THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

A Randomized Phase II Study of Letrozole Versus Observation in Patients with Newly Diagnosed Uterine Leiomyosarcoma
2006-0453

Core Protocol Information

Short Title	Letrozole versus observation in patients with newly diagnosed uterine leiomyosarcoma
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Which Committee will review this protocol?

(•) The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

To prolong the time to recurrence for patients with clinical stage I and II uterine LMS assigned to letrozole therapy. The primary endpoint of this study will be a prolongation of time to disease recurrence.

2.0 Background

Letrozole (4,4'-(1H-1,2,4-Triazol-1-ylmethylene)bis-benzonitrile) is a synthetic achiral benzydryltriazole derivative. It is an orally active highly selective non-steroidal competitive inhibitor of the aromatase enzyme system [1,2]. Aromatase inhibitors block the aromatase enzyme, consequently lowering estrogen levels and thereby deprive the tumor of its growth stimulus. Letrozole effectively inhibits the conversion of androgens to estrogens in both *in vitro* and *in* vivo [1]. This property makes it in particular suitable for postmenopausal women whose main source of estrogen is via peripheral aromatization of androgen precursors.

Letrozole is up to 150-250 times more potent than the first generation aromatase inhibitor Aminoglutethimide (AG), *in vitro* and more than 10,000 times as potent as AG in inhibiting aromatase *in* vivo [3]. The high potency of letrozole is not accompanied by any significant effect on adrenal steroidogenesis *in vitro* or *in vivo* over its maximally effective dose range [1,4]. Inhibition of adrenal steroidogenesis resulting in adrenal hypertrophy does occur with therapeutic doses of AG. The high potency and selectivity of letrozole explains its pharmacological profile and high therapeutic index. In postmenopausal patients with advanced breast cancer, daily doses of 0.1 to 5 mg letrozole suppressed plasma levels of estradiol, estrone and estrone sulfate to 75-95% from baseline [1,5]. A Phase III global, multicenter, randomized clinical trial evaluated Letrozole (2.5 mg/day) as a first line hormonal therapy as compared to the present standard of treatment, tamoxifen (20 mg once daily) [6]. This trial accrued 907 postmenopausal women with ER and/or PR positive or unknown receptor breast cancer and locally advanced disease, metastatic disease, or loco-regional recurrence not amenable to treatment by surgery or radiotherapy. Patients received treatment until disease progression or discontinuation for any other reason.

The primary endpoint was time to progression. letrozole was superior to tamoxifen in TTP, reducing the risk of progression by 28% (hazard ratio 0.72, $p < .0001$). The median TTP was prolonged by 57%, from 6.0 months for tamoxifen to 9.4 months for letrozole The secondary endpoints included overall tumor response rate, clinical benefit, and time to treatment failure. Overall tumor response rate (complete and partial response) was significantly higher with letrozole (32 % vs 21%, p= .0002, irrespective of dominant site of disease. Clinical benefit (CR, PR or stabilization of disease lasting at least 24 weeks was 50% for letrozole vs 38% tamoxifen, p=. 0004. Time to treatment failure was significantly better for letrozole 9.0 months vs 5.7 months for tamoxifen, p =. 0001.

The median overall survival was slightly prolonged for letrozole 34 versus 30 months for tamoxifen. This difference is not significant. However, the study design included a crossover to the other treatment arm at the discretion of the investigator. An analysis was done in the patients

who did not crossover, which demonstrated a 15-month survival advantage in the letrozole treatment group [7]. The data cutoff for this analysis was September 2001, when median follow-up was 32 months, with a maximum observation period of 57 months [6].

Tolerability was similar in both arms of the trial, with 2% of patients on letrozole and 3% of patients on tamoxifen discontinuing core therapy due to adverse events. In conclusion, letrozole has a highly favorable toxicity profile and is superior in TTP and CR compared to tamoxifen in patients with locally advanced and metastatic breast cancer. Based on this study and other supportive data, FDA approved letrozole for first-line hormonal therapy in locally advanced or metastatic breast cancer in January 2001.

