ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A091202

A PHASE II STUDY OF THE PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA AGONIST, EFATUTAZONE IN PATIENTS WITH PREVIOUSLY TREATED, UNRESECTABLE MYXOID LIPOSARCOMA

Industry-supplied agent: Efatutazone (IND #121997, NSC #776711)

ClinicalTrials.gov Identifier: NCT02249949

Study Chair
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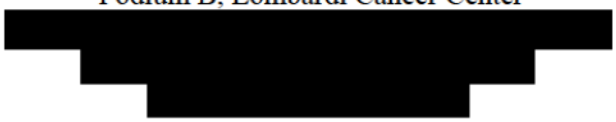

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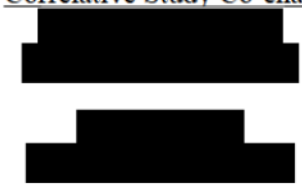
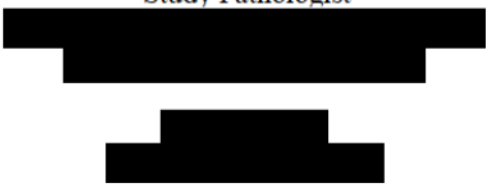


Study Pathologist



Experimental Therapeutics Committee Co-Chair

Experimental Therapeutics Committee Co-Chair

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Participating Organizations:
ALLIANCE / Alliance for Clinical Trials in Oncology
ECOG-ACRIN/ ECOG-ACRIN Cancer Research Group
NRG / NRG Oncology
SWOG / SWOG

Study Resources:

Expedited Adverse Event Reporting
[redacted]

Medidata Rave® iMedidata8 portal
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Protocol-related questions may be directed as follows:

Questions	Contact (via email)
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox [redacted]
Questions regarding CTEP-AERS reporting:	Alliance Pharmacovigilance Inbox: [redacted]
Questions regarding specimens/specimen submissions:	Alliance Biorepository At Ohio State (OSU)

CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at [redacted] to receive further instruction and support. Contact the CTSU Regulatory Help Desk at [redacted] for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at [redacted]	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. *Include this statement if applicable:* Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (i.e. patient eligibility or treatment-related) contact the Study PI of the Lead Protocol Organization		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – [redacted]. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

A PHASE II STUDY OF THE PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA AGONIST, EFATUTAZONE IN PATIENTS WITH PREVIOUSLY TREATED, UNRESECTABLE MYXOID LIPOSARCOMA

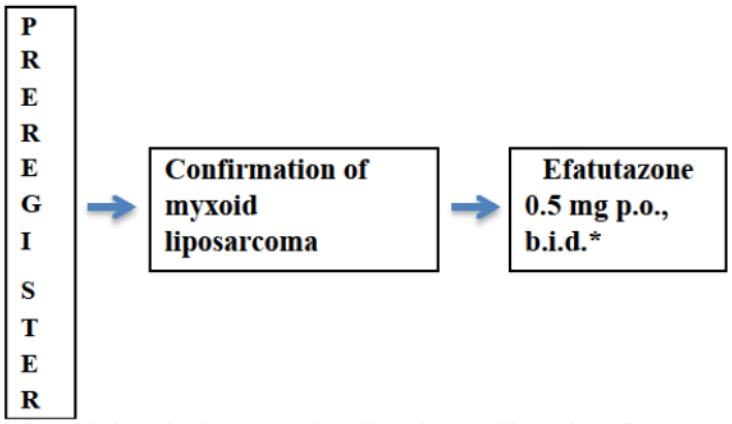
Pre-Registration Eligibility Criteria (see Section 3.2)
Central pathology review submission (see δ3.2.1)
Registration/Randomization Eligibility Criteria (see 3.3)
Measurable disease **as defined in Section 11.0**
Prior treatment: progression on at least 1 prior systemic chemotherapy; there is no limit to the number of prior lines of therapy; no treatment with biologic therapy, immunotherapy, chemotherapy, investigational agent for malignancy, or radiation ≤ 28 days before registration; no Nitrosourea or mitomycin ≤ 42 days of registration; patients should have resolution of toxic effects of prior therapy (see δ3.3.2)

Required Initial Laboratory Values

Absolute neutrophil count (ANC)	≥ 1,000/mm^3
Platelet Count	≥ 75,000/mm^3
Creatinine	< 1.5 mg/dL x ULN
Calc. Creatinine Clearance (see section 3.3.10)	**OR** ≥ 30 mL/min
Total Bilirubin	≤ 1.5 x ULN
SGOT (AST) and SGPT (ALT)	≤ 2.5 x ULN

No history of: Class III or IV congestive heart failure (CHF); Grade 3 or 4 thromboembolic event ≤ 6 months, Pericardial effusion ≤ 12 months (any grade), Pericardial involvement with tumor, Grade 2 or higher pleural effusion ≤ 6 months
No symptomatic, untreated, or uncontrolled brain metastases present.
Not pregnant and not nursing (see δ3.3.6)
Concomitant medications: Patients with: diabetes mellitus requiring concurrent treatment with insulin or TZD oral agents are not eligible; known hypersensitivity to any TZD oral agents are not eligible
Age ≥ 18 years
ECOG Performance Status 0-2
Histologic Documentation: Eligible patients must have histopathologically confirmed myxoid liposarcoma with confirmation of DDIT3 rearrangement

Schema
1 Cycle = 21 Days



* Effective with Update #02 this is a single arm study. All patients will receive efatutazone.
Treatment is to continue until disease progression or unacceptable adverse event. After disease progression or unacceptable adverse event, patients will be followed for a maximum of 5 years from time of registration. **Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.**

Table of Contents

1.0 BACKGROUND

1.1 An Unmet Need in Advanced Myxoid Liposarcomas

Liposarcoma (LPS) is the most common subtype of soft tissue sarcoma, constituting about 20% of the 13,000 soft tissue sarcomas diagnosed in the United States each year (about 2500 cases) [1, 2]. Liposarcomas are classified into three main subtypes, as per the 2002 WHO classification [1, 3, 4]. This includes well-differentiated and de-differentiated liposarcomas, accounting for about 45-50% of all LPS; myxoid and round cell liposarcomas (MLS), accounting for 30-35% of all LPS; and pleomorphic liposarcomas, accounting for only 5-10% of all LPS.

Like most solid cancers, liposarcomas are only curable if surgically resectable. However, as a group, 50% of liposarcomas are advanced – either locally advanced unresectable or metastatic. For these patients, treatment is palliative, aimed at extending survival while maintaining as high a quality of life as possible. Treatment for such advanced patients is generally chemotherapy, and while for many patients with liposarcomas, chemotherapy can be effective, the toxicities are significant, and the efficacy can be short lived [1, 2]. Adriamycin-based regimens have resulted in a wide range of response rates, generally around 30% [1]. Combination therapy can induce a higher response rate, but has not been shown to improve survival. Other commonly used regimens in STS, including gemcitabine plus docetaxel [5] and pazopanib [6] have shown modest benefits in LPS. The marine-derived anti-cancer agent trabectedin has also been tested in LPS and initially demonstrated a promising response rate as high as 51% and a progression free survival (PFS) up to 17 months, specifically for patients with MLS [7]. However, subsequent results in LPS in general showed tempered enthusiasm. For example, a large expanded access program of trabectedin revealed a response rate of only 6.9% and a median progression-free survival of only 3.3 months [8]. Moreover, trabectedin does have significant toxicity and is still not FDA approved in the United States. Thus, for MLS, newer therapies are needed that could offer increased anti-tumor activity, ideally with fewer toxicities.

1.2 PPARgamma Agonists as Anti-Cancer Therapy

1.2.1 Overview

Peroxisome proliferator activated receptors (PPARs) are members of the nuclear hormone receptor family of ligand activated transcription factors [9-12]. The PPARs were first identified as the targets of compounds found to induce peroxisomal proliferation in the liver, but soon after were found to be effective agents in the treatment of diabetes, acting as insulin sensitizing agents. Further study has revealed a significant role in adipocyte regulation, inflammation, and atherosclerosis.

Specifically, agonists of the nuclear hormone receptor PPARγ, such as the thiazolidinediones (TZDs) have shown promising potential in the treatment of a variety of cancer types, and particularly in liposarcoma, *in vitro* and in mouse models [9-12]. PPARγ ligands have been shown to reduce cell growth and induce differentiation in a number of cancer cell lines including breast, colon, gastric, pancreatic, bladder, