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MD Anderson Cancer Center

Protocol Page

Phase II Study of Letrozole (Femara) Plus Imatinib Mesylate (Gleevec) for Postmenopausal Patients with ER and/or PR Positive Metastatic Breast Cancer 2003-0384

Core Protocol Information

Short Title	Phase II Femara Plus Gleevec
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Which Committee will review this protocol?

(●) The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

1. To determine the efficacy of Letrozole plus Imatinib Mesylate in patients with ER and or PgR positive metastatic breast cancer. Efficacy will be measured by the rate of clinical tumor response.

2. To determine the safety and tolerability of Letrozole plus Imatinib Mesylate in patients with metastatic breast cancer.

3. To determine the time to disease progression and overall survival in patients with metastatic breast cancer who are treated with Letrozole plus Imatinib Mesylate.

2.0 Background

2.1 Metastatic Breast Cancer

Breast cancer is the most common malignant disease in women and the second leading cause of female cancer death. Approximately 200,000 women are yearly diagnosed with breast cancer and over 40,000 patients die from breast cancer in the United States[1].

Although patients with early-stage breast cancer can be cured by surgery, radiation and systemic therapy, once the disease has spread to distant organs it is not curable by conventional therapies. Patients with metastatic disease whose tumors spread the estrogen receptor (ER) or the progesterone receptor (PR) can be effectively palliated using a range of endocrine therapies. These include tamoxifen and aromatase inhibitors. Chemotherapy is reserved for patients with hormone-insensitive or hormone-resistant metastatic breast cancer. Endocrine and chemotherapeutic agents are also not curative in most patients with late stage breast cancer, in part because women who progress to stage IV often become refractory to hormonal therapy and chemotherapy. Consequently, patients with refractory stage IV disease are often treated primarily with palliative intent.

The median survival of patients with stage IV breast cancer is approximately two years. However, the outlook for survival in stage IV patients who have failed at least one chemotherapy regimen is often fewer than 12 months. Due to the limited treatment options available for patients with refractory stage IV breast cancer, and the poor prognosis for this disease population, it is clear that new therapeutic options for treatment should be investigated.

2.2 Letrozole

Letrozole molecular weight is 285.31. It is freely soluble in dichloromethane, slightly soluble in ethanol, and practically insoluble in water. In human liver microsomes, femara strongly inhibits the cytochrome P450 (CYP) isoenzyme 2A6 (CYP 2A6) and moderately inhibits the CYP isoenzyme 2C19 (CYP 2C19). Letrozole has not been shown to affect synthesis of adrenal corticosteroids, aldosterone, or thyroid hormones. Rapidly and completely absorbed. Absorption is not affected by food. The volume of distribution (Vol D) is approximately 1.9 liters per kg of body weight. It is biotransformed in the liver, by the CYP isoenzymes 3A4 and 2A6 (CYP 3A4 and CYP 2A6), to an inactive carbinol metabolite and its ketone analog. Its half life is approximately 2 days. Time to steady-state concentration in the plasma is 2 to 6 weeks. Letrozole is eliminated renally, approximately 90% of a dose (approximately 75% as the glucuronide conjugate of the inactive metabolite, 9% as two unidentified metabolites, and 6% unchanged). Letrozole does not go under any metabolism through the CYP450.

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. 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*. 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*. 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. 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. A study done in postmenopausal breast cancer patients comparing Letrozole to Anastrozole concluded that Letrozole suppresses plasma estrogen levels more completely than Anastrozole [2]. 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' Anastrozole to 6 weeks' Letrozole consistently achieved further estrogen suppression. Conversely, patients switching from 6 weeks' Letrozole to 6 weeks' Anastrozole experienced an increase in estrogen plasma levels.

2.2.1 Clinical Experience with Letrozole

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) [3]. 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 disease progression. Letrozole was superior to tamoxifen in TTP, reducing the risk of progression by 30% [hazard ratio 0.70, 95% confidence interval 0.60 to 0.82, P=0.0001, Cox regression], with median time to progression 41 weeks for Letrozole and 26 weeks for tamoxifen. Fewer patients progressed on Letrozole (69%) than on tamoxifen (77%). 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 (30%) than with tamoxifen (20%) (odds ratio 1.71, 95% confidence interval 1.26 to 2.31, P=0.0006, Mantel-Haenszel) with higher response rates seen irrespective of dominant site of disease. Clinical benefit (CR, PR or stabilization of disease lasting at least 24 weeks) was significantly superior for Letrozole as compared to tamoxifen [P=0.001, Mantel-Haenszel]. Time to treatment failure (P=0.0001, Cox regression) was significantly superior for Letrozole compared to tamoxifen. At the time of the analysis cutoff, 178 patients remain in the core portion of the trial (111 patients on Letrozole and 67 patients on tamoxifen).

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 comparing the efficacy of 4 months of therapy with Letrozole and tamoxifen as primary treatment in the pre-operative setting, confirms the superior efficacy of Letrozole over tamoxifen [4]. 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.

2.3 Imatinib mesylate (Gleevec)

Imatinib mesylate (Gleevec) is a phenylaminopyrimidine derivative and is a member of a new class of drugs collectively known as signal transduction inhibitors. More specifically, it is an inhibitor of several protein-tyrosine kinases that are believed to play a role in the proliferation of tumor cells. These include the tyrosine kinases associated with Bcr-Abl, the PDGF-R and c-Kit. Because these kinases are either uniquely or preferentially expressed in tumor cells, it is reasoned that the use of compounds causing inhibition of these targets may result in fewer or less debilitating side effects than those associated with standard anti-cancer chemotherapy.

The Bcr-Abl fusion protein, with enhanced tyrosine kinase activity, is an end product of a reciprocal translocation between chromosomes 9 and 22, replacing the first exon of c-*abl* with sequences from the BCR gene Bcr-Abl fusion protein. Bcr-Abl expression can induce a disease resembling CML in mice, and the tyrosine kinase domain of the molecule is essential for leukemic transformation. These observations provide evidence that the Bcr-Abl protein is a major factor in the pathogenesis of CML and indicate that inhibition of the Bcr-Abl kinase is a rational therapeutic target for the treatment of CML.