A recently completed randomized, double-blind, multicenter study compared the efficacy of 4 months of therapy with letrozole 2.5 mg daily and tamoxifen 20 mg daily as primary treatment in the neoadjuvant setting [8]. The response rate, assessed by clinical palpation (primary endpoint), was 55% for letrozole compared to 36% for tamoxifen ($p<0.001$). Response rates were similarly significant in favor of letrozole when assessed by ultrasound or mammography.

A double-blind crossover study was conducted in 12 estrogen receptor-postive postmenopausal metastatic breast cancer patients to compare the effects of letrozole and anastrozole on total-body aromatization and plasma estrogen levels. Each regimen was administered for 6 weeks. The data revealed that letrozole suppresses plasma estrogen levels more completely than anastrozole [9]. Letrozole was statistically superior to anastrozole in reducing plasma levels of both estrone sulfate ($p=0.019$) and estrone ($p=0.0037$). Patients switching from 6 weeks of anastrozole to 6 weeks of letrozole consistently achieved further estrogen suppression. Conversely, patients switching from 6 weeks of letrozole to 6 weeks of anastrozole experienced an increase in estrogen plasma levels.

A multicenter, double-blind study randomized over 8,000 postmenopausal women with resected, receptor-positive early breast cancer to one of the following arms:

A. Tamoxifen for 5 years
B. Femara for 5 years
C. Tamoxifen for 2 years followed by Femara for 3 years
D. Femara for 2 years followed by Tamoxifen for 3 years

Of 8,010 women with evaluable data, 4,003 were in the letrozole group and 4,007 in the tamoxifen group. After a median follow-up of 25.8 months, there were 351 events of recurrence, locally or at distant sites, in the letrozole group, and 428 events in the tamoxifen group. Five-year disease-free survival estimates were 84.0% and 81.4%, respectively. [25]

Compared with tamoxifen, letrozole reduced the risk for an event ending a period of disease-free survival (hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.70 - 0.93; $P = .003$). This reduction especially applied to the risk for distant recurrence (HR, 0.73; 95% CI, 0.60 - 0.88; $P = .001$).

Adverse events have been analyzed irrespective of whether a symptom was present or

absent at baseline. Most adverse events reported (82%) were Grade 1 and Grade 2 applying the Common Toxicity Criteria Version 2.0.

When considering all grades, a higher incidence of events were seen for Femara regarding fractures (5.7% vs 4%), myocardial infarctions (0.6% vs 0.4%), and arthralgia (21.2% vs 13.5%) (Femara vs tamoxifen respectively). A higher incidence was seen for tamoxifen regarding thromboembolic events (1.2% vs 2.8%), endometrial cancer (0.2% vs 0.4%), endometrial proliferative disorders (0.3% vs 1.8%) Femara vs tamoxifen respectively.

In the adjuvant setting, an increase in total cholesterol (generally non-fasting) in patients who had baseline values of total serum cholesterol within normal range, and then subsequently had an increase in total serum cholesterol of 1.5 ULN was 173/3203 (5.4%) on letrozole vs 40/3224 (1.2%) on tamoxifen. Lipid lowering drugs were used by 18% of patients on letrozole and 12% on tamoxifen.

Uterine leiomyosarcomas (LMS) are rare, accounting for less than five percent of all malignant uterine neoplasms. Approximately 85% of women present with clinical stage I or II disease (i.e., disease limited to disease that is limited to the uterus and cervix). Lymph node metastasis is not common for patients with LMS, therefore, clinical staging is adequate and surgical re-exploration is not necessary for patients who are not initially staged [10]. Despite the low incidence of high stage disease, approximately 50% of patients will recur within two years [10-12]. Most of these patients recur outside of the pelvis. The Gynecologic Oncology Group evaluated the role of adjuvant radiation therapy in patients (n=48) with clinical stage I and II disease [11]. There was no difference in the progression-free interval, absolute two-year survival rate, or site of first recurrence between patients who received pelvic radiation (n= 11) and those that did not (n=37). This is not surprising since most recurrences were outside of the pelvis (83%). 48% of the patients recurred and most of these patients recurred within 17 months of diagnosis. Adjuvant chemotherapy was also evaluated for patients with this disease [12]. In patients treated with adjuvant adriamycin, 44% recurred versus 61% in patients who did not receive chemotherapy. This difference was not statistically significant.

Several studies have evaluated the rate of hormone receptor expression in patients with LMS of the uterus [13-21]. 40-87% of leiomyosarcomas express the estrogen receptor (ER) and 38-80% express the progesterone receptor (PR). Because of this high expression, estrogen may act as a growth factor that stimulates cell proliferation and tumor growth.

Hormonal manipulation is commonly used to control the growth of benign leiomyomas. Given the relatively high rate of hormone receptor positivity for LMS, we hypothesize that by decreasing systemic estrogen using an aromatase inhibitor, we may be able to prolong the time to recurrence for patients with this disease. [26-28]

3.0 Treatment Plan

3.1. Overall study design

This is a randomized phase II study of Femara (letrozole) administered orally on a daily basis to patients with newly diagnosed clinical stage I and II LMS. Using an adaptive randomization,

patients will be assigned to either the treatment arm (letrozole group) or observation. The primary outcome for this trial is the time to progression or death.

3.3. Study population

3.3.1. Patient population

Patient enrollment will be open to any individual with clinical stage I and II uterine LMS seen in the Gynecologic Oncology Center at M. D. Anderson Cancer Center. Hormone receptor positivity is an eligibility requirement.

3.3.2. Inclusion and exclusion criteria

Inclusion criteria

To be eligible for the study, patients must fulfill all of the following criteria:

1. Patients must have signed an approved informed consent.
2. Histologically confirmed uterine leiomyosarcoma with disease limited to the uterus (determined by surgical staging or radiologic imaging).
3. Tumors must express ER positivity by immunohistochemistry (ER expression >10% by immunohistochemistry).
4. Patients must have a hysterectomy and bilateral oophorectomy prior to initiation of therapy.
5. All patients must have no measurable disease. Measurable disease is defined as lesions that can be measured by physical examination or by means of imaging techniques. Imaging must be done within 6 weeks of study entry.
6. Patients must have a Zubrod performance status of 0, 1, or 2.
7. Patients must have a pretreatment granulocyte count (i.e., segmented neutrophils + bands) of >1,000/Fl, a hemoglobin level of $\geq$9.0 gm/dL and a platelet count of >75,000/dL.
8. Patients must have an adequate renal function as documented by serum creatinine $\leq$2.0 mg/dL.
9. Patients must have adequate hepatic function as documented by a serum bilirubin $\leq$2.5 mg/dL.
10. Aspartate transaminase (SGOT) must be $\leq$3x institutional upper limit of normal.
11. Patients must have recovered from the effects of prior surgery.
12. No more than 12 weeks must have elapsed from hysterectomy.
13. Patients must be 18 years of age or older.

Exclusion criteria

Patients meeting any of the following criteria are ineligible to participate in this study:

1. Patients who do not have pure uterine sarcomas (i.e., no mixed malignant mullerian tumors).
2. Patients with any other severe concurrent disease, which would make the patient inappropriate for entry into this study, including significant hepatic, renal, or gastrointestinal diseases.
3. Patients with a history of prior malignancy except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer for

which the patient has been disease-free for at least five years.

4. Patients who were taking or have a history of taking letrozole or any other aromatase inhibitor.
5. Patients with active or uncontrolled systemic infection.
6. Patients with history of uncontrolled cardiac disease; i.e., uncontrolled hypertension, unstable angina, recent myocardial infarction (within prior 6 months), uncontrolled congestive heart failure, and cardiomyopathy with an ejection fraction under 40%.
7. Patients who are pregnant or breast-feeding.
8. Presence of clinically apparent untreated central nervous system metastases
9. Presence of carcinomatous meningitis.
10. Patients currently receiving chemotherapy or radiation therapy.

MDACC will not exclude any potential subject from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the MDACC cancer population.

3.3.3. Interruption or discontinuation of treatment

A genuine effort must be made to determine the reason(s) why a patient fails to return for the necessary visits or is discontinued from the trial. Information regarding the reason for not completing the trial will be recorded in the patient's medical record.

Reasons that a patient may discontinue participation in this clinical study include:

1. adverse event(s)
2. abnormal laboratory value(s)
3. abnormal test procedure result(s)
4. unsatisfactory therapeutic effect
5. subject's condition no longer requires study drug
6. protocol violation
7. subject withdrew consent
8. lost to follow-up
9. death.

Any patient who receives at least one dose of trial medication will be included in the safety analysis.

3.4. Drug Information

Description:

Letrozole is used to treat certain types of breast cancer in women. Female hormones that occur naturally in the body can increase the growth of some cancers. Letrozole works by decreasing the amounts of these hormones in the body. The medicine is meant to be used

only by women who have already stopped menstruation.

The most commonly used brand name is Femara. The chemical name is 4,4'-(1H-1,2,4-Triazol-1-ylmethylene)dibenzonitrile.

Drug Supply: Letrozole will be supplied by Norvartis Pharmaceuticals.

Availability and storage: Available as 2.5 mg tablet or oral administration. Should be stored at room temperature.

Dosage: 2.5mg tablet PO daily

Pharmacokinetics: Letrozole is rapidly and completely absorbed from the gastrointestinal tract. The terminal elimination half-life is about two days. Daily doses of 0.1mg to 5 mg Letrozole suppresses plasma concentrations of estrone, and estrone sulfate by 75% to 95% from baseline with maximal suppression achieved within two to three days.

Toxicity: Letrozole is well tolerated by most patients. The common adverse effects reported with daily administration of letrozole include headache, mild nausea, hot flashes, diarrhea, fluid retention and muscle cramps. Other side affects include burning, dryness or itching of the vagina. It may cause vaginal bleeding or discharge.

Letrozole may cause breast pain, chills, fever, flu-like symptoms and mental depression. It may also cause bone pain, joint or muscle pain. It may cause anxiety, confusion, increased thirst and urination, loss of appetite or weight loss. It has also been associated with skin rash, or itching, sleepiness, trouble sleeping, unusual tiredness and weakness. Letrozole sometimes causes a loss of hair. Letrozole may increased risk for blood clots, which could lead to a heart attack or a stroke.

Adverse Effects are usually mild to moderate and rarely necessitate discontinuation of treatment

Treatment compliance
Patients will remain on study until disease progression. For the purposes of this trial the final data collection point is at the time of disease progression. For those patients assigned to the treatment group, records of study medication used and dosages administered will be kept during the study. Drug accountability will be noted during follow-up visits and at the completion of the trial. Patients will be asked to return all unused medication.

3.5. Visit schedule and assessments

3.5.1. Visit schedule

Examination	Screening	Pre-treatment	Q 12 Weeks	Q 24 Weeks	Q 12 months	End of study

Informed consent	X					
Medical history	X		X		X	X
Concurrent medications	X	X	X		X	X
Inclusion/exclusion criteria	X					
Zubrod performance status	X	X	X		X	X
Vital signs/weight	X	X	X		X	X
Physical examination	X	X[b]	X		X	X
Pelvic exam	X	X[b]	X		X	X
ECG	X					
CBC/DIFF/PLT		X[b]	X		X	X
Magnesium, SGOT, total bilirubin, BUN, serum creatinine, electrolytes		X[b]	X		X	X
Serum cholesterol		X	X		X	X
Toxicity assessment		X	X[c]		X[c]	X[c]
CXR	X			X	X	
CT scan of chest, abdomen/pelvis[a]			-	X		

a. within 6 weeks of study entry
b. within 14 days of study entry
c. treatment-related toxicities (study drug arm)

3.5.2. Screening/Baseline

To be completed within 6 weeks of study entry

1. CT scan of the chest, abdomen/pelvis

To be completed within four weeks prior to initiation of therapy

1. Medical history including list of current medications and dosing schedules, history of previous therapies for current disease; and any residual toxicity from prior therapies should be recorded by using the grading schema in NCI Common Terminology Criteria for Adverse Events, Version 3.0.
2. Chest x-ray
3. ECG

To be completed within 14 days of initiation of therapy:

1. Weight
2. Complete blood count with leukocyte differential and platelet count, serum chemistries (magnesium, SGOT, total bilirubin, BUN, serum creatinine), and electrolytes.
3. Serum cholesterol
4. Vital Signs (blood pressure, pulse, respiratory rate, temperature)
5. Physical exam including pelvic exam
6. Zubrod performance status

To be obtained every 12 weeks (+/- 7 days)**:**

1. Weight
2. Complete blood count with leukocyte differential and platelet count, serum

chemistries (magnesium, SGOT, total bilirubin, BUN, serum creatinine), electrolytes
3. Serum cholesterol
4. Vital Signs (blood pressure, pulse, respiratory rate, temperature)
5. Physical exam (including pelvic exam)
6. Zubrod performance status
7. Assessment of treatment-related toxicities (study drug arm) using the grading schema in NCI Common Terminology Criteria for Adverse Events, Version 3.0.

To be obtained every 24 weeks (+/- 7 days):

1. Chest Xray
2. CT scan of the chest, abdomen and pelvis

To be obtained every 12 months (+/-7 days):

1. Weight
2. Complete blood count with leukocyte differential and platelet count, serum chemistries (magnesium, SGOT, total bilirubin, BUN, serum creatinine), electrolytes
3. Serum cholesterol
4. Vital Signs (blood pressure, pulse, respiratory rate, temperature)
5. Physical exam (including pelvic exam)
6. Zubrod performance status
7. Assessment of treatment-related toxicities (study drug arm) using the grading schema in NCI Common Terminology Criteria for Adverse Events, Version 3.0.

To be obtained at the end of treatment:

1. Weight
2. Complete blood count with leukocyte differential and platelet count, serum chemistries (magnesium, SGOT, total bilirubin, BUN, serum creatinine), and electrolytes.
3. Serum cholesterol
4. Vital signs (blood pressure, pulse, respiratory rate, temperature)
5. Physical exam (including pelvic exam)
6. Zubrod performance status
7. Assessment of treatment-related toxicities (study drug arm) using the grading schema in NCI Common Terminology Criteria for Adverse Events, Version 3.0.

Follow-up and further imaging:

Follow-up will be at the discretion of the patient's primary physician and based on physical findings.

3.5.3. Safety assessments

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry and urine values, regular measurement of vital signs and the performance of physical examinations.

Adverse events

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded. An adverse event is any undesirable sign, symptom or medical condition occurring after starting study drug (or therapy) even if the event is not considered to be related to study drug (or therapy). Study drug (or therapy) includes the drug (or therapy) under evaluation, and any reference or placebo drug (or therapy) given during any phase of the trial.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events occurring before starting study treatment but after signing the informed consent form will also be recorded.

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for adverse event reporting. A copy of the CTCAE version 3.0 can be downloaded from the CTEP home page (http:/www.ctep.info.nih.gov/) and is appended to this protocol. Life-threatening toxicities should be reported immediately to the Study Chairman, who in turn must notify the IRB. Reporting of adverse reactions is in addition to and does not supplant the reporting of toxicities as part of the results of the clinical trial.

This protocol will follow the Guidelines for Adverse Event Reporting appended to this protocol. In addition, the reporting requirements for Novartis are defined below.

<u>Protocol Safety Requirements for Novartis</u>

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Novartis Pharmaceuticals Clinical Safety and Epidemiology Department (CS&E).

Any Serious Adverse event occurring in a patient after providing informed consent, while receiving study drug, and until four weeks after stopping study drug must be reported by FAX [redacted]) to Novartis Pharmaceuticals CS&E Department within 24 hours of learning of it's occurrence, even if it is not felt to be drug related. It is requested that SAEs are reported to Novartis using the Norvartis SAE form (Appendix E)

Serious adverse events
A serious adverse event is an undesirable sign, symptom or medical condition which:

1. is fatal or life-threatening
2. required or prolonged hospitalization
3. results in persistent or significant disability/incapacity
4. constitutes a congenital anomaly or a birth defect
5. are medically significant, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation must be reported.

Grading/Rating Scale

1. All adverse events reported during the study will be evaluated and graded on a scale of 1-5. The NCI Common Terminology Criteria for Adverse Events, v3.0 (CTCAE) will be used to determine the grade for all toxicities.
2. For any adverse events, which are not listed in the CTCAE the following rating system, will be used:

Grade	Description
0	No AE or within normal limits
1	Mild AE (minor; no specific medical intervention; asymptomatic laboratory findings only, radiographic findings only; marginal clinical relevance)
2	Moderate AE (minimal intervention; local intervention; noninvasive intervention [packing, cautery])
3	Severe and undesirable AE (significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation)
4	Life-threatening or disabling AE (complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis. Life-threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation)
5	Fatal AE

Attribution is the determination of whether an AE is related to medical treatment or procedure. CTCAE does not define an AE as necessarily ‘caused by a therapeutic intervention.’ The clinical investigator must assign attribution for an adverse event after naming and grading of the event.

Attribution	Description
Unrelated	The AE is clearly NOT related to the intervention
Unlikely	The AE is doubtfully related to the intervention
Possible	The AE may be related to the intervention
Probable	The AE is likely related to the intervention
Definite	The AE is clearly related to the intervention

3.5.4. Drug levels and pharmacokinetic assessments
Drug levels/pharmacokinetic assessments will not be performed

3.6 Efficacy Assessment
Patients receiving letrozole will continue until progression or drug related toxicity. Those assigned to the observation group will be followed until disease progression. Progression will be defined as appearance of one or more new lesions on clinical exam or on radiologic imaging. At the physician's discretion, clinical findings can warrant further radiologic imaging. If the imaging reveals a new lesion, recurrent disease should be biopsy proven.

4.0 Protocol amendments

Any changes to the protocol will be made in the form of an amendment and will be approved by Novartis and the MD Anderson Cancer Center Institutional Review Board. Changes in study conduct are not permitted. Any unforeseen changes in study conduct will be recorded per institutional policy.

5.0 Data management

Registration:
This is a randomized, phase II trial of letrozole verses observation for patients with newly diagnosed, stage I and II, uterine leiomyosarcoma. All patients who meet eligibility criteria and are enrolled in this trial will be registered in Clinical Oncology Research Database (CORe) at the University of Texas MD. Anderson Cancer Center. The date in the current informed consent document is displayed to ensure only the most current IRB approved version is used. Consent date, registration date, off study date, and evaluability data are required for all registrants.

Data Collection:
Data will be collected and stored in the MD Anderson Protocol Data Management System (PDMS). Reporting to the sponsor, if applicable, will follow the contract agreement.

6.0 Statistical Design

We will accrue a minimum of 10 patients and a maximum of 80 patients at a rate of 2 patients per month. The primary outcome for this trial is the time to progression or death. Patients treated with standard of care (observation) have median progression-free survival (PFS) of 24 months [10]. We will follow all patients for at least 24 months following treatment.

Patients will be randomized between observation and letrozole using a Bayesian adaptive algorithm [22]. Details of this methodology are given in the "Technical Details" section below. The first 10 patients will be randomized fairly between the 2 treatment arms. After 10 patients are enrolled there will be 5 patients on each treatment arm. As the trial progresses and data accrue the randomization will become unbalanced in favor of the treatment that, on average, has better results in terms of PFS, so that each successive patient is more likely to receive the treatment showing better results.

The trial will be stopped early and a treatment selected as being "better" if the probability is 0.90 or more that one treatment's PFS is longer than the other treatment's PFS. However, if all 80 patients are enrolled, then a treatment will be selected as being "better" if the probability is 0.80 or more that one treatment's PFS is longer than the other treatment's PFS.

The operating characteristics of this study design are summarized in Table 1. These operating characteristics are based on 1000 simulations of the study design for 6 possible scenarios.

6.1 Outcomes

6.1.1 Primary Outcome

We will report the posterior probability that the letrozole arm has longer PFS than the observation arm. We will also provide a 95% posterior credible interval for the probability that the letrozole arm has longer PFS than the observation arm.

We will estimate the PFS with the Kaplan-Meier 23 product-limit estimator for each arm, and we will compare the PFS between the 2 arms with the log-rank test. We will model PFS with the Cox [24] proportional hazards regression model to estimate the hazard ratio for treatment (letrozole : observation), and we will construct the 95% confidence interval for this hazard ratio.

