CITY OF HOPE
1500 E. DUARTE ROAD
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DEPARTMENT OF MEDICAL ONCOLOGY AND THERAPEUTICS RESEARCH

TITLE: Intermittent Exemestane Therapy for Metastatic Breast Cancer

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COH Amendment 09 (Title Page dated 01/12/2012)	Version 09
COH Amendment 10 (Protocol dated 7/9/13)	Version10
COH Amendment 11 (Protocol dated 10-25-13, DSMP and CBC/CMP)	Version 11
COH Amendment 12 (Title page only dated 06/19/14)	Version 12
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SITE: Breast

HISTOLOGY: Breast Cancer

STAGE (If applicable): Stage IV

MODALITY: Hormone Therapy

TYPE: Pilot, Phase II

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DIVISION OF MEDICAL ONCOLOGY AND THERAPEUTICS RESEARCH

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VERSION: June 18, 2008
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SCHEMA

N=36

- Postmenopausal Women
- Biopsy proven Metastatic Breast Cancer (MBC)
- ER and/or PR Positive Breast Cancer
- Two prior chemotherapy regimens for MBC allowed
- Disease recurrence while on adjuvant hormonal therapy (as long as treatment was taken for at least six months) or after discontinuation/completio djuvant hormonal therapy.
- Disease progression following either 0, 1 or 2 prior hormonal therapies for MBC
- No prior exposure to exemestane (EXE)
- Measurable or non-measurable (but evaluable) disease
- ECOG performance status 0-1
- Adequate hematologic, renal and hepatic functions

REGISTER

Protocol Treatment

Exemestane
25 mg daily X 14 days then
7 days off treatment, for each
21-day cycle of treatment

Study Endpoints:

Measurements of:
Efficacy
Toxicity
Compliance
Quality of Life

1.0 OBJECTIVES

1.1. Primary Objective:

- Progression free survival (PFS) at 4 months, as measured by Response Evaluation Criteria in Solid Tumors (RECIST).

1.2 Secondary Objectives:

- Objective response rate [compete response (CR), partial response (PR)]
- Clinical benefit [CR +PR + Stable disease≥ 6 months]
- Assessment of toxicity
- Assessment of compliance with medication adherence
- Assessment of quality of life
- Assessment of bone health

1.3 Exploratory Objectives:

- Serial measurement of serum estradiol, estrone and estrone sulfate.
- To investigate treatment resistance (e.g. expression of amphiregulin, EGFR), using molecular and immunohistochemical analyses of blood and tumor samples of pre- and post- (when available) treatment tissues. Microarraay analyses to quantitate the expression of specific estrogen-responsive genes (e.g. TTF1 and (PDZk1) will also be performed.

2.0 BACKGROUND AND RATIONALE

The efficacy of aromatase inhibitors (AI) in the treatment of postmenopausal women with hormone receptor positive, metastatic breast cancer (MBC) is undisputed. In this regard, prior randomized clinical trials have documented the superiority of exemestane (EXE) over tamoxifen, as first line therapy [1] and the superiority of EXE over megestrol acetate, as second line therapy after tamoxifen failure [2]. Prior phase II studies have also documented the efficacy of EXE in the treatment of MBC after failure of several lines of prior hormonal therapies [3], including prior exposure to nonsteroidal AIs [4, 5]. While the utility of EXE has been proven with respect to several important clinical indicators (e.g. response rate, time to progression, median survival time and median duration of response), eventually all patients will develop disease progression due to the development of acquired resistance to further treatment. In addition, as has recently been reported, some patients with breast cancer may derive less than maximal benefit from AI therapy due to noncompliance because of musculoskeletal-related adverse effects [6, 7]. The aim of this research proposal, therefore, is to determine whether there may be an effective strategy to delay the time to development of resistance to EXE in the treatment of MBC, while minimizing potential toxicities and ensuring patient compliance with treatment.

In order to achieve our study objectives, we propose a phase II pilot, translational trial incorporating the use of intermittent EXE therapy in the

treatment of postmenopausal women with hormone receptor positive MBC. The rationale for this trial stems from preclinical data derived at the City of Hope, in the laboratory of our collaborator, Dr. Shiuan Chen (Figure 1). As Dr. Chen's research interests have been in identifying mechanisms of AI resistance, he has generated a unique research tool, MCF-7aro, an estrogen receptor positive breast cancer cell line in which aromatase is over-expressed [8,9]. Using this cell line, it was demonstrated that continuous exposure to EXE initially inhibited cell growth, indicative of the sensitivity of this cell line to treatment. With prolonged, continuous exposure to EXE, however, cells eventually resumed growth after 6-8 weeks of treatment, reflecting the gradual development of acquired resistance to further treatment. In contrast, in cells exposed to intermittent treatment with EXE, either on a schedule of 1 week on/1week off, 2 weeks on/1 week off or 3 weeks on/1 week off, sensitivity to growth inhibition by EXE was maintained beyond 12 weeks. These data suggest that the scheduling of EXE therapy may influence the clinical efficacy of this AI in the treatment of MBC.

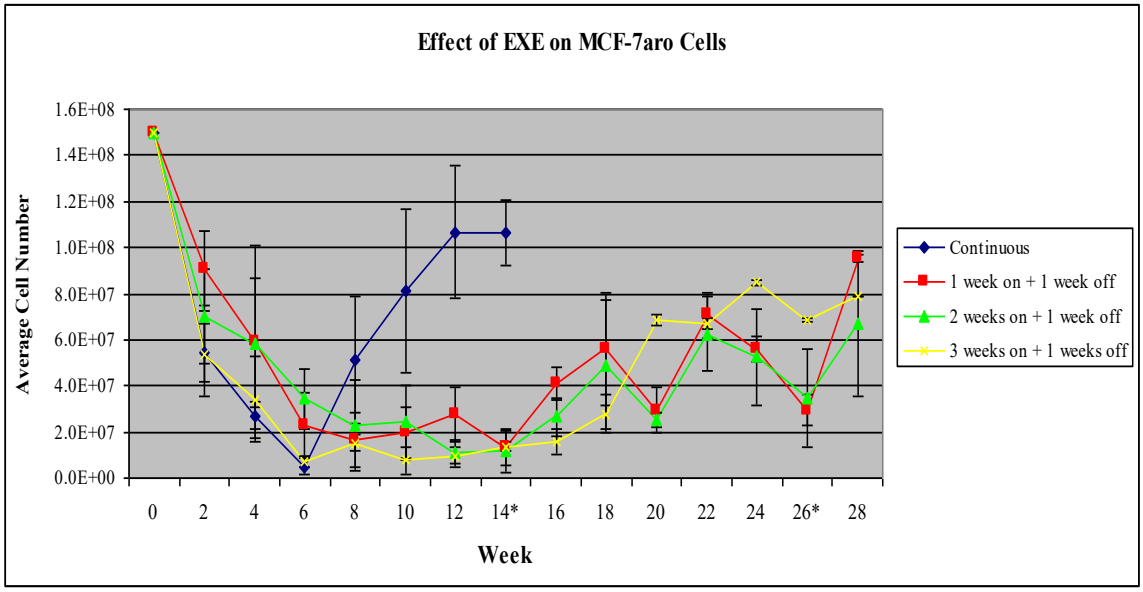

Figure 1.Effect of continuous and intermittent schedules of EXE (1μM) treatment on the growth of MCF-7aro cells in the presence of testosterone (T, 1nM). (Unpublished data)

While molecular mechanisms underlying this observation of delayed resistance are not yet fully elucidated, a clinical trial of intermittent EXE therapy in the treatment of MBC, is supported by both anecdotal clinical reports, as well as data derived from other laboratories. Clinical case reports have documented, for example, that patients with MBC can demonstrate regression of disease in response to withdrawal of antiestrogen treatments [10, 11]. This effect is presumed to result from of an adaptive hypersensitivity to low estrogen levels which over time, can lead to a paradoxical inhibitory effect of estrogen on breast cancer cell growth. A similar phenomenon has also been observed *in vitro* in that in LTED cells (i.e., MCF-7 breast cancer cells cultured under conditions of long-term estrogen deprivation), exposure to estrogen results in growth inhibition and induction of apoptosis [12]. In this regard, the current standard method of continuous daily dosing of EXE may not be as effective in inhibiting breast cancer cell growth, as sequencing intermittent periods of EXE

withdrawal. Moreover*, in vitro* and mouse xenograft models have shown that reversal of resistance to tamoxifen can be achieved with the administration of estrogen [13,14], suggesting that in patients with advanced, hormone receptor positive breast cancer, resistance to anti-estrogen therapy may possibly be delayed by allowing intermittent periods of exposure to low levels of estrogen. An alternative hypothesis to account for the development of acquired resistance to EXE is the recent finding of elevated expression of the epidermal growth factor (EGF)-like protein, amphiregulin (AREG), in MCF-7 aro cells treated continuously with 1μmol/L of EXE. As AREG binds to the EGF receptor, it is postulated that AREG may mediate the development of acquired resistance to EXE via activation of EGFR and MAPK, leading to cell proliferation. As such, it is possible that intermittent withdrawal of EXE may also delay the development of acquired endocrine resistance due to diminished expression of AREG [15]. In addition to the potential beneficial effects of intermittent EXE therapy in terms of prolongation of time to drug resistance, this new method of drug scheduling may also allow improvements of other clinically important endpoints, such as better quality of life due to reduced exposure to drug-related toxicities.