PDGF is a ubiquitous growth factor driving cell proliferation during normal development and in a variety of pathological conditions. The PDGF-dependent mitogenic pathway has been implicated in pathological conditions including cancer and connective tissue disorders. Interest in the role of PDGF in cancer stems from the finding that the transforming protein of the simian sarcoma retrovirus (v-sis oncogene product) is highly related to the B-chain of PDGF (c-sis proto-oncogene product). Expression of the v-sis or c-sis genes in cells expressing the PDGF receptor has been shown to cause cellular transformation and tumorigenicity *in vivo*. Dysregulation of PDGF-R signaling in tumors can lead to either autocrine or paracrine stimulation of cell growth. The PDGF-R pathway has been implicated in the growth of tumors of mesenchymal origin, most notably sarcomas and gliomas.

SCF is thought to play a central role in the proliferation and differentiation of stem cells. SCF synergizes with other growth factors to stimulate formation of both differentiated progenitor cells and primitive multi-lineage progenitor cells of the myeloid and erythroid lineages. Dysregulation of SCF receptor signaling has been implicated in some human cancers including SCLC, breast cancer, acute myeloid leukemia (AML), glioma, testicular and gynecological cancers. c-Kit and SCF over-expression is seen in most SCLC cell lines and primary tumors, raising the possibility of an autocrine loop. In GIST and mastocytosis mutations in c-*kit* resulting in ligand-independent constitutive activation of the receptor have been reported.

Accumulating evidence for the involvement of protein-tyrosine kinases in human proliferative disorders has led to a search for specific inhibitors. Imatinib Mesylate has been identified as a potent inhibitor of the Bcr-Abl tyrosine kinase at the *in vitro*, cellular and *in vivo* level. Furthermore, the compound inhibits PDGF- and SCF-mediated cellular events. These findings provided a cogent rationale for testing imatinib in human cancers where dysregulation of these pathways may contribute to malignant growth.

2.3.1. Clinical Experience with Imatinib Mesylate

Pharmacokinetics

The pharmacokinetics of Imatinib Mesylate have been evaluated in healthy subjects and in population pharmacokinetic studies in over 900 patients. Imatinib is well absorbed after oral administration with C_{max} achieved within 2-4 hours post-dose. Mean absolute bioavailability for the capsule formulation is 98%. Following oral administration in healthy volunteers, the elimination half-lives of imatinib and its major active metabolite, the N-desmethyl derivative, were approximately 18 and 40 hours, respectively. Mean imatinib AUC increased proportionally with increasing dose in the range 25mg - 1000mg. There was no significant change in the pharmacokinetics of imatinib on repeated dosing, and accumulation is 1.5-2.5 fold at steady state when Imatinib Mesylate is dosed once daily. At clinically relevant concentrations of imatinib, binding to plasma proteins in *in vitro* experiments is approximately 95%, mostly to albumin and a

$_1$-acid glycoprotein. CYP3A4 is the major enzyme responsible for metabolism of imatinib. Other cytochrome P450 enzymes, such as CYP1A2, CYP2D6, CYP2C9, and CYP2C19, play a minor role in its metabolism.

Chronic Myeloid Leukemia

Proof of activity was first obtained in a phase I clinical trial in patients with chronic and acute Philadelphia chromosome-positive (Ph+) leukemias [5]. This was followed by phase II studies in Ph+ leukemias as well as patients with a range of solid tumors.

Three international, open-label, single-arm Phase 2 studies were conducted to determine the safety and efficacy of Imatinib Mesylate in patients with Ph+ CML: 1) in the chronic phase after failure of Interferon (IFN) therapy [6], 2) in accelerated phase disease [7], or 3) in myeloid blast crisis [8]. Doses administrated and efficacy results are shown in Table 1.

Table 1 Response in CML studies

	Chronic Phase IFN Failure (N=532) 400 mg	**Accelerated Phase (N=181) 400mg n=62 600mg n=119**	**Blast Crisis (N=229) 400mg n=37 600mg n=223**
Cytogenetic response			
Major	60%	24%	16%
Complete	41%	17%	7%
Partial	19%	7%	9%
Minor	5%	7%	2%
Minimal	11%	17%	13%
Complete hematologic response	95%	53%	15%
No evidence of leukemia		10%	9%
Return to chronic phase		19%	28%

Cytogenetic response criteria: complete (0% Ph+ metaphases), partial (1-35%), minor (36-65%) or minimal (66-95%). A major response (0-35%) combines both complete and partial responses.

Imatinib Mesylate is indicated for the treatment of patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.

Chronic Phase, Newly Diagnosed

An open-label, multicenter, randomized phase III study of Interferon vs. STI571 (IRIS) has been conducted in patients with newly diagnosed Ph+ CML within 6 months of their initial diagnosis [9]. In the Imatinib Mesylate arm, patients were treated with 400mg daily. In the IFN arm, patients were treated with a target dose of IFN of 5 MIU/m^2/day subcutaneously in combination with subcutaneous Ara-C 20 mg/m^2

/day for 10 days/month. A total of 1106 patients have been randomized. An interim analysis done at the time when all patients had a minimum follow-up of 12 months was presented at the ASCO 2002 Meeting (Abstract #1). Response data are shown in Table 2. Complete hematologic response, major cytogenetic response and complete cytogenetic response were significantly higher in the Imatinib Mesylate arm compared to the IFN + Ara-C arm.

Table 2 Response in newly diagnosed CML (IRIS Study)

	Imatinib Mesylate	**IFN+Ara-C**
(Best response rates)	n=553	n=553
Hematologic response		
CHR [95% CI]	94.4%* [92.1%, 96.2%]	54.6%* [50.4%, 58.8%]
Cytogenetic response		
Major response [95% CI]	82.6%* [79.2%, 85.7%]	20.3%* [17.0%, 23.8%]
Complete CyR n (%)	67.8%*	7.4%*
Partial CyR n (%)	14.8%	12.8%

* p<0.001, Fisher's exact test

Hematologic response criteria (all responses to be confirmed after 4 weeks):

WBC<10 x10^9/L, platelet <450 x10^9/L, myelocyte + metamyelocyte <5% in blood, no blasts and promyelocytes in blood, basophils<20%, no extramedullary involvement

Cytogenetic response criteria: complete (0% Ph+ metaphases), partial (1-35%), minor (36-65%) or minimal (66-95%). A major response (0-35%) combines both complete and partial responses.

2.4 Rationale for Study

Targeted therapy offers the promise of reduced toxicity by targeting specific well-defined pathways. The estrogen receptor (ER) is one of the best characterized targets for breast cancer therapy. Successful ER-directed approaches include antiestrogens and aromatase inhibitors. A randomized phase III clinical trial showed that Letrozole is superior to tamoxifen as first-line therapy for metastatic breast cancer [3.] Overall, 49% of patients treated with Letrozole had an objective response or were stable for longer than 6 months. However, half of the patients did not respond to Letrozole despite expressing estrogen and/or progesterone receptors. The mechanisms of resistance to endocrine therapy are complex and not well defined. One such mechanism involves the overexpression of tyrosine kinase receptors such as EGFR and HER-2. C-kit, a 145-kd transmembrane glycoprotein, is a member of tyrosine kinase subclass III. It is structurally related to other receptors of the same family; those include platelet-derived growth factor (PDGF), macrophage colony-stimulating factor, and flt-3 ligand [10]. The c-kit gene product is expressed in hematopoietic progenitor cells, mast cells, germ cells and some solid tumors including breast cancer [11, 12]. In some types of tumors, inhibition of c-kit activity reduces cellular proliferation, suggesting a role for the use of pharmacological inhibitors of c-kit in the treatment of c-kit dependent malignancies [13, 14]. Kit is expressed at high levels in normal breast ductal epithelial cells. Expression of c-kit protein has been demonstrated in 10% to 20% by immunohistochemical staining; c-kit mRNA has been detected in 80% of primary breast tumors in one study. Studies have also shown that co expression of c-kit and its ligand, stem cell factor (SCF), is seen in the majority of surgical breast tumor specimens as well as in the

majority of established breast tumor cell lines. In particular, MCF-7 cells (that naturally express ER and SCF) transfected with a c-kit expression vector exhibit enhanced growth in serum-free medium supplemented with IGF-1 and EGF [15]. Preliminary investigations suggest that co expression of SCF and kit may be involved in the response to erbB ligands through activation of MAPK and PI3K.

Platelet-derived growth factor (PDGF) is composed of two chains, A and B, held together by disulfide bonds and present in three dimeric forms AA, AB, BB [16]. The dimers bind to two receptor types: α and β. The β receptor has a ligand-activated protein kinase. Platelet-derived growth factor (PDGF) is secreted by most human breast carcinoma cells; PDGF has been demonstrated in malignant breast tissue and mostly localized in the periepithelial stroma [17]. Recent studies of plasma and tissue PDGF concentrations in breast patients indicated that PDGF levels predict for shorter survival times and a lower response to chemotherapy [18].

Imatinib Mesylate is a known inhibitor of the c-abl, bcr-abl, PDGF receptor and c-kit kinase activity [19]. Imatinib Mesylate showed antitumor activity in the syngeneic BN-472 rat breast carcinoma model. When administered at 50mg/kg/ twice daily for four weeks, the compound inhibited primary tumors transplanted orthotopically and reduced the incidence and severity of metastatic disease. This drug is presently being investigated in hematological malignancies as well as solid tumors.

As mentioned previously, abnormalities in growth factor signaling pathways may account for the endocrine-resistant phenotype and thus may represent a target for new therapies to overcome endocrine resistance and enhance clinical response rate. For example growth factor signaling via tyrosine kinase growth factor receptor family (EGFR and HER2) may be up-regulated during endocrine treatment and thus allowing cells to grow in a hormone-independent manner [20]. In lines with that, it was shown that the EGFR tyrosine kinase inhibitor ZD-1839 blocked tyrosine kinase activity and profoundly inhibited cell growth in Tamoxifen resistant MCF-7 breast cancer cells [21].

A recent study demonstrated that Letrozole induces high response rates in breast cancer patients [4], especially in those tumors which express higher levels of the tyrosine kinase receptors (Erb-B1 (EGFR) and Erb-B2 (Her-2/neu). Preclinical studies have shown that hormone-resistant MCF-7 breast cancer cells with up-regulated tyrosine kinase signaling, had maximal growth inhibition and significantly delayed time to disease progression when they were treated with tyrosine kinase inhibitors in combination with antiestrogen agents [22]. Therefore blockage of the estrogenic activity pathway and the tyrosine kinase pathway might not only have additive effects, but might also, by overcoming hormonal resistance caused by tyrosine kinase activity, synergistic effects. The aim of this study is to evaluate the efficacy and safety of Imatinib Mesylate in combination with Letrozole in patients with ER and /or PgR positive and C-kit and/or PDGFR positive metastatic breast cancer.

3.0 Study Design

This is a single-institution phase II study of once daily doses of Letrozole 2.5 mg and Imatinib Mesylate 400 mg administered orally twice a day in postmenopausal women with hormone-sensitive metastatic breast cancer. Even though no overlapping toxicity from the combination is expected, the starting dose for Imatinib Mesylate will be 300 mg twice a day for the first 3 patients and will be escalated up to 400mg twice a day within the same patient after 2 weeks. The dose of Letrozole will remain stable at 2.5 mg daily. If no toxicity occurs, subsequent patients will continue to start at 800 mg daily dose of Imatinib Mesylate as outlined in section 5.0.

3.1 Sample Size

45 postmenopausal women with the diagnosis of metastatic breast cancer will be enrolled into the study

3.2 Study Population

3.2.1 Inclusion criteria

1. Postmenopausal women able to comply with the protocol requirements with metastatic breast cancer, whose tumors are estrogen (ER) and/or progesterone (PgR) positive, defined by core biopsy immunohistochemistry with > 10% positive malignant epithelial cells.

2. Patients must have documented expression of either PDGFR or CD117 (c-kit) by immunohistochemistry.

3. Patients may have received tamoxifen in the adjuvant/neoadjuvant setting. Patients may have previously received chemotherapy in the adjuvant/ neoadjuvant setting, though this is not required. Prior chemotherapy for metastatic breast cancer is allowed. Concomitant bisphosphonates are allowed for patients with bone metastases and who have another site of measurable disease.

4. Post menopausal status defined by one of the following :

   - no spontaneous menses for at least 1 year, in women **>**55 years
   - spontaneous menses within the past 1 year in women $\leq$ 55 years with postmenopausal gonadotrophin levels (LH and FSH levels >40 IU/L) or postmenopausal estradiol levels (<5 ng/dl) or according to the definition of "postmenopausal range" for the laboratory involved
   - bilateral oophorectomy

5. Performance status, ECOG $\leq$ 2

6. Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$10 mm with conventional techniques. See section 8.2 for the evaluation of measurable disease. Bone disease only will not be accepted as measurable disease. Pleural or peritoneal effusions will not be accepted as measurable disease.

7. Adequate bone marrow function (ANC $\geq$ 1.5 x 10^9/L and platelets $\geq$ 100.0 x10^9 /L, and hemoglobin > 10.0 g/dL).