6.1.2 Secondary Outcome

We will estimate the overall survival (OS) with the Kaplan-Meier product-limit estimator for each arm, and we will compare the OS between the 2 arms with the log-rank test. We will model OS with the Cox proportional hazards regression model to estimate the hazard ratio for treatment (letrozole : observation), and we will construct a 95% confidence interval for this hazard ratio.

6.2 Technical Details

Let MO and ML be the median PFS for treatments "observation" (O) and "letrozole" (L), respectively. We assume that MO and ML each have an inverse gamma prior distribution with mean 24 months and variance 57.6 months. The middle 95% of this prior distribution is between 13.4 and 42.6 months.

For each patient, the randomization probability for treatment O will be the posterior probability that it has the longer PFS, that is pO(data) = Pr(MO > ML| data) and the randomization probability for treatment L is pL(data) = 1- pO(data). If at any point during the trial pL(data) > 0.90 (< 0.10) the trial will be terminated and treatment L will

be selected as superior (inferior). If the maximum number of patients is enrolled in the trial and pL(data) > 0.80 (< 0.20) treatment L will be selected as superior (inferior). If at any time during the trial we find that Pr(MO > 24 | data) < 0.05 or Pr(ML > 24 | data) < 0.05 we will suspend accrual to arm O or L, respectively, until this probability is 0.05 or greater.

7.1 Administrative procedures

7.1.1. Changes to the protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by the principle investigator, Novartis and the IRB before implementation. Examples of amendments requiring such approval are:

1. an increase in drug dosage or duration of exposure of subjects
2. a significant change in the study design (e.g. addition or deletion of a control group)
3. an increase in the number of invasive procedures to which subjects are exposed
4. addition or deletion of a test procedure for safety monitoring.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all subjects included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented by him/her for safety reasons, the IRB/IEC/REB at the center should be informed within 10 working days.

7.2 Recording of data and retention of documents

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the investigational product or entered as a control in the investigation.

The Investigator must retain investigational product disposition records and source documents for the maximum period required by applicable regulations and guidelines, or Institution procedures.

If the Investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another Investigator, IRB). Notice of such transfer will be given in writing to Novartis.

7.2.3 Handling of study medication

It is the responsibility of the Investigator to ensure that a current record of study drug disposition is maintained at each study site where the study drug is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines.

7.2.4. Publication of results

Any formal presentation or publication of data from this trial may be considered as a joint publication by the Principle Investigator and appropriate Novartis personnel. Authorship will be determined by mutual agreement. For multicenter studies, it is mandatory that the first publication is based on data from all centers, analyzed as stipulated in the protocol, and not by the investigators. Investigators participating in multicenter studies agree not to present data gathered from one center or a small group of centers before the full publication, unless formally agreed to by the Principle Investigator and Novartis.

Novartis must receive copies of any intended communication in advance of publication (at least 15 working days for an abstract or oral presentation and 45 working days for a journal submission). Novartis will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that confidential information is not being inadvertently divulged and provide any relevant supplementary information.

7.2.5. Disclosure and confidentiality

By signing the protocol, the investigator agrees to keep all information provided by Novartis in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by Novartis (protocols, investigators' brochures, and other material) will be stored appropriately to ensure their confidentiality. The information provided by Novartis to the investigator may not be disclosed to others without direct written authorization from Novartis, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

7.2.6. Discontinuation of study

Novartis reserves the right to discontinue any study under the conditions specified in the clinical trial agreement.

7.3. Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and in accordance with Good Clinical Practice, as described in:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
3. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
4. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong

1989, Somerset West 1996).

7.3.1. Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC/REB). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

7.3.2. Informed consent

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that she may withdraw from the study at any time and that withdrawal of consent will not affect her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and must be submitted by the investigator for IRB/IEC/REB approval. Novartis supplies a proposed informed consent form, which complies to regulatory requirements and is considered appropriate for the study. Any changes to the proposed consent form suggested by the Investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to Novartis after IRB/IEC/REB approval.

7.3.3. Declaration of Helsinki

The investigator must conduct the trial in accordance with the Declaration of Helsinki.

8.0 References

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