To correlate with observations obtained in cell culture (i.e. that intermittent EXE therapy delays the time to re-growth of MCF-7aro breast cancer cells), the selected primary endpoint of this study will be progression free survival (PFS), although other clinically meaningful endpoints, such as objective response rates and clinical benefit will also be measured. That PFS correlates with acquired resistance to treatment is exemplified by prior clinical trials in which it was shown that as first line therapy, median duration of response to EXE was reported as 10 months [1]. However, as second [2] and third [3] line therapies, time to tumor progression was reported as 20.3 weeks and 2 months, respectively. In other clinical trials in which EXE was used after multiple lines of prior endocrine therapy (≥ 2), including use of prior non-steroidal AIs, time to tumor progression ranged between 14.7 weeks to 3.7 months [4,5,16]. In view of these previously reported data and in consideration of the desire to be able to complete this study in a timely manner, we have chosen to measure PFS at 4 months as a benchmark for comparison (10 months for first line patients, see statistical considerations) and as such, have incorporated eligibility criteria to reflect the patient population from which these historical data were obtained [5,16]. The rationale for inclusion of this study population was also derived in consideration of the hypothesis that after long-term estrogen deprivation of hormone receptor positive breast cancer cells *in vitro*, (presumed to be clinically equivalent to long-term exposure to anti-estrogens), estrogen may actually induce apoptosis [12].

3.0 TREATMENT PLAN

3.1 Study Design

In order to test the study hypothesis that intermittent EXE may delay the time to development of acquired resistance, a pilot, phase II clinical trial will be conducted in which all study participants will receive treatment with EXE.

3.2 Treatment Dosage and Schedule

As is currently recommended, the standard approved dose of EXE is 25 mg orally per day, after a meal. Absorption of EXE is rapid, and after peak plasma levels are reached, plasma levels of EXE decline in a polyexponential manner, resulting in a terminal half life of approximately 24 hours. Given these pharmacokinetic properties and in consideration of convenience/ease of dosing, a 21-day treatment cycle, consisting of a schedule of 2 weeks on (consecutive daily dosing of 25 mg of EXE from Days 1-14), followed by 1 week off (cessation of dosing from Days 15-21), will be used.

3.3 Concurrent Treatment

Bisphosphonates

Concurrent bisphosphonates for the treatment of bone metastases will be permitted. In addition, throughout the study, concomitant medications deemed necessary for the supportive care of patients will be given at physician discretion.

Radiation

Subjects with measurable disease per RECIST criteria, who require palliative radiation to a non-target lesion, will be permitted to receive treatment without being considered as having disease progression. However, patients with measurable disease who require radiation to a target lesion will be considered as having disease progression and will be removed from study.

Subjects with non-measurable disease by RECIST criteria, who require palliative radiation to a single site, will be permitted to receive treatment and remain on study. However, subjects with non-measurable disease who required palliative radiation to more than one site will be considered as having disease progression and will be taken off study.

3.4 Number of Subjects

This trial will entail enrollment of a maximum of 36 patients for treatment, as discussed in section 6.0. The target accrual goal will be 18 subjects/year.

3.5 Treatment Duration and Follow-Up

Study subjects will remain on treatment until disease progression, the development

of unacceptable toxicities, consent withdrawal, PI discretion (in cases where further treatment on protocol would not be in the best interest of the study participant) or death. Study participants will be followed for one year after completion of study treatment.

4.0 SUBJECT ELIGIBILITY

4.1 Inclusion Criteria

4.1.1 Histologically or cytologically confirmed metastatic carcinoma of the breast.

4.1.2 Hormone receptor (ER and/or PR) positive disease [defined as: ER and/or PR positivity as ≥ 5% staining], as confirmed by immunohistochemistry (IHC) based on primary breast tissue or metastatic tissue.

4.1.3 Females ≥ 18 years old and determined to be postmenopausal, as defined by any of the following:
- Natural menopause, with at least one year since last menses.
- Chemotherapy-induced menopause with at least 1 year from last menses and serum LH/FSH and estradiol levels within the postmenopausal range.
- History of surgical or radiation-induced ovarian ablation.
  For women ≤ 56 years old and with a history of hysterectomy but at least one ovary intact, serum LH/FSH and estradiol levels must be within the postmenopausal range.

4.1.4 Postmenopausal women with disease recurrence while receiving either tamoxifen or a non-steroidal AI as adjuvant therapy (as long a adjuvant hormonal therapy was taken for 6 months before disease progression) or with disease recurrence following the discontinuation/ completion of adjuvant hormonal therapy.

4.1.5 Postmenopausal women with disease progression following either 0, 1 or 2 prior hormonal therapies for metastatic breast cancer, as long as subject has had no prior exposure to EXE.

4.1.6 Measurable or non-measurable (but evaluable) disease, as defined by RECIST criteria.

4.1.7 ECOG performance status (Appendix B) of 0-1 and adequate hematologic (neutrophil count ≥ $1.5X10^9$ cells/L; platelet count ≥ 100 X 10^9 cells/L), renal (serum creatinine ≤ 1.5 times the upper limit of normal) and hepatic (total serum bilirubin ≤ 1.5 times the upper limit of normal; AST/ALT levels ≤ 2.5 times the upper limit of normal in patients without liver metastases or ≤ 5 times the upper limit of normal in patients with liver metastases; alkaline phosphatase ≤ 2.5 times the upper limit of normal for patients without bone or liver metastasis) function.