8. Adequate renal function (creatinine less than 1.5 mg/dl) and hepatic function (T. Bilirubin less than 1.5 x normal, AST less than 2.5 x normal)

9. A life expectancy of at least 6 months

10. Localized radiotherapy, which does not influence the signal of evaluable lesion, is allowed prior to the initiation of Imatinib Mesylate. Patients must have recovered from the myelosuppressive effects of previous radiotherapy (at least 2-4 weeks).

11. Ability to understand and the willingness to sign a written informed consent.

3.2.2. Exclusion Criteria

1. Prior treatment with Letrozole or Imatinib Mesylate.
2. Uncontrolled endocrine disorders such as diabetes mellitus, confirmed hypo- or hyperthyroidism, Cushing's Syndrome, Addison's disease (treated or untreated).
3. Patients with unstable angina, or uncontrolled cardiac disease (e.g. Class III or IV New York Heart Association's Functional Classification).
4. Other concurrent malignant disease with the exception of cone-biopsied *in situ* carcinoma of the cervix uteri, or adequately treated basal or squamous cell carcinoma of the skin, or other curable cancers e.g. Hodgkin's disease or NHL, provided 5 years have elapsed from completion of therapy, and there has been no recurrence.

5. Concomitant treatment with steroids, e.g. glucocorticoids for indications other than cancer, except aerosol for obstructive airways diseases and steroid injection to the joints for treatment of inflammation.
6. Other investigational drugs within the past 3 weeks and the concomitant use of investigational drugs.
7. History of non-compliance to medical regimens and patients who are considered potentially unreliable.
8. Patients with known brain metastasis.
9. Patients with known chronic liver disease (i.e., chronic active hepatitis, and cirrhosis).
10. Patients with known diagnosis of human immunodeficiency virus (HIV) infection.
11. Patients who received chemotherapy within 4 weeks (6 weeks for nitrosourea or mitomycin-C) prior to study entry, unless the disease is rapidly progressing.
12. Patients who previously received radiotherapy to $\geq$ 25 % of the bone marrow.
13. Patients who had a major surgery within 2 weeks prior to study entry.

4.0 Study Drug Information

4.1 Letrozole (Femara, Novartis)

Letrozole is commercially available as 2.5 mg tablets and is supplied in bottles of 30 tablets each. Letrozole is stored at 25 °C.

4.2 Imatinib Mesylate (Gleevec, Novartis)

Novartis will supply Imatinib Mesylate (STI571) as 100 mg tablets packaged in bottles for an exposure period of up to 12 months or so long as the patient remains on study provided the patient shows continuous benefit from treatment with Imatinib Mesylate and there are no safety concerns. Continuing treatment beyond this period will be at the discretion of the investigator and may become the financial responsibility of the patient if no alternative method of obtaining or paying for the drug can be identified at that time. Medication labels will comply with the legal requirements of the US and will be printed in English. The storage conditions for Imatinib Mesylate will be described on the medication label. Bottles must be stored in a safe, secure location.

5.0 Treatment Plan

5.1 Phase I Part

The first 3 patients will be started at a dose of 300 mg Imatinib Mesylate twice a day and the dose will be escalated to 400 mg twice a day after 2 weeks in the same patient if no toxicity occurs. If grade 3/4 toxicity is observed, the dose of Imatinib Mesylate will be reduced as outlined in section 6.2 and 6.3 and the subsequent patients will be treated at that dose levels. The dose for Letrozole will be 2.5 mg, per oral, given once a day.

5.2 Phase II Part

The dose for Imatinib Mesylate will 400 mg, twice a day (total daily dose 800 mg), per oral. Imatinib Mesylate is a local irritant and must be taken in a sitting position with a large (250 mL) glass of water. (Direction of use on medication label: Take as directed with a large glass of water). Imatinib Mesylate should not be taken with grapefruit juice.

The dose for Letrozole will be 2.5 mg, once a day, per oral.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for 8 weeks or until one of the following criteria applies:

- X Disease progression,
- X Intercurrent illness that prevents further administration of treatment,
- X Unacceptable adverse event(s),
- X Patient decides to withdraw from the study, or
- X General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6.0 Expected Adverse Events/Dose Modifications

Expected Adverse Events Associated with Imatinib Mesylate

Chronic Myeloid Leukemia

The majority of Imatinib Mesylate-treated patients experienced adverse events at some time. Most events were of mild to moderate grade, but drug was discontinued for adverse events in 2% of patients in chronic phase, 3% in accelerated phase and 5% in blast crisis.

The most frequently reported drug-related adverse events were nausea, vomiting, diarrhea, edema, and muscle cramps (Table 3 for newly diagnosed CML, Table 1-5 for other CML patients). Edema was most frequently periorbital or in lower limbs and was managed with diuretics, other supportive measures, or by reducing the dose of Imatinib Mesylate. The frequency of severe superficial edema was 0.9%-5%.

Table 3 Adverse Experiences Reported in Newly Diagnosed CML Clinical Trial (>10% of all patients)

Preferred term[(1)]	All grades		CTC grades 3/4	
	Gleevec N=551 (%)	**IFN+Ara-C** N=533 (%)	**Gleevec** N=551 (%)	**IFN+Ara-C** N=533 (%)
Fluid retention	54.1	10.1	0.9	0.9
- Superficial edema	53.2	8.8	0.9	0.4
- Other fluid retention events	3.4	1.5	0	0.6
Nausea	42.5	60.8	0.4	5.1
Muscle cramps	35.4	9.9	1.1	0.2
Musculoskeletal pain	33.6	40.5	2.7	7.7
Rash	31.9	25.0	2.0	2.1
Fatigue	30.7	64.7	1.1	24.0
Diarrhea	30.3	40.9	1.3	3.2
Headache	28.5	41.8	0.4	3.2
Joint pain	26.7	38.3	2.2	6.8
Abdominal pain	23.4	22.9	2.0	3.6
Myalgia	20.9	38.6	1.5	8.1
Nasopharyngitis	19.2	7.7	0	0.2
Hemorrhage	18.9	19.9	0.7	1.3
Dyspepsia	15.1	9.0	0	0.8
Vomiting	14.7	26.6	0.9	3.4
Pharyngolaryngeal pain	14.2	11.4	0.2	0
Dizziness	13.2	23.1	0.5	3.4
Cough	12.5	21.6	0.2	0.6
Upper respiratory tract infection	12.5	7.9	0.2	0.4
Pyrexia	11.8	38.6	0.5	2.8
Weight increased	11.6	1.5	0.7	0.2
Insomnia	11.4	18.4	0	2.3

[(1)] All adverse events occurring in ≥10% of patients are listed regardless of suspected relationship to treatment.

Table 4 **Adverse experiences in greater than or equal to 10% of patients during phase II leukemia studies**

Preferred term (% of patients)	Myeloid blast crisis n= 260		Accelerated phase n=235		Chronic phase n=532	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Nausea	70	4	71	5	60	2
Fluid retention	71	12	73	6	66	3
Superficial edemas	67	5	71	4	64	2
Other fluid retention events	22	8	10	3	7	2
Muscle cramps	27	0.8	42	0.4	55	1
Diarrhea	42	4	55	4	43	2
Vomiting	54	4	56	3	32	1
Hemorrhage	52	19	44	9	22	2
CNS hemorrhage	7	5	2	0.9	1	1
Gastrointestinal hemorrhage	8	3	5	3	2	0.4
Musculoskeletal pain	43	9	46	9	35	2
Skin rash	35	5	44	4	42	3
Headache	27	5	30	2	34	0.2
Fatigue	29	3	41	4	40	1
Arthralgia	25	4	31	6	36	1
Dyspepsia	11	0	21	0	24	0
Myalgia	8	0	22	2	25	0.2
Weight increased	5	0.8	14	3	30	5
Pyrexia	41	7	39	8	17	1
Abdominal pain	31	6	33	3	29	0.6
Cough	14	0.8	26	0.9	17	0
Dyspnea	14	4	20	7	9	0.6
Anorexia	14	2	17	2	6	0
Constipation	15	2	15	0.9	6	0.2
Nasopharingitis	8	0	16	0	18	0.2
Night sweats	12	0.8	14	1	10	0.2
Pruritus	8	1	13	0.9	12	0.8
Epistaxis	13	3	13	0	5	0.2
Hypokalemia	13	4	8	2	5	0.2
Petechiae	10	2	5	0.9	1	0
Pneumonia	12	6	8	6	3	0.8
Weakness	12	3	9	3	7	0.2
Upper respiratory tract infection	3	0	9	0.4	15	0
Dizziness	11	0.4	12	0	13	0.2
Insomnia	10	0	13	0	13	0.2
Sore throat	8	0	11	0	11	0

With the exception of grade1/2 edema (but not grade 3/4), there were no obvious differences in the incidence of AEs in patients treated at 400 and 600mg. However, the interpretation of a dose relationship is confounded by the fact that many patients were dose-escalated over time and in all studies AEs were analyzed according to starting dose. Patients aged ≥ 65 years also experienced a higher incidence of edema.

Less than 50% of patients required dose reduction at any time. Temporary treatment interruptions were required in 25-40% of patients. Despite these dose changes, the overall median dose-intensity (expressed in mg/day) in each study remained close to the initially planned dose.

Clinically important adverse events

Because of their relative frequency and clinical significance, several AEs occurring during the phase II leukemia trials were analyzed in greater detail, as summarized below.

Edema and fluid retention

Superficial edema was one of the most frequently reported AEs but was rarely severe (2-5% Grade 3/4). The most frequently involved sites included the periorbital region, face and lower limbs. The edema usually appeared within the first two months of treatment. A minority of patients with severe edema required dose reduction.

A minority (<5%) of patients developed central collections of fluid (described collectively using the term 'fluid retention') including one or more of the following: congestive heart failure, pleural effusion, ascites, pericardial effusion and pulmonary edema. It is unclear if the mechanisms underlying peripheral edema and fluid retention are the same. Fluid retention was usually managed with diuretics and/or dose reduction, or with temporary treatment interruption.

Gastrointestinal and CNS hemorrhages

In toxicology studies, imatinib was shown to be a local irritant and for that reason, the pattern of GI tract hemorrhages was carefully reviewed. These events were rare, and severe (Grade 3/4) cases were reported only in advanced CML patients. GI hemorrhages occurred in 3-5% of patients with advanced CML, were considered drug-related in 0-2% and severe in <1.5%. Contributing factors such as severe thrombopenia, the use of concomitant NSAIDS and a history of gastric ulcer were present in most but not all cases. Upper GI ulceration (esophageal, gastric or duodenal) or gastritis/duodenitis were visualized at gastroscopy in approximately 50% of patients with GI bleeding. Less than 1% of patients discontinued therapy as a result of these events.

Cerebral hemorrhages (including subdural hematomas and hygromas) were also reported almost exclusively in advanced CML patients (1-7%). The majority occurred in the context of rapidly progressive disease, with concomitant thrombocytopenia..

Skin rash

An erythematous, pruritic, maculopapular skin rash, most prominent over the forearms and trunk but occasionally present also on the face, was reported in up to 44% of patients treated with imatinib. Onset was generally within the first month of therapy. Eosinophilia was rarely seen and skin biopsies showed the typical appearances of a toxic drug reaction with a mixed infiltration of cells. Occasional patients reported pruritus without accompanying rash. In most cases, the rash was mild, easily manageable with antihistamines and/or topical steroids, and gradually subsided without interrupting therapy. However, a troublesome skin rash was the most frequent reason (in <1% of patients overall) for the permanent discontinuation of therapy. Approximately 3% of patients developed severe skin rashes, some with an exfoliative component. Re-challenge was usually but not always positive.

GIST

Treatment with Imatinib Mesylate was generally well tolerated, although nearly every patient experienced at least some minor adverse events. The most frequently reported adverse events were edema, nausea, diarrhea, musculoskeletal pain, fatigue, rash, headache, and abdominal pain. Most events were of mild to moderate severity. Superficial edema, most frequently periorbital or lower limb edema, was managed with diuretics, other supportive measures, or by reducing the dose of Imatinib Mesylate. Severe (CTC grade 3/4) superficial edema was observed in 2 patients including face edema in one patient. No major differences were seen in the severity of adverse events between the 400mg or 600mg treatment groups, although overall incidence of adverse events was somewhat higher in the 600mg treatment group. Adverse events with a suspected relationship to therapy occurring in greater than 10 % of patients in any group are presented in Table 5.

Table 5 Adverse events with suspected relationship to therapy in GIST (≥ 10% in any group)

	All grades			**Grade 3 / 4**		
Preferred terms	400 mg	600 mg	All doses	400 mg	600 mg	All doses
Percentage of patients	n = 73	n = 74	N = 147	n = 73	n = 74	N = 147
Any AE	97	99	98	21	22	21
Edema/fluid retention	71	77	74	1	1	1
Periorbital edema	45	50	48	0	0	0
Edema lower limb	26	15	20	0	0	0
Face edema	8	12	10	1	0	1
Edema	7	14	10	0	0	0
Eyelid edema	7	8	8	0	0	0
Nausea	51	54	52	1	1	1
Diarrhea	40	50	45	1	3	2
Myalgia / musculoskeletal pain	37	42	40	0	0	0
Fatigue	30	39	35	0	0	0
Dermatitis / rash	25	37	31	3	3	3
Headache	19	32	26	0	0	0
Abdominal pain	26	26	26	1	0	1
Flatulence	19	24	22	0	0	0
Vomiting	14	12	13	0	1	1
Any hemorrhage	11	14	12	4	5	5
Tumor hemorrhage	1	4	3	1	4	3
Upper GI bleed / perforation	4	3	3	4	1	3
Dyspepsia	10	12	11	0	0	0
Lacrimation increased	7	12	10	0	0	0
Anemia	6	12	9	1	3	2
Loose stools	7	10	8	0	0	0
Taste disturbance	3	14	8	0	0	0

There was no hyperuricemia or evidence of tumor lysis syndrome, even in patients with very rapid

decreases in tumor volume. The most medically significant adverse events were gastrointestinal or intra-abdominal hemorrhage in patients with large bulky tumors, which occurred in approximately 5 % of patients.

6.2 Dose Modifications for Non-Hematological Toxicity

Grade 2

If the patient experiences a Grade 2 non-hematologic toxicity, study drug must be withheld until the toxicity has resolved to $\leq$ Grade 1. Imatinib Mesylate may then be resumed at the same daily dose. If the Grade 2 toxicity recurs, Imatinib Mesylate must be withheld until the toxicity has resolved to $\leq$Grade 1, and the daily dose must be reduced to 400 mg for patients receiving 600mg of Imatinib Mesylate or to 600mg for patients receiving 800mg of Imatinib Mesylate.

Grade 3/4

If the patient experiences Grade 3/4 toxicity study drug must be withheld until the toxicity has resolved to $\leq$ Grade 1 and the daily dose must be reduced to 400mg for patients receiving initially 600mg of Imatinib Mesylate or to 600 mg for patients receiving 800 mg. If the Grade 3/4 toxicity recurs, Imatinib Mesylate must be withheld until the toxicity has resolved to $\leq$Grade 1, and the daily dose must be reduced to 300mg once daily for patients receiving 400mg of Imatinib Mesylate or to 400mg daily for patients receiving 600mg of Imatinib Mesylate.

6.3 Dose modifications for hematological toxicity

Grade 2

No dose interruptions or reductions will be performed for Grade 1/2 hematological toxicity.

Grade 3/4

If patient experiences a Grade 3/4 hematological toxicity, defined as an ANC $< 1 \times 10^9$/L, or a platelet count $< 50 \times 10^9$/L, Imatinib Mesylate must be withheld until the toxicity has resolved to $\leq$ Grade 2. ANC will takes precedence over a WBC count in determining the degree of neutropenia (doses should not be interrupted for a patient with a WBC $< 2.0 \times 10^9$ /L but ANC $> 1 \times 10^9$/L). If the toxicity resolves within two weeks, Imatinib Mesylate treatment may be resumed at the same dose. If the Grade 3/4 toxicity recurs or persists for longer than two weeks, Imatinib Mesylate must be withheld and then recommenced at the dose of 300mg once daily for patients receiving 400mg of Imatinib Mesylate or 400 mg for patients receiving 600 mg of Imatinib Mesylate or 800mg of Imatinib Mesylate, once toxicity has resolved to $\leq$ Grade 2.

No dose reductions will be performed for grade 3/4 anemia. If the patient develops anemia, s/he may be transfused at the discretion of the investigator.

6.4 Dose Modifications for Other Reasons

The optimal dose of Imatinib Mesylate in an as-yet undefined spectrum of diseases is unknown, however, the possibility of a clinically relevant dose-response may be of importance. Therefore, it is possible that higher doses of Imatinib Mesylate might induce responses even if a lower dose fails. If vomiting occurs, no additional trial medication should be taken that day in an effort to replace the material that has been vomited.

6.5 Concomitant Therapy

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient, such as biphosphonates, are allowed, provided their use is documented in the patient records and on the appropriate case report form. The administration of any other therapies intended to treat the primary condition including chemotherapy and biologic agents is not, however, permitted. Similarly, the use of other concurrent investigational drugs is not allowed.

Because of the inherent risk of either reduced activity or enhanced toxicity of the concomitant medication and/or Imatinib Mesylate, drugs known to interact with the same CYP450 isoenzymes (2D6 and 3A4) as Imatinib Mesylate should be used with caution. Patients using concomitant medications known to be metabolized by these cytochrome p450 enzymes will not be excluded from the study. (See Appendix D) However, the patients must be carefully monitored for potentiation of toxicity due to individual concomitant medication Special care has to be given to the concomitant use of acetaminophen (e.g. Tylenol or Percocet, paracetamol Panadol, etc.) with Imatinib Mesylate. Any use of concomitant medication must be captured in the concomitant medication CRF.

Since warfarin is metabolized through the CYP450 system, no therapeutic anticoagulation with warfarin (e.g. Coumadin® or Coumadine®) will be permitted in patients participating in this study. As an alternative, therapeutic anticoagulation may be accomplished using low-molecular weight heparin (e.g. Lovenox) or heparin. A mini-Dose coumarin derivative (equivalent to 1 mg QD Coumadin®) is permitted for prophylaxis of central venous catheter thrombosis, at the discretion of the treating physician. In general, the use of Coumadin® is discouraged on this protocol.

The routine use of systemic corticosteroid therapy is not permitted. Prophylactic anti-emetics should be withheld until the patient has experienced grade 1 nausea or vomiting.

Prophylactic use of loperamide (e.g. Imodium® , with suggested dosing as start: 4mg p.o. x 1, than 2mg p.o. after each loose stool, max 16mg/d) is recommended for patients experiencing grade 1 or 2 diarrhea, before dose interruption.

6.6 Treatment Compliance

Records of study medication used, dosages administered, and intervals between visits will be kept during the study. Drug accountability will be noted and at the completion of the trial. Patients will be asked to return all unused medication at the end of the study.

7.0 Conduct of the Study

7.1 Visit Schedule

7.1.1 Baseline laboratory must be done within 14 days of study entry.

7.1.1 Baseline imaging studies must be done within 4 weeks of study entry.

7.1.3 Baseline imaging studies will include computed tomography of chest and abdomen and bone scan (correlating bone X-rays is required if bone scan is positive), or PET scan.

7.1.4 Baseline laboratory studies will include a complete blood count, electrolytes, liver functions, tumor markers (CEA and CA 27.29), creatinine.

7.1.5 Laboratory tests: Week 1 2, 3, 4, 6, 8: Complete blood count, liver, electrolytes and creatinin. These laboratory tests will be performed monthly thereafter.

7.1.6 Clinic visits with physical exam: Baseline, months 1, 2, 4, 6, 9, 12 (Tumor markers (CEA and CA 27.29) will be drawn during these visits.

7.1.7 Radiologic imaging/restaging: Months 2, 4, 6, 9, 12 : Affected area will be evaluated. Patients with stable or responsive disease will be followed every 3 months thereafter.

7.1.8 Correlative studies: Serum for angiogenic molecules and cytokines including: serum vascular endothelial growth factor (sVEGF), basic fibroblast growth factor (bFGF), Interleukine-8 (IL-8), platelet-derived growth factor (PDGF), E-selectin, tumor-necrosis factor-α (TNF-α), tumor-necrosis factor-β (TNF-β), IGF-II and IGFBP-3 and proteomic analysis: Baseline and months 2 and 4.

Table 7 Evaluation and Visit Schedule

Examination	Prestudy	Week					Month				
		1	2	3	4	6	2	4	6	9	12
Informed consent	X										
Demographics	X										
Medical History	X										
Concurrent Medications	X				X		X	X	X	X	X
Inclusion/exclusion criteria	X										
Vital signs	X				X		X	X	X	X	X
Physical examination	X				X		X	X	X	X	X
Performans Status	X				X		X	X	X	X	X
Body Weight	X				X		X	X	X	X	X
Height	X										
ECG	X										
Laboratory test	X	X	X	X	X	X	X	X	X	X	X
Imaging studies	X						X	X	X	X	X
Serum markers	X						X	X			
Tissue markers	X						X				

8.0 Efficacy Assessment

8.1 Definitions

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term “evaluable” in reference to measurability will not be used because it does not provide additional meaning or accuracy

8.1.1 **Measurable disease**

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with conventional techniques (PET, CT, MRI, x-ray) or a with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of

centimeters).

8.1.2 **Non-measurable disease**

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

8.1.3 **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 response.

8.1.4 **Non-target lesions**

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

8.2 Guidelines for Evaluation of Measurable Disease

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

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

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

Spiral CT and MRI. For CT, cuts of 7 or 7.5 mm slice thickness (contiguously), for MR 6-10 mm slice thickness should be used. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Ultrasound (US). When the primary endpoint of the study is objective response evaluation, 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.

Tumor markers. 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.

8.3 Response Definitions:

Complete Response (CR). Disappearance of all evidence of tumor for at least one cycle of therapy (four weeks). Bone lesions must have improved by scan and shown complete reossification by x-ray. The patient must be free of all symptoms of cancer. Markers must be normal.

Partial Response (PR). 30% or greater decrease in the sum of the products of diameters of all measured lesions persisting for at least one cycle of therapy or 4 weeks. Non-measurable, but evaluable, lesions must decrease by at least 30%. No lesion may increase in size and no new lesion may appear. Bone lesions must have improved by scan and shown some reossification by x-ray. Markers must have improved.

Minor Response (MR). A measurable decrease in measurable lesion(s), which is too small or too brief to qualify as a Partial Response. MR is considered a failure, but should be noted as a possible signal of biologic activity.

Progressive Disease (PD). Any increase of $\geq$ 25% in the sum of the products of diameters of any measurable lesion or in estimated size of non-measurable lesions or appearance of an unequivocally new lesion. Patients should have received at least two cycles of therapy before a designation of progression is made. An increase of 50% or development of unequivocally new lesions between the first and second cycle will be considered progression without repeat measurements.

No Change (NC). No change in tumor size, or <25% increase in size.

MR and PD are considered failures.

Development of a new brain lesion will be considered progressive disease.

Confirmation of Response. To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks.

Response and Survival Durations. The survival of patients will be measured from entry into protocol. Duration of response will be measured from first observation of the response until progression of disease.

9.0 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 on the appropriate case report forms.

It will be documented whether or not each patient completed the clinical study. If for any patient study treatment or observations were discontinued the reason will be recorded on the appropriate case report form. Reasons that a patient may discontinue participation in a clinical study are considered to constitute one of the following:

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. administrative problems
10. Death.

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

10.0 Toxicity Monitoring

Toxicity will be assessed using the NCI Common Toxicity Criteria.

10.1 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 and followed as appropriate. 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.

- if it is unclear what study treatment includes, list all drug(s), other therapies, changes to existing therapy, diagnostic procedure, etc. that are specified by the protocol

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 are recorded. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy, and are recorded.

Serious adverse events

Information about all serious adverse events will be collected and recorded on the Serious Adverse Event Report Form. To ensure patient safety each serious adverse event must also be reported to Novartis within 24 hours of learning of its occurrence. 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.

Events not considered to be serious adverse events are hospitalizations for the:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen
- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

Pregnancy, although not itself a serious adverse event, should also be reported on a serious adverse event form or pregnancy form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

Any serious adverse event occurring in a patient after providing informed consent and until 4 weeks after stopping the trial must be reported. The period after discontinuing study drug may be extended if there is a strong suspicion that the drug has not yet been eliminated. All serious adverse events must also be reported for the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of

concomitant medication).

10.2 Adverse Drug Reaction Reporting

10.2.1 All adverse experiences occurring after administration of the first dose of study medication and on or before the final visit, will be reported on the Adverse Experience form in the patient's CRF.

7.2.1 At each visit/assessment, adverse experiences will be evaluated by the Investigator. Adverse experiences not previously documented in the study will be recorded in the adverse experience record form within the patient's CRF. The nature of each experience, date and time (where appropriate) of onset, outcome, course (i.e. intermittent or constant), maximum intensity, action taken with respect to dosage and relationship to treatment will be established. Details of changes to the dosage schedule or any corrective treatment will be recorded on the appropriate pages of the CRF.

7.2.3 Any serious adverse experiences which occur at any time during the clinical study or within 30 days of receiving the last dose of study medication, whether or not related to the study drug, will be reported immediately to the UT MD Anderson Cancer Center Institutional Review Board

10.3 Instructions for rapid notification of serious adverse events

Reporting responsibility

Each serious adverse event (but not pregnancies) must be reported by the investigator to Novartis within 24 hours of learning of its occurrence, even if it is not felt to be treatment-related. Follow-up information about a previously reported serious adverse event must also be reported to Novartis within 24 hours of receiving it. If the serious adverse event has not been previously documented (new occurrence) and it is thought to be related to study drug (or therapy), the Medical Safety Expert of the Clinical Safety & Epidemiology (CS&E) Department may contact the investigator to obtain further information. If warranted, an investigator alert may be issued, to inform all investigators involved in any study with the same drug (or therapy) that this serious adverse event has been reported.

Reporting procedures

The investigator must complete the Serious Adverse Event Report Form in English, assess the relationship to study treatment and send the completed form by fax **1.888.299.4565** within 24 hours to the local Novartis Clinical Safety & Epidemiology (CS&E) Department ensuring that the form is accurately and fully completed, must then fax it to Novartis CS&E Department within 2 to 3 calendar days for deaths or life-threatening events and 5 calendar days for other serious adverse events. The original and the duplicate copies of the Serious Adverse Event Form, and the fax confirmation sheet must be kept with the case report forms at the study site.

Follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or discontinued study participation. The form and fax confirmation sheet must be retained. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects.

11.0 Patient Withdrawal From Study

11.1 Evidence of disease progression

11.2 Development of a DLT that does not resolve within 2 weeks of stopping therapy.

11.3 Intercurrent illness which prevents further therapy
General or specific changes in the patients condition which render the patient unacceptable for further treatment in the judgment of the investigator.

11.4 Protocol violation (including non-compliance).
The patient or physician are free to discontinue treatment at any time if it is believed to be in the best interest of the patient.

12.0 Administrative Procedures

12.1 Changes to the protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by Novartis and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, require additional approval by the IRB/IEC/REB. A copy of the written approval of the IRB/IEC/REB, must be sent to Novartis

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC/REB approval but the IRB/IEC/REB of each center must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB/IEC/REB approval that can be treated as administrative amendments include:

1. changes in the staff used to monitor trials

12.2 Discontinuation of study

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

12.3 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and 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).

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

12.4 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. The name and occupation of the chairman and the members of the IRB/IEC/REB must be supplied to Novartis. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

12.5 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 he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/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 non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. 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 with it for IRB/IEC/REB approval.

13.0 Statistical Methods

The major trial objective is to assess the efficacy of a regimen, which adds Imatinib Mesylate to Letrozole for the first-line treatment of metastatic breast cancer. A maximum of 45 patients will be accrued at MDACC at an expected rate of 2 patients per month, taking into consideration recent historical experience for this category of patients. The accrual period should thus be completed within 24 months. The maximum sample size of 45 patients will provide an estimate of ORR with 90% credibility interval (assuming targeted rate of 40%) of width 0.24. The final analysis will also report a summary of time to disease progression, any toxicities observed during treatment, and separate estimates of objective response rate (ORR) by type and extent of prior chemotherapy. All patients who receive any dose of therapy will be included in assessments of all outcomes, with patients removed from trial for any reason counted as failures in computing ORR.

Further investigation of Imatinib Mesylate is warranted only if its addition can substantially improve the efficacy of Letrozole alone. In a large randomized trial, single-agent Letrozole resulted in objective responses in 136 of 453 patients (30%). The trial will be monitored using a Bayesian method and with cohorts of size 15; termination will be recommended if there is strong evidence that ORR is unlikely to be more than 10% greater than with Letrozole alone. (Formally, the trial will be terminated after 15 or 30 patients if $\Pr[\text{ORR (Letrozole + Imatinib Mesylate)} > \text{ORR (Letrozole)} + .10 \text{ data}] < 0.05$. The comparative response rate for Letrozole alone is represented by a distribution of beta (136, 317), and a beta (0.60, 1.40) prior distribution is assumed for ORR of the experimental group. Maximum sample size is set at 45 patients.)

The first interim analysis will be conducted after the initial 15 patients have been evaluated for response. The trial will continue to accrue another 15 patients if at least 4 responses have been observed. At the second interim analysis, the trial will continue to accrue to the maximum sample size only if at least 8 objective responses have been observed among 30 patients.

A simulation study evaluated the properties of these stopping rules under several possible scenarios:

True ORR rate	**Probability of early termination**
.20	.83
.30	.40
.35	.22
.40	.11
.45	.05
.50	.02

14.0 Correlatives Laboratory Studies

14.1 Tissue biopsies (fresh and fixed) (Optional)

Imatinib Mesylate is expected to affect the activation status of sensitive receptor tyrosine kinase targets and associated signaling effectors. In patients with disease amenable to biopsy (Chest wall, Skin, LNs, or some visceral disease) patients will have a biopsy (at baseline and at approximately 8 weeks) in order to assess mechanisms of anti-tumor activity through analysis of receptor activation (phosphorylation) and downstream signaling through known pathways (EGFR, HER-2/neu, kit, phospho-kit, akt, Stat, phospho-akt, MAPkinase, phospho-MAPkinase).

14.2 Ductal Lavage (optional)

Epithelial breast cells will be obtained from the opposite, unaffected breast to evaluate Letrozole and Imatinib Mesylate's effect on non-malignant, but "high-risk breast epithelium". Ductal lavage procedure will be performed at baseline and at months 2 . Changes in proliferation and apoptosis markers (Ki-67, ER, Her-2/Neu, EGFR, bcl-2, kit, phospho-kit, akt, phospho-akt, Mapkinase, phospho-MAPkinase), as well as changes in proteomic patterns and single nucleaotide polymorphisims in CYP isoforms will be evaluated.

14.3 Serum

All patients will have initial and month 2 and 4 collection of blood to analyze proteomic patterns in the serum before and after treatment as well as changes in IGF-II, IGFBP-3, serum vascular endothelial growth factor (sVEGF), basic fibroblast growth factor (bFGF), Interleukine-8 (IL-8), platelet-derived growth factor (PDGF), E-selectin, tumor-necrosis factor-α (TNF-α), tumor-necrosis factor-β (TNF-β), and proteomic analysis

Attempts would be made to detect and quantify c-kit receptor in CEC using flowcytometry and, when becomes available Cell Track technology by Immunicon.

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