re-administered when the neutrophil count is $\geq 1.0 \times 10^9$/L. If neutrophils / platelets are below these values, re-administration is delayed for 3-7 days. If neutrophils/platelets improve over these limits, the treatment is re-administered at the previous dose level. However, if neutrophil count is still $\leq 1.5 \times 10^9$/L, or platelets $< 120 \times 10^9$/L or the treatment is delayed during two subsequent cycles, the next cycle will be administered at 80% of the previous doses.

Patients experiencing absolute neutrophil counts $< 0.5 \times 10^9$/L (grade 4) for more than 1 week or febrile neutropenia (grade 3/4 neutropenia with fever $\geq 38.5^\circ$C) should have the dosage of all chemotherapeutic agents reduced by 20%. Those patients experiencing grade 3/4 neutropenia with a documented infection (clinical or microbiologic) follow the same guidelines as patients with febrile neutropenia. Administration of capecitabine should also be interrupted if any grade 2 clinical event (e.g. diarrhea, stomatitis, fever) coincides with any neutropenic phase. If clinically indicated, the patient should be hospitalized and closely monitored. The next treatment cycle can only start once the neutrophil / granulocyte count has recovered to grade 1.

### 8.3.3.2 Hypersensitivity reactions

Patients who develop severe hypersensitivity reactions (hypotension with a decrease of $\geq 20$ mm Hg, or bronchospasm, or generalized rash/erythema) should stop treatment immediately and be given appropriate therapy. These patients should not be rechallenged with the drug suspected to have caused the hypersensitivity.

### 8.3.3.3 Diarrhea

The use of drugs with laxative properties should be avoided because of the potential for exacerbation of diarrhea. Patients should be advised to contact their physician to discuss any laxative use.

Capecitabine can induce diarrhea, which can sometimes be severe. In patients receiving capecitabine monotherapy, the median time to first occurrence of grade 2-4 diarrhea was 31 days, and median duration of grade 3 or 4 diarrhea was 4.5 days.

Patients with severe diarrhea should be carefully monitored and, if they become dehydrated, should be given fluid and electrolyte replacement. If grade 2, 3 or 4 diarrhea occurs, administration of capecitabine should be immediately interrupted until the diarrhea resolves or decreases in intensity to grade 1. Following grade 2 or higher diarrhea, subsequent doses of capecitabine should be decreased (see Table 9). Standard anti-diarrhea treatments (e.g. loperamide) should be initiated, as medically appropriate, as early as possible. Capecitabine can not be re-started until diarrhea has resolved to grade 0-1 with the last loperamide dose given at least 24 hours beforehand.
8.3.3.4 Grade $\geq$ 2 nausea/vomiting

For nausea and vomiting, the patients must be supplied with anti-emetics in order to treat themselves in case nausea or vomiting occurs at home. The administration of 5-HT3 antagonists is recommended for docetaxel-induced emesis and metoclopramide +/- 5-HT3 antagonists for capecitabine-induced nausea. Adequate secondary therapeutic and prophylactic treatment has to be initiated once nausea or vomiting has occurred. If the nausea/vomiting recurs despite adequate prophylaxis, then dose modifications should also be made according to Table 9 above.

8.3.3.5 Grade 2/3 Hand-Foot Syndrome

Hand-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy induced acral erythema) is a cutaneous toxicity with a severity range of grades 1 to 3 (see CTCAE Appendix 6).

If grade 2 or 3 hand-foot syndrome occurs, administration of capecitabine should be interrupted until the event resolves or decreases in intensity to grade 1. Subsequent doses of capecitabine should be decreased and administered as per Table 9.

Hand-foot syndrome should be treated symptomatically (i.e. use of emollients is recommended). The use of vitamin B6 pyridoxine (50 to 150 mg twice-daily) has been reported to be of possible benefit\cite{73,74} and is permitted for symptomatic or secondary prophylactic treatment of hand-foot syndrome.

8.3.3.6 Fluid retention

Severe (grade 3 or 4) toxicity such as pleural effusion, pericardial effusion or ascites, which is possibly related to docetaxel, should be closely monitored. In case of appearance of such toxicity, docetaxel treatment should be discontinued; capecitabine treatment may be continued without dose modification.

8.3.3.7 Hepatic impairment

Bilirubin, ALAT and alkaline phosphatase values should be obtained prior to each cycle of docetaxel therapy and reviewed by the treating physician.

Docetaxel should generally not be given to patients with serum bilirubin equal to or above the ULN, or to patients with ALAT $\geq$ 1.5 x ULN, concomitant with alkaline phosphatase $\geq$ 2.5 x ULN. Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Patients with isolated elevations of transaminase $\geq$ 1.5 x ULN also had a higher rate of grade 4 febrile neutropenia but did not have an increased incidence of toxic death.

If the patient has serum bilirubin equal to or above the ULN, or ASAT or ALAT $\geq$ 1.5 x ULN, concomitant with alkaline phosphatase $\geq$ 2.5 x ULN, then the docetaxel therapy must be delayed for at least one week. If there has been no
recovery in the above laboratory values (serum bilirubin below the ULN, and ASAT or ALAT < 1.5 x ULN), then docetaxel should be discontinued.

Capecitabine can induce hyperbilirubinemia. Administration of capecitabine should be interrupted if treatment-related elevations in bilirubin of ≥ 3.0 x ULN or treatment-related elevations in ALAT of ≥ 2.5 x ULN occur. Treatment may be resumed when bilirubin decreases to < 3.0 x ULN and ALAT decrease to < 2.5 x ULN.

8.4 Criteria for Premature Withdrawal

Patients have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw patients from the study in the event of intercurrent illness, adverse events, treatment failure after a prescribed procedure, protocol violations, cure, administrative reasons or other reasons. An excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible. Subsequent to a patient’s refusal of further treatment, investigators should continue to record patient data unless the patient withdraws their consent for such recording to occur.

The investigator or research personnel should contact the patient or a responsible relative either by telephone or through a personal visit, to determine as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient’s withdrawal should be made with an explanation of why the patient is withdrawing from the study. If the reason for removal of a patient from the study is an adverse event or an abnormal laboratory test result, the principal specific event or test will be recorded on the CRF.

After withdrawal, patients will be followed at approximately 1, 3 and 5 years post-randomization for survival and recurrence (if this is not the reason for early termination) until recurrent or 5 years.

8.5 Warnings and Precautions

8.5.1 Capecitabine

Capecitabine is foreseen as an outpatient treatment, and in certain circumstances adverse events that could occur, such as diarrhea, can rapidly become serious. In the case where a patient experiences any toxicity in between scheduled visits, the patient should be encouraged to contact the clinic as soon as is practical, for further directions, or for treatment.

Most adverse events described after the use of capecitabine are reversible and do not need to result in discontinuation, although doses may need to be withheld or reduced.

It is essential that the patients are informed to interrupt capecitabine treatment as soon as a grade 2 toxicity occurs, therefore the patients will need specific
explanations what to do in the case of the occurrence of the most frequent toxicities (diarrhea, hand-foot syndrome and stomatitis).

Renal Impairment: Capecitabine is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min [Cockroft and Gault, see Appendix 2]); treatment should not be started or continued in patients with severe renal impairment. Patients with moderate or severe renal impairment at baseline will be ineligible for the study, as per the exclusion criteria.

In patients with mild renal impairment (creatinine clearance 51-80 mL/min), no adjustment of the starting dose is recommended. Careful monitoring and prompt treatment interruption is recommended if patients develop grade 2, 3, or 4 adverse events with subsequent dose adjustments as outlined in Section 7.3.

Coagulopathy: Patients receiving concomitant capecitabine and oral coumarin-derived anticoagulants should have their anticoagulant response (INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose accordingly. A clinically important capecitabine-warfarin drug interaction was demonstrated in a clinical pharmacology trial. Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking capecitabine concomitantly with coumarin-derived anticoagulants such as warfarin and phenprocoumon. Postmarketing reports have shown clinically significant increases in prothrombin time (PT) and INR in patients who were stabilized on anticoagulants at the time capecitabine was introduced. These events occurred within several days and up to several months after initiating capecitabine therapy and, in a few cases, within one month after stopping capecitabine. These events occurred in patients with and without liver metastases. Age greater than 60 and a diagnosis of cancer independently predispose patients to an increased risk of coagulopathy. The use of low molecular weight heparin instead of coumarin is at the discretion of the investigator.

Diarrhea: Capecitabine can induce diarrhea. Patients with severe diarrhea should be carefully monitored and given fluid and electrolyte replacement. If grade 2, 3 or 4 diarrhea occurs, administration of capecitabine should be immediately interrupted until the diarrhea resolves or decreases in intensity to grade 1 (see also Table 9).

Pregnancy: Female patients must be instructed to stop taking capecitabine if they become pregnant during the study and immediately inform the investigator. The investigator should counsel the patient, and discuss the risk of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. The investigator should report all pregnancies in the study to Roche.

Hand-Foot Syndrome: Hand-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy induced acral erythema) is a cutaneous toxicity with a severity range of grades 1 to 3. If grade 2 or 3 hand-foot syndrome occurs, administration of capecitabine should be interrupted until the event resolves or decreases in
intensity to ≤ grade 1. Subsequent doses of capecitabine should be decreased and administered as per Table 9.

Hyperbilirubinemia: Administration of capecitabine should be interrupted if treatment-related elevations in bilirubin of ≥ 3.0 x ULN or treatment-related elevations in hepatic aminotransferases (ALAT, ASAT) of ≥ 2.5 x ULN occur. Treatment may be resumed when bilirubin decreases to < 3.0 x ULN and hepatic aminotransferases decrease to < 2.5 x ULN.

Cardiotoxicity: There has been cardiotoxicity associated with fluorinated pyrimidine therapy (including capecitabine) including myocardial infarction, angina, dysrhythmias, cardiogenic shock, sudden death and electrocardiograph changes. These adverse events may be more common in patients with a prior history of coronary artery disease.

Hepatic Insufficiency: In patients with mild to moderate hepatic dysfunction due to liver metastases, caution should be exercised when capecitabine is administered but no dose reduction is necessary. The effect of severe hepatic dysfunction on capecitabine is not known.

Contraindications: Capecitabine is contraindicated in patients with known hypersensitivity to capecitabine 5-fluorouracil or to any of the excipients, in patients who have a history of severe and unexpected reactions to fluoropyrimidine therapy, and in patients with known DPD deficiency. Capecitabine is contraindicated in patients with severe leukopenia, neutropenia, or thrombocytopenia, severe hepatic impairment, or severe renal impairment (creatinine clearance below 30 mL/min). Use of capecitabine is contraindicated during pregnancy and lactation, and concomitantly with sorivudine or its chemically related analogues, such as brivudine.

8.5.1.1 Docetaxel

Docetaxel for Injection Concentrate should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available. See Boxed Warnings of the docetaxel package insert.

The incidence of treatment-related mortality associated with docetaxel therapy is increased in patients with abnormal liver function and in patients receiving higher doses. See Boxed Warnings of the docetaxel package insert.

Toxic Deaths: Docetaxel administered at 100 mg/m² was associated with deaths considered possibly or probably related to treatment in 2.4% (34/1435) of patients with normal liver function and in 11% (6/55) of patients with abnormal liver function (ASAT and/or ALAT > 1.5 times UNL together with alkaline phosphatase > 2.5 times ULN). Among patients dosed at 60 mg/m², mortality related to treatment occurred in 0.6% (3/481) of patients with normal liver function, and in 3 of 7 patients with abnormal liver function. Approximately half of
these deaths occurred during the first cycle. Sepsis accounted for the majority of
the deaths.

**Hepatic Impairment:** (see Boxed Warning of the docetaxel package insert).

Three breast cancer patients with severe liver impairment (bilirubin > 1.7 times
ULN) developed fatal gastrointestinal bleeding associated with severe drug-
induced thrombocytopenia. Docetaxel should generally not be given to patients
with bilirubin > upper limit of normal (ULN), or to patients with ASAT and/or ALAT
> 1.5 x UNL concomitant with alkaline phosphatase ≥ 2.5 x ULN. Patients with
elevations of bilirubin or abnormalities of transaminases concurrent with alkaline
phosphatase are at increased risk for the development of grade 4 neutropenia,
febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis,
severe skin toxicity, and toxic death. Patients with isolated elevations of
transaminases > 1.5 x UNL also had a higher rate of febrile neutropenia grade 4
but did not have an increased incidence of toxic death. Bilirubin, ASAT or ALAT,
and alkaline phosphatase values should be obtained prior to each cycle of
docetaxel therapy and reviewed by the treating physician.

**Hypersensitivity Reactions:** Patients should be observed closely for
hypersensitivity reactions, especially during the first and second infusions.
Severe hypersensitivity reactions characterized by hypotension and/or
bronchospasm, or generalized rash/erythema occurred in 0.9% of patients who
received the recommended dexamethasone premedication. Hypersensitivity
reactions requiring discontinuation of the docetaxel infusion were reported in 5
out of 1260 patients who did not receive premedication. These reactions
resolved after discontinuation of the infusion and the administration of
appropriate therapy. Docetaxel must not be given to patients who have a history
of severe hypersensitivity reactions to docetaxel or to other drugs formulated with
polysorbate 80. Patients with a history of severe hypersensitivity reactions should
not be rechallenged with docetaxel. See Boxed Warnings of the docetaxel
package insert.

**Hematologic Effects:** Neutropenia (less than 2000 neutrophils/mm³) occurs in
virtually all patients given 60-100 mg/m² of docetaxel and grade 4 neutropenia
(less than 500 cells/mm³) occurs in nearly all patients given 100 mg/m² and 75-
80% of patients given 60-75 mg/m². Frequent monitoring of blood counts is,
therefore, essential so that dose can be adjusted. Docetaxel should not be
administered to patients with neutrophils < 1500 cells/mm³ (see Boxed Warnings
doctor the docetaxel package insert). Febrile neutropenia occurred in about 12% of
patients given 100 mg/m² of docetaxel but was very uncommon in patients given
60-75 mg/m². Hematologic responses, febrile reactions and infections, and rates
of septic death for different regimens are dose related and are described in
clinical studies.

**Fluid Retention:** (see Boxed Warning of the docetaxel package insert). Severe
fluid retention occurred in 6% of patients despite use of a 5-day dexamethasone
premedication regimen. It was characterized by one or more of the following
events: poorly tolerated peripheral edema, generalized edema, pleural effusion
requiring urgent drainage, dyspnea at rest, cardiac tamponade, or pronounced abdominal distention (due to ascites).

Pregnancy: Docetaxel can cause fetal harm when administered to pregnant women. Studies in both rats and rabbits at doses equal to or greater than 0.3 and 0.03 mg/kg/day, respectively (about 1/50 and 1/300 the daily maximum recommended human dose on a mg/m² basis), administered during the period of organogenesis, have shown that docetaxel is embryotoxic and fetotoxic (characterized by intrauterine mortality, increased resorption, reduced fetal weight, and fetal ossification delay). The doses indicated above also caused maternal toxicity. There are no adequate and well-controlled studies in pregnant women using docetaxel. If docetaxel is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with docetaxel.

9. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

9.1 Primary and Secondary Study Variables

The primary study variable is the comparison the rate of recurrence-free survival between the two treatment arms.

Secondary study variables include:

Efficacy:
- Overall survival

Safety:
- Incidence of all adverse events
- Incidence of serious adverse events
- Time to onset of adverse events
- Laboratory parameters
- Premature withdrawals
- Vital signs

Other:
- Research blood / serum sample (optional)
9.2 Analysis Populations

Assignment of patients to specific populations will be performed prior to database closure.

9.2.1 Intent-to-Treat population

All randomized patients will be included in the intent-to-treat population.

9.2.2 Per-Protocol population

The per-protocol population excludes randomized patients who did not receive at least one dose of capecitabine and/or docetaxel, or who had a major violation of protocol inclusion or exclusion criteria.

9.2.3 Safety population

All patients who received at least one dose of capecitabine and/or docetaxel will be included in the safety population. The safety population will be used for all analyses of safety (Section 8.3.3).

9.3 Efficacy and Safety Analyses

9.3.1 Primary efficacy analysis

The primary efficacy variable is the rate of recurrence-free survival.

Time to recurrence will be measured as the time from when the patient was randomized to the time the patient is first recorded as having disease recurrence or the date of death if the patient dies due to causes other than disease recurrence. Patients without any such event will be censored using the time they were last confirmed to have not had a recurrence.

The primary efficacy (per-protocol) analysis will be repeated for the intent-to-treat population (all randomized patients). The results of this intent-to-treat analysis will be compared to the results of the per-protocol analysis. Possible inconsistencies in the results of the two analyses will be investigated and clarified in the study report.

In addition to hazard ratios and associated 95% confidence intervals, the results from these analyses will, for each treatment arm, also be summarized by Kaplan-Meier plots, medians and 95% confidence intervals.

The primary analysis will be performed when 200 events (recurrence or death) have been reached among the intent-to-treat population. This is expected to occur about 5.5 years after the first patient is enrolled, see Section 9.4 below.

Also the results of all secondary endpoints shall be presented at that time.
9.3.2 Secondary efficacy analyses

9.3.2.1 Overall survival

Survival will be measured as the time from the date of randomization to the date of death. Patients who were not reported as having died at the time of the analysis will be censored using the date they were last known to be alive.

9.3.2.2 Adverse events, laboratory data, premature withdrawals

All adverse events occurring up to 28 days after last intake of study medication are to be recorded in the case report form. These adverse events will be reported as listings and summarized as frequency tables. Additional presentations will include summaries by severity and relationship to trial treatment. Laboratory data will be reported in the form of listings, frequency tables, and shift tables. Withdrawals of patients from study medication will be reported as listings and summary tables. All summaries and listings of adverse events and laboratory data will be based on the safety population.

Besides frequency tables and listings, the treatment arms will also be compared (using pairwise 95% confidence intervals) with regard to the overall percentage of patients experiencing grade 3 or grade 4 toxicities typically associated with each treatment regimen. The analysis will consider all grade 3 or grade 4 adverse events and will also be repeated for treatment related grade 3 or grade 4 adverse events. Using the same types of adverse events, additional analyses will investigate the time to the first onset. Medians and associated 95% confidence intervals will be reported for each study arm. The time to the first onset of adverse events will be measured as the time from the first active drug intake to the cycle of the first occurrence of any of the adverse events under investigation. Patients without any of these adverse events will be censored at the date that corresponds to 28 days after the last intake of study medication. As this endpoint thus considers the frequency as well as the timing of adverse events, it is deemed more powerful than the analysis of frequency rates alone.

An interim safety review will occur once 80 patients have completed study treatment. Results will be reviewed by the Independent Safety Monitoring Committee (see Section 10.4). The safety review can be performed earlier or later than this time point based on the recommendation of the Safety Monitoring Committee. The toxicity and tolerability of the treatments may be analyzed when approximately 600 patients have been treated according to the protocol. The feasibility of the treatment arms will be reported either at that time point and/or within the final study report.

9.3.2.3 Vital signs

Vital signs will be collected over time. In addition to listings, summaries of the actual values and the change from baseline will be reported by time windows for weight and WHO performance status. All summaries and listings of vital sign data will be based on the safety population.
9.4 Sample Size Considerations

Assuming 5-year recurrence-free survival will improve from 75% to 83%, $\alpha=0.05$, $1-\beta=0.90$, using 2-sided testing about 200 events (recurrences or deaths) are needed for the main analysis. Allowing for a 3% annual drop-out rate, approximately 1,500 patients will need to be randomized. Based on a recruitment period of 3.5 years and 2 years of follow-up after the last patient has been enrolled, the anticipated total study duration is 5.5 years.

9.5 Replacement Policy

9.5.1 For patients

No patient prematurely discontinued from the study for any reason will be replaced.

9.5.2 For centers

A center may be closed and replaced for the following reasons:

- Excessively slow recruitment,
- Poor protocol adherence.

9.6 Late Survival Analyses

Approximately 5-year follow-up time is short in early breast cancer, since it may recur up to 3 decades after breast surgery. Three time-driven late survival analyses are planned to be carried out:

1) A survival analysis focusing on patients who have HER2-positive breast cancer. The primary endpoint will be recurrence-free survival (RFS). In this analysis the study cohort is stratified by the trastuzumab treatment given (adjuvant trastuzumab vs. no trastuzumab; the trastuzumab administration schedule). The analysis is carried out when all study patients have been followed up for a minimum of 5 years (this will occur in May 2012).

2) The second late survival analysis. This analysis will be carried out when the estimated median follow-up time of the patients alive exceeds 10 years since the date of randomization. This duration of follow-up is estimated to be achieved in October 2015 at the earliest, and the analysis is planned to be carried out in 2015 to 2016. The primary endpoint is RFS. RFS will be assessed in the entire study population and in the biological subgroups formed by ER and HER2 (ER+, HER2-; ER+, HER2+; ER-, HER2+; and ER-, HER2-).

3) The third late analysis. This analysis will be carried out when the estimated median follow-up time of the patients alive exceeds 15 years since the date of randomization. This duration of follow-up is estimated to be achieved in October 2020 at the earliest, and the analysis is planned to be carried out in late 2020-2021. The primary endpoint is overall survival (OS). OS will be assessed in the entire study population, and in the biological subgroups formed by ER and HER2 (ER+, HER2-; ER+, HER2+; ER-, HER2+; and ER-, HER2-).
10. REFERENCES


36. Data on file, Roche.


47. Fujimoto-Ouchi K, Tanaka Y, Tominaga T. Schedule dependency of antitumor activity in combination therapy with capecitabine/5'-deoxy-5-


58. Tonkin K, Scarfe AG, Koske S, et al. Preliminary results of a phase I/II study of weekly docetaxel (Taxotere®) combined with intermittent capecitabine (Xeloda®) for patients with anthracycline pre-treated...


2045 68. Roche data on file.


PART II: ETHICS AND GENERAL STUDY ADMINISTRATION

11. ETHICAL ASPECTS

11.1 Local Regulations/Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformance with the principles of the “Declaration of Helsinki” or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in “Guideline for Good Clinical Practice” ICH Tripartite Guideline (January 1997) or with local law if it affords greater protection to the patient. In countries where “Guidelines for Good Clinical Practice” exist, Roche and the investigators will strictly ensure adherence to the stated provisions.

11.2 Informed Consent

It is the responsibility of the investigator to obtain written informed consent from each patient participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. For patients not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. The investigator or designee must also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason. The Case Report Forms for this study contain a section for documenting informed patient consent, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All patients (including those already being treated) should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

11.3 Institutional Review Board

It is the understanding that this protocol (and any modifications) as well as appropriate consent procedures, will be reviewed and approved by an Institutional Review Board. This board must operate in accordance with the current national Regulations. The investigator will send a letter or certificate of approval to Roche prior to initiation of the study, and also whenever subsequent modifications to the protocol are made.

11.4 Independent Safety Monitoring Committee

An Independent Safety Monitoring Committee with three members, not participating in the study, will be created. The committee will assess the safety of study patients based on listings of adverse and serious adverse events. The committee will also review the process of the study and treatment efficacy.
11.5 Study Steering Committee

The board of the Finnish Breast Cancer Group will act as a Steering Committee of this study. The principal investigator of the study must be a member of the Steering Committee.

12. CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications to ongoing studies must be made only after consultation between an appropriate representative of Roche and the investigator.

All protocol modifications must be submitted to the appropriate Institutional Review Board for information and approval in accordance with local requirements, and to Regulatory Agencies if required. Approval must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial patients, or when the change(s) involves only logistical or administrative aspects of the trial (e.g. change in monitor(s), change of telephone number(s)).

13. CONDITIONS FOR TERMINATING THE STUDY

The Study Steering Committee reserve the right to terminate the study at any time. Should this be necessary, the study steering committee will arrange the procedures on an individual study basis after review and consultation. In terminating the study, the Steering Committee will assure that adequate consideration is given to the protection of the patient’s interests.

14. STUDY DOCUMENTATION, CRFS AND RECORD KEEPING

14.1 Investigator’s Files / Retention of Documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories (1) Investigator’s Study File, and (2) patient clinical source documents.

The Investigator’s Study File will contain the protocol/amendments, Case Report and Query Forms, Institutional Review Board and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence etc.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the CRFs) would include patient hospital/clinic records, physician’s and nurse’s notes, appointment book, original laboratory reports, ECG, EEG, X-ray, pathology and special assessment reports, signed informed consent forms, consultant letters, and patient screening
and enrollment logs. The investigator must keep these two categories of
documents on file for at least 15 years after completion or discontinuation of the
study. After that period of time the documents may be destroyed, subject to local
regulations.
Should the investigator wish to assign the study records to another party or move
them to another location, Roche must be notified in advance.

14.2 Source Documents and Background Data

The investigator shall supply the monitor on request with any required
background data from the study documentation or clinic records. This is
particularly important when Case Report Forms are illegible or when errors in
data transcription are suspected. In case of special problems and/or
governmental queries or requests for audit inspections, it is also necessary to
have access to the complete study records, provided that patient confidentiality is
protected.

14.2.1 Audits and inspections

The investigator should understand that source documents for this trial should be
made available to appropriately qualified personnel from the Finnish Breast
Cancer Group, Roche Research Quality Assurance Unit or its designees or to
health authority inspectors after appropriate notification. The verification of the
Case Report Form data must be by direct inspection of source documents.

14.3 Case Report Forms

For each patient enrolled, a Case Report Form must be completed and signed by
the investigator or authorized delegate from the study staff. This also applies to
records for those patients who fail to complete the study (even during a pre-
randomization screening period if a Case Report Form was initiated). If a patient
withdraws from the study, the reason must be noted on the Case Report Form. If
a patient is withdrawn from the study because of a treatment-limiting adverse
event, thorough efforts should be made to clearly document the outcome.
All forms should be typed or filled out using indelible black ink, and must be
legible. Errors should be crossed out but not obliterated, the correction inserted,
and the change initialed and dated by the investigator or his/her authorized
delegate. The investigator should ensure the accuracy, completeness, legibility,
and timeliness of the data reported in the CRFs and in all required reports.

15. MONITORING THE STUDY

The responsible Roche monitor (or designee) has the responsibility to familiarize
the investigator(s) and the entire center staff involved in the study with all study
procedures including the administration of study drug.
It is understood that the monitor will contact and visit the investigator regularly
and will be allowed, on request, to inspect the various records of the trial (Case
Report Forms and other pertinent data) provided that patient confidentiality is
maintained in accord with local requirements.
It will be the monitor’s responsibility to inspect the Case Report Forms at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The monitor should have access to laboratory test reports and other patient records needed to verify the entries on the Case Report Form. The investigator (or his/her deputy) agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

16. CONFIDENTIALITY OF TRIAL DOCUMENTS AND PATIENT RECORDS

The investigator must assure that patients’ anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted outside the study center, patients should not be identified by their names, but by an identification code. The investigator should keep a separate confidential patient enrollment log showing codes, names and addresses. The investigator should maintain documents not for submission outside the study center e.g., patients’ written consent forms, in strict confidence.

17. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to Roche prior to submission. This allows Roche to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accord with standard editorial and ethical practice, the publication of a multicenter trial should only be done in entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

It is anticipated that safety data might be published once all patients have completed study treatment. Publication of efficacy data will follow once sufficient follow-up data has been collected.

18. SPECIFIC RESPONSIBILITIES

18.1 General Responsibilities

Roche will provide the Xeloda Package Insert and/or an updated Product Monograph.

Roche provides all investigators with a sufficient number of case report forms.

Roche will monitor the study according to a separate monitoring plan.

18.2 Site Closure

Center closure will only occur once all patients have come off treatment, survival data is no longer being collected and all discrepancy issues have been resolved. The center will therefore remain “ACTIVE” such that the investigator will be notified of any reportable serious adverse events occurring with the drug.
19. **APPENDICES**

19.1 **Appendix 1 - WHO Performance Status**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Able to carry out all normal activity without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out light work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care, but unable to carry out any work; up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable only of limited self-care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled; cannot carry out any self-care; totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>


19.2 Appendix 2 - Calculated Creatinine Clearance

Calculated Creatinine Clearance (Cockroft and Gault)

For females:

Creatinine clearance (mL/min) =

\[
\frac{[(140 - \text{age}) \times \text{actual body weight (in kg)} \times 0.85]}{[0.81 \times \text{serum creatinine (in } \mu\text{mol/L)}]}\]

or

\[
\frac{[(140 - \text{age}) \times \text{actual body weight (in kg)} \times 0.85]}{[72 \times \text{serum creatinine (in } \text{mg/dL})]}\]
19.3 Appendix 3 - Nomogram for BSA Determination

Nomogram for determination of body surface from height and mass

  - $A = 0.0072 	imes H^0.425 	imes W^{0.725}$
  - $A$: body surface in m², $H$: height in cm, $W$: mass in kg.

Height

| cm 200 | cm 195 | cm 190 | cm 185 | cm 180 | cm 175 | cm 170 | cm 165 | cm 160 | cm 155 | cm 150 | cm 145 | cm 140 | cm 135 | cm 130 | cm 125 | cm 120 | cm 115 | cm 110 | cm 105 | cm 100 |
|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| 70     | 72     | 75     | 77     | 79     | 80     | 82     | 84     | 86     | 88     | 90     | 92     | 94     | 96     | 98     | 100    | 102    | 104    | 106    | 108    | 110    |
| 1.60 m²| 1.70 m²| 1.80 m²| 1.90 m²| 2.00 m²| 2.10 m²| 2.20 m²| 2.30 m²| 2.40 m²| 2.50 m²| 2.60 m²| 2.70 m²| 2.80 m²| 2.90 m²| 3.00 m²| 3.10 m²| 3.20 m²| 3.30 m²| 3.40 m²| 3.50 m²| 3.60 m²|

Mass

<table>
<thead>
<tr>
<th>kg 150</th>
<th>kg 140</th>
<th>kg 130</th>
<th>kg 120</th>
<th>kg 110</th>
<th>kg 100</th>
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<th>kg 10</th>
<th>kg 5</th>
<th>kg 2.5</th>
<th>kg 1.5</th>
<th>kg 1.0</th>
<th>kg 0.5</th>
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<tr>
<td>33 lb</td>
<td>37 lb</td>
<td>40 lb</td>
<td>44 lb</td>
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<td>88 lb</td>
<td>92 lb</td>
<td>96 lb</td>
<td>100 lb</td>
<td>105 lb</td>
<td>110 lb</td>
</tr>
</tbody>
</table>
19.4 Appendix 4 - Capecitabine Dosing (with CEX)

Capecitabine Dose Calculations According To BSA
With Docetaxel And As Part of CEX

500 Mg Tablet Only

Where 100% dose level is twice-daily 900 mg/m² (total daily dose of 1800 mg/m²). The first dose of each cycle will be administered as the evening dose on day 1 and the last dose of each cycle is scheduled the morning of day 15, followed by a 7-day rest period.

### 100% Dose Level

<table>
<thead>
<tr>
<th>Surface Area (m²)</th>
<th>Average Dose per Administration (mg)</th>
<th>Morning</th>
<th>Evening</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.29</td>
<td>1000</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>1.30 - 1.52</td>
<td>1250</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>1.53 - 1.80</td>
<td>1500</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>1.81 - 2.08</td>
<td>1750</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>≥ 2.09</td>
<td>2000</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

### 80% Dose Level

<table>
<thead>
<tr>
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<th>Average Dose per Administration (mg)</th>
<th>Morning</th>
<th>Evening</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.29</td>
<td>750</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>1.30 - 1.52</td>
<td>1000</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>1.53 - 1.80</td>
<td>1250</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>≥ 1.81</td>
<td>1500</td>
<td>3</td>
<td>3</td>
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</tbody>
</table>

### 60% Dose Level

<table>
<thead>
<tr>
<th>Surface Area (m²)</th>
<th>Average Dose per Administration (mg)</th>
<th>Morning</th>
<th>Evening</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.29</td>
<td>500</td>
<td>1</td>
<td>1</td>
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<tr>
<td>1.30 - 1.52</td>
<td>750</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>1.53 - 2.08</td>
<td>1000</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>≥ 2.09</td>
<td>1250</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
19.5 Appendix 5 - Capecitabine Interruptions And Extended Rest Periods

Normal Treatment:

<table>
<thead>
<tr>
<th>Day</th>
<th>Day 8</th>
<th>Day 15</th>
<th>Day 22</th>
<th>Day 29</th>
<th>Day 36</th>
<th>Day 43</th>
<th>Day 50</th>
</tr>
</thead>
</table>

Interruptions During Treatment:

Interruptions are regarded as lost treatment days and the planned treatment schedule should be maintained.

Extended Rest Periods:

If a rest period is extended due to toxicity, the "complete" cycle should be given afterwards.

14 days 7 days 14 days
Appendix 6 - Common Terminology Criteria for Adverse Events
v3.0 (CTCAE)

The Common Terminology Criteria for Adverse Events (CTCAE) version 3 can be found by referring to the website [http://ctep.cancer.gov/reporting/ctc.html](http://ctep.cancer.gov/reporting/ctc.html).

Hard copies can be made available to sites through contacting Roche.
19.7 Appendix 7 - Clinical Safety Data Management

ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any adverse event that at any dose fulfills at least one of the following criteria:

- is fatal; (results in death)
- (NOTE: death is an outcome, not an event)
- is life-threatening;
- (NOTE: the term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe)
- required unexpected in-patient hospitalization or prolongation of existing hospitalization;
- (NOTE: "inpatient hospitalization" refers to an unplanned, overnight hospitalization)
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is medically significant or requires intervention to prevent one or other of the outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether expedited reporting to Roche is appropriate in other situations, such as 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 outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

An unexpected adverse event is an event, the nature or severity of which is not consistent with the applicable product information found in the SMPC.

Causality is initially assessed by the investigator. For Serious Adverse Events, causality can be one of 2 possibilities:

- No (unrelated; equals not drug related).
- Yes (remotely, possibly, probably or definitely drug related).
The term severe is a measure of intensity, thus a severe adverse event is not necessarily serious. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.

Only serious, unexpected, related adverse events occurring during the study or which comes to the attention of the investigator within 15 days after stopping the treatment or during the protocol-defined follow-up period, if this is longer, must be reported. In addition, a serious adverse event that occurs after this time, if considered related to test "drug", should be reported.

Such preliminary reports will be followed by detailed descriptions later which will include copies of hospital case reports, autopsy reports and other documents when requested and applicable.

For serious adverse events, the following must be assessed and recorded on the adverse events page of the Case Report Form: intensity, relationship to test substance, action taken, and outcome to date.

The investigator must notify the Institutional Review Board of a serious unexpected adverse event in writing at least annually and in accordance with international and local laws and regulations.

ROCHE LOCAL COUNTRY CONTACT for SAEs: Local Monitor