4.1.8 Subjects must have an estimated life expectancy of greater than 6 months.

4.2 Exclusion Criteria

4.2.1 Prior exposure to EXE, whether in the adjuvant or metastatic setting.

4.2.2 Prior history of any other cancer with the exception of non-melanoma skin cancer and treated *in situ* carcinoma of the cervix.

4.2.3 Active or symptomatic CNS metastasis (stable or treated brain metastasis allowed but patients must be off decadron, if given for CNS disease).

4.2.4 Hormone receptor negative or unknown breast cancer.

4.2.5 More than two prior chemotherapy regimen for treatment of metastatic disease (any prior chemotherapy given in the adjuvant setting is permitted).

4.2.6 Administration of any other anti-cancer therapy within 2 weeks of initiating study treatment. Use of bisphosphonates, however, are permitted for patients with known bone metastases.

4.2.7 Treatment with any other concurrent investigational agent or anti-tumor drug (chemotherapy, antibody therapy or other biologic agents), will not be permitted.

4.2.8 Any uncontrolled medical co-morbidity or psychiatric disorder which interferes with the ability to provide informed consent or comply with study procedures.

4.3 Minorities and Women Statement

Female subjects of all racial/ethnic groups are eligible for this study if they meet the eligibility criteria specified in sections 4.1 and 4.2. To address disparities in healthcare and breast cancer treatment among women from underserved populations, all efforts will be made to accrue subjects from ethnically diverse, underserved and minority populations. In order to achieve this goal, this study will be conducted with the collaboration of Dr. Kimlin Ashing-Giwa who has established the City of Hope Center of Community Alliance for Research and Education (CCARE), an organization charged with increasing the awareness of cancer clinical trials among underserved populations.

5.0 STUDY PROCEDURES

5.1 Screening

A signed and dated IRB approved protocol consent form must be obtained before any study specific procedures can be performed. Procedures that are considered part of routine care are not considered study specific procedures but may

be used to determine eligibility during screening. The following assessments must be performed within 28 days of initiation of treatment:

- Review of inclusion and exclusion criteria.
- Recording of concomitant mediation, including date of last use of prior therapy for treatment of breast cancer.
- Complete review of medical history (documentation of diagnosis, hormone receptor status of tumor, most recent radiologic assessment of disease status and prior treatment history)
- Complete physical examination, including assessment of ECOG performance status.
- Laboratory assessment for hematologic, renal and hepatic function.
- Disease assessment according to RECIST criteria. All baseline radiologic scans (CT, MRI, bone scans) must be performed within 28 days of study initiation. *[**Note**: PET/CT Scan may be used in lieu of Bone Scan when patient is symptomatic]*
- If available, submission of archival paraffin-embedded or fresh frozen tumor tissue samples.

5.2 Tumor Assessments

Radiologic assessment of disease must include computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen and pelvis and the imaging modality selected should remain consistent throughout the entire study. All subjects will additionally undergo a bone scan at baseline *[**Note**: PET/CT Scan may be used in lieu of Bone Scan when patient is symptomatic]*. Subjects with a positive bone scan at baseline will continue to have bone scans as part of their radiologic assessments throughout the study period. Subjects with a negative bone scan at baseline, will not be required to continue with further bone scans during the study period, unless clinically indicated. All imaging studies will be required at baseline and will be repeated every 3 cycles (i.e. day 15-21 of every 3rd cycle). Tumor response assessments will be performed according to RECIST criteria:

Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference

Eligibility

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

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease,

lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques.

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

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

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

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

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

- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.

- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions).

Baseline documentation of "Target" and "Non-Target" lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria

Evaluation of target lesions

* Complete Response (CR):	Disappearance of all target lesions
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions

* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
* Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
* Progressive Disease	Appearance of one or more new lesions and/or unequivocal

(PD): progression of existing non-target lesions (1)

(1) Although a clear progression of "non target" lesions only is exceptional. In such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

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

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

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

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

5.3 Toxicity Assessments

To protect against and minimize potential risks, assessments of treatment-related toxicities will be performed by the study nurse every three weeks (via telephone). The NCI, Common Toxicity Criteria for Adverse Events (CTCAE, version 3.0, available at http://ctep.cancer.gov//forms/CTAEv3.pdf)), will be used as a guide to assess severity. To assess musculoskeletal adverse effects associated with EXE use, all subjects will complete modified Health Assessment Questionnaires (HAQ DI©) (Appendix A) at the start of each cycle of treatment, as previously validated [7, 17].

5.4 Quality of Life Assessment (Appendix C)

For determination of quality of life associated with EXE use, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) will be used. This instrument consists of a 30-item, cancer-specific tool which encompasses measures of physical, emotional, cognitive and social well being, in addition to measures of symptoms and overall quality of life. Questionnaires will be completed at the start of every new cycle of treatment.

5.5 Exemestane Drug Diary

To assess compliance with treatment, all patients will be supplied with a calendar of the treatment schedule at the start of each new cycle and will be instructed to track their daily consumption of EXE at home. Completed calendars will be collected at the end of each cycle of treatment.

6.0 STATISTICAL CONSIDERATIONS

6.1 Maximum Accrual: 36 Subjects

While toxicity is safely assumed to be reduced, the improvement in PFS is less clear and interim stopping conditions in case the PFS is dramatically worse than historical data [5], are incorporated in the design. The following design operating characteristics were calculated by the method of Simon, but the specific design chosen differs slightly from the Optimum or Minimax design to take into consideration the sawtooth nature of the power function [18, 19]. Patients will be defined as a "success" or "failure" based on whether they have obtained the appropriate benchmark for median PFS (see below). An interim analysis will be performed at 21 subjects. If fewer than six of the first 21 subjects are a "success", the study will be stopped for futility. If fewer than fourteen patients out of the 36 subjects are a success this will also be suggestive that this regimen does not warrant further study. This design discriminates between an encouraging "success" rate of 50% and a discouraging "success" rate of 30%. The probability of early stopping if the true success rate is 50%, is 1% whereas the probability of early stopping if the true success rate is 30%, is 36%.The overall type II error for the decision on whether or not the treatment is promising is 7%, whereas the type I error is less than 17%, when comparing a discouraging success rate of 30% to an encouraging rate of 50%.

For second or third line patients (as was done prior to the amendment to include first line patients) if patients are progression-free at the 4 month evaluation this will be considered a success. Based on recent publication (e.g. Paridaens, et al , Vol 26, No. 30, pp-4883-4890, JCO 2008) the median PFS for first line patients on EXE is approximately 10 months. As a result, we will view a "success" for first line patients if they are progression-free at 10 months.

Patients who are not first line will be assigned to Treatment Arm 1. Patients who are first line will be accrued to treatment Arm 2. These arms are used simply as a convenience for easier determination of the primary endpoint, and no specific accrual goals are made for each treatment arm, with a total goal of 36 subjects.

While it is assumed that reduced exposure to EXE results in fewer and less severe drug-related toxicities, a sufficient sample size must be accrued in order to obtain a reasonable estimate of the frequency of treatment related toxicities. One benchmark will look at the incidence of joint disorders,reported by Gradishar [5], at approximately 30%. A one-sided exact binomial test with a nominal 10% significance level, will have 81% power to detect a difference from a historical 30% complication rate, to a 15% complication rate with 36 subjects. Generally, however, if the PFS is equivalent to historical data, this will be considered successful, based on the assumption that reduced drug exposure will result in less toxicity. While progression free survival (time to progression or death) at 4 months (and 10 months) is calculated as a binomial (all treated patients will count and

patients lost to follow-up before 4 months (10 months for first line) will count as a failure), progression-free survival will also be reported using the method of Kaplan-Meier.

6.2 Correlative Analysis

With 36 patients, correlative analysis will be exploratory in nature. No attempt will be made to adjust for multiple comparisons (except as part of standard microarray analysis) and this will be noted in any report. Changes from baseline and comparison between responders and non-responders, will be summarized. We will also do a more refined analysis of 1st line, second line and third-line patients to explore the potential impact of EXE in these different patient populations.

6.3 Reporting of results

- All patients included in this study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are later determined to be ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

7.0 DATA AND SAFETY MONITORING

7.1 Definition of Risk Level

This is a Risk Level 3 study, as defined in the "City of Hope Data and Safety Monitoring Plan", http://www.coh.org/dsmc/Pages/forms-and-procedures.aspx because it is a pilot, Phase II clinical trial where the risks are at least balanced by the potential benefit to subjects and the importance of the knowledge that may result.

7.2 Monitoring and Personnel Responsible for Monitoring

The Protocol Management Team (PMT), consisting of the PI, Collaborating Investigator, CRA/protocol nurse and statistician, is responsible for monitoring the data and safety of this study, including implementation of any stopping rules for safety and efficacy.

Data and safety will be reported to the COH DSMC using the PMT report and submitted according to the timelines in Table 1 below. Protocol specific data collection will include the following items: summary of accrual, adverse events, and treatment related mortality.

Risk Level	Phase	Standard Reporting Requirement
RL 1, RL2, and Compassionate Use Studies	No reports required	

3	I	Every 3 months from activation date, as indicated in MIDAS
3	Pilot, Feasibility, II-IV	Every 6 months from activation date, as indicated in MIDAS
4	Pilot, Feasibility, I-IV	Every 3 months from activation date, as indicated in MIDAS

.

7.3 Definitions

Adverse event (AE) - An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

Unexpected Adverse Event [21 CFR 312.32 (a) – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Expected Adverse Event - Any event that does not meet the criteria for an unexpected event OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event

Serious Adverse Event (SAE) [21 CFR 312.32] is defined as *any expected or unexpected adverse event* that results in any of the following outcomes:

- Death
- Is life-threatening experience (places the subject at immediate risk of death from the event as it occurred)
- Unplanned hospitalization (equal to or greater than 24 hours) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Secondary Malignancy
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasisas of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Unanticipated problem (UP) – Any incident, experience, or outcome that **meets all three** of the following criteria:

1. Unexpected (in term nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

7.4 Reporting of Unanticipated Problems and Adverse Events

Unanticipated Problems: Most unanticipated problems must be reported to the COH DSMC and IRB **within 5 calendar days** according to definitions and guidelines at http://www.coh.org/hrpp/Pages/hrpp-policies.aspx. Any unanticipated problem that occurs during the study conduct will be reported to the DSMC and IRB by submitting electronically in iRIS (http://iris.coh.org).

Serious Adverse Events - All SAEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be reported according to definitions and guidelines at http://www.coh.org/hrpp/Pages/hrpp-policies.aspx and Table 2 below. Those SAEs that require expedited reporting will be submitted electronically in iRIS (http://iris.coh.org/).

Adverse Events - Adverse events will be monitored by the PMT. Adverse events that do not meet the criteria of serious OR are not unanticipated problems will be reported only in the protocol continuation reports and PMT report (see Table 2 below).

Table 2: City of Hope Adverse Event and Unanticipated Problem Reporting Timelines for the DSMC and IRB

Required Reporting Timelines to DSMC for AE/SAEs
Investigator Initiated Studies

Required Reporting Timeframe to DSMC		
Attribution	**UNEXPECTED**	**EXPECTED**

	Death while on active treatment or within 30 days of last day of treatment	
Possibly, Probably, Definitely	5 calendar days	
Unlikely, Unrelated		
	Death after 30 days of last active treatment/therapy	
Possibly, Probably, Definitely	5 calendar days	No reporting required
Unlikely, Unrelated	No reporting required	No reporting required
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	5 calendar days	10 calendar days
	Grades 1 and 2 AND resulting in "hospitalization"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	10 calendar days	10 calendar days

Externally Sponsored Studies

Required Reporting Timeframe to DSMC		
Attribution	**UNEXPECTED[1]**	**EXPECTED**
	Death while on active treatment or within 30 days of last day of treatment	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	
Unlikely, Unrelated		
	Death after 30 days of last active treatment/therapy	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	
Unlikely, Unrelated		
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	
Unlikely, Unrelated		
	Grades 1 and 2	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	

An event determined by the IRB of record to be an Unanticipated Problem (UP) will be communicated to the Investigator and COH DSMC through the COH IRB Operations Director. The DSMC will review the case and make a determination as to whether the study will be suspended, terminated, amended, or allowed to continue without amendment.

Required Reporting Timeframe to IRB of Record		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grades 3 and 4 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grade 1 and 2 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual

Additional Reporting Criteria

Pfizer

In addition to requirements of reporting of adverse events to the COH DSMB and IRB, serious adverse events resulting in death or considered life threatening will be submitted to Pfizer within 24 hours of awareness, via FDA MedWatch Form 3500A-Mandatory Reporting, obtained from the FDA website (http://www.fda.gov/medwatch/report/hcp.htm). The period that serious adverse events will be reported to Pfizer will be from the occurrence after the first dose of EXE, through 28 days after discontinuation of study treatment.

Fax FDA MedWatch Form 3500A to:

Pfizer U.S. Clinical Safety
Fax: 1-866-997-8322

8.0 DRUG INFORMATION

8.1 Description

EXE is an oral, irreversible, steroidal aromatase inactivator, structurally similar to the natural substrate, androstenedione. In postmenopausal women, estrogens are produced primarily by the conversions of androgens into estrogens through the aromatase enzyme in peripheral tissues. By acting as a false substrate and irreversibly binding to the active site of the aromatase enzyme, EXE causes inactivation of the aromatase enzyme,

resulting in significant inhibition of circulating estrogen concentrations in postmenopausal women, but has no detectable effect on adrenal biosynthesis of corticosteroids or aldosterone. In postmenopausal breast cancer patients treated with 25 mg of EXE daily, whole body aromatization was suppressed by greater than 90%. EXE is currently approved by the FDA for use in the treatment of postmenopausal women with advanced breast cancer, whose disease has progressed following tamoxifen therapy. EXE is also approved for use as adjuvant therapy for postmenopausal women with estrogen receptor positive breast cancer. The recommended dose of EXE is 25 mg orally once daily after a meal.

8.2 Toxicology

In clinical trials of 1058 postmenopausal women with advanced breast cancer, daily doses of EXE consisting of 25 mg, was generally well tolerated and adverse events were usually mild to moderate. Adverse effects of EXE which have been reported among postmenopausal women receiving this therapy in either the adjuvant or metastatic setting, include:

More Common

Endocrine/metabolic: diaphoresis (6-17.8%), hot sweats (13-32.9%)
Gastrointestinal: nausea (8.5-18%), diarrhea (4-9.6%), vomiting (7%)

Musculoskeletal: arthralgia (14.6-28.8%), myalgia (5.5%), osteoporosis (4.6%), pain in limb (9%), osteoarthritis (5.9%)
Neurologic: headache (6.9-13.1%), insomnia (11-13.7%), dizziness (8-9.7%)
Constitutional: fatigue (11-22%), asthenia (6%)
Dermatologic: alopecia (15.1%), dermatitis (8.2%)
Psychiatric: depression (6.2-13%), anxiety (4.1-11%)

Severe

Cardiovascular: heart failure (0.4%), myocardial infarction (1.6%)
Musculoskeletal: fracture of bone (4.2%)
Neurologic: cerebrovascular accident (6 deaths due to stroke, N=2252)
Hematologic: thromboembolic event (0.9%)

8.3 Pharmacology

Kinetics: EXE is rapidly absorbed after oral administration and high-fat food increases plasma levels. It is metabolized hepatically via the CYP3A4 pathway and converted into an active 17-dihydro metabolite. Routes of systemic excretion of EXE consist of fecal (42%) and renal (42%), with < 1% of drug remaining unchanged. Elimination half life is 24 hours. Based on experience with EXE in multiple doses up to 200 mg daily, the manufacturer does not recommend dosage adjustment in patients with renal or hepatic impairment. In postmenopausal women, suppression of plasma estrogen was observed 8-24 h after single oral doses of EXE [20].

Formulation: EXE is supplied as a 25 mg tablet.

Storage and Stability: Store at controlled room temperature, 25^0 C.

Administration: Oral

Supplier: This study will supply all study participants with EXE, as provided by the manufacturer (Pfizer).

9.0 REGULATORY OBLIGATIONS

9.1 Informed Consent

All patients will have signed an informed consent for participation in research activities, according to all institutional, NCI and federal regulations and will have been given a copy of the Experimental Subject's Bill of Rights. The original signed consent form will be placed in the medical record. A copy will be given to the subject and a copy will be filed in the research record.

9.2 Confidentiality of Records

The study protocol will strictly adhere to all HIPAA and COH IRB regulations. Confidentiality of subjects will be strictly maintained. All research records and data collection forms will be stored in secured cabinets at the data coordinating center at COH.

9.3 Registration Process

9.3.1 Registrations for this protocol must be made through the CRIM office at the City of Hope between the hours of 8:30 a.m. to 4:30 p.m., Monday through Friday (except holidays).

9.3.2 Patients must be registered within 2 weeks prior to initiation of protocol therapy.

9.3.3 A patient failing to meet all protocol requirements may not be registered. If you have any questions regarding eligibility, contact (626) 256-4673 ext. 62468 and ask for the CRA in charge of this study.

9.3.4 Pre-study laboratory tests, scans and x-rays must be completed prior to registration according to study calendar.

9.3.5 Patients must sign an informed consent prior to registration.

9.3.6 Confirm that the patient meets all inclusion and exclusion eligibility criteria for this protocol.

9.3.7 Complete the eligibility checklist.

9.3.8 Verify that all required pre-study tests were performed.

9.3.9 Fax the completed eligibility checklist and the signed, dated informed consent to CRIM. The FAX number is (626) 301-8393.

9.3.10 Call the CRA at (626) 256-4673 x 62468 to confirm the FAX arrival. If the coordinator is not in the office, have her paged.

9.3.11 If the patient qualifies, the City of Hope coordinator will assign the patient's study ID number.

9.3.12 Once a patient has been registered, the CRA will confirm registration of the patient.

9.4 Data Collection Forms and Submission Schedule

All data will be collected using COH Biostatistics Information Tracking System (BITS) data collection forms. Forms to be completed include:

Eligibility Checklist:	This form will be completed at the time of registration.
On-Study Form:	To be completed within two weeks of registration.
Treatment Form:	To be completed within four weeks of completion of one cycle of treatment.
Flow Sheets:	Protocol specific flow sheets are to be submitted along with each treatment form.
Response/Off-Study/ Follow-Up:	Form F/U is to be submitted each time a patient is evaluated for response and/or new follow-up information is obtained.
Supplemental Data Form:	The timeline for submission of the supplemental data form will be protocol specific, if applicable.

Additionally, Health Assessment Questionnaires (Appendix A), EORTC Quality of Life Questionnaires (Appendix C) and treatment diaries will be collected per study calendar (section 10).

10. STUDY CALENDAR

STUDY CALENDAR

	Screen	Study Treatment																		Study Termination
Cycle		1			2			3			4			5			6			
Cycle Days[5]		1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	
Study Week		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
Treatment Schedule[5]																				
Exemestane		X	X	OFF	X	X	OFF	X	X	OFF	X	X	OFF	X	X	OFF	X	X	OFF	
GENERAL ASSESSMENTS																				
Informed consent	X																			
Review of Eligibility	X																			
Medical History/Clincal Evaluation[1]	X							X									X			
Weight/Height/Vitals	X							X									X			
Prior & Current Medication List	X	X			X			X			X			X			X			
Assessment of Compliance/Toxicity								X									X			
LABORATORY ASSESSMENTS																				
Blood Chemistry[6]	X	X			X			X			X			X			X			
Hematology[6]	X	X			X			X			X			X			X			
TUMOR RELATED ASSESSMENTS																				
Bone Scan[2]	X									X									X	
Radiologic Assessments[3]	X									X									X	
Quality of Life (Appendix C)		X			X			X			X			X			X			X
Tumor Sample[4]	X																			X
HAQ Questionnaire (Appendix A)		X			X			X			X			X			X			

Continue Assessments Until PD, Unacceptable Toxicity, Consent Withdrawal, PI Discretion or Death

[1]Clinical evaluation including physical examination and assessment of performance status (ECOG Score)	
[2]Patients with a positive bone scan at screening ***[note**: PET/CT Scan may be used in lieu of Bone Scan when patient is symptomatic]* will continue to have bone scans performed every 9 weeks while on study. Subjects with a negative bone scan at the start of study will not be required to continue with follow-up bone scans, unless clinically indicated.	
[3]Radiologic assessments may be performed by CT or MRI but the same modality used at the time of screening must be used throughout the study. Studies will be repeated every 9 weeks.	
[4]Tumor samples of primary and metastatic sites (archived block, slides or fresh tissue collected for clinical care purposes), will be collected at study initiation. If possible, pre- and post-treatment biopsy specimens will also be obtained.	
[5] All tests, procedures and treatment will have +/- 3 day window.	
[6] Research Patient Numbers (RPNs) will be used as identifiers for blood samples collected. After Cycle 6, Blood Chemistry and Hematology will be done per MD discretion.	

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APPENDIX A: HEALTH ASSESSMENT QUESTIONNAIRE (HAQ DI©)

Name:_____ Date_____

Please place and "x" in the box which best describes your abilities OVER THE PAST WEEK:

ARE YOU ABLE TO:	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE T0 DO
DRESSING AND GROOMING				
Dress yourself, including shoelaces and buttons?	☐	☐	☐	☐
Shampoo your hair?	☐	☐	☐	☐
ARISING				
Stand up from a straight chair?	☐	☐	☐	☐
Get in and out of bed?	☐	☐	☐	☐
EATING				
Cut your own meat?	☐	☐	☐	☐
Lift a full cup or glass to your mouth?	☐	☐	☐	☐
Open a new milk carton?	☐	☐	☐	☐
WALKING				
Walk outdoors on flat ground?	☐	☐	☐	☐
Climb up five steps?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

☐ Devices used for Dressing (button hook, zipper pull, etc.) ☐ Built up or special utensils ☐ Crutches

☐ Special or built up chair ☐ Cane ☐ Walker ☐ Wheelchair

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Dressing and grooming ☐ Arising ☐ Eating ☐ Walking

Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

ARE YOU ABLE TO:	**WITHOUT ANY DIFFICULTY**	**WITH SOME DIFFICULTY**	**WITH MUCH DIFFICULT**	**UNABLE TO DO**
HYGIENE				
Wash and dry your body?	☐	☐	☐	☐
Take a tub bath?	☐	☐	☐	☐
Get on and off the toilet?	☐	☐	☐	☐
REACH				
Reach and get down a 5 pound object (such as a bag of sugar) from above your head?	☐	☐	☐	☐
Bend down to pick up clothing from the floor?	☐	☐	☐	☐
GRIP				
Open car doors?	☐	☐	☐	☐
Open previously opened jars?	☐	☐	☐	☐
Turn faucets on and off?	☐	☐	☐	☐
ACTIVITIES				
Run errands and shop?	☐	☐	☐	☐
Get in and out of a car?	☐	☐	☐	☐
Do chores such as vacuuming or yard work?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

☐ Raised toilet seat ☐ Bathtub bar ☐ Long-handled applicances for reach

☐ Bathtub seat ☐ Long-handled appliances in bathroom ☐ Jar opener (for jars previously opened)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Hygiene ☐ Reach ☐ Gripping and opening things ☐ Errands and chores

Your ACTIVITIES: To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries or moving a chair?

Completely	Mostly	Moderately	A Little	Not at All
☐	☐	☐	☐	☐

Your PAIN: How much pain have you had IN THE PAST WEEK?
On a scale of 0 to 100 (where zero represents "no pain" and 100 represents "severe pain"), please record the number below.

Your HEALTH: Please rate how well you are doing on a scale of 0 to 100 (zero represents "very well" and 100 represents "very poor" health), please record the number below.

APPENDIX B: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX C

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:

	Not at All	AQuite Little	a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

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

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

1 2 3 4 5 6 7

Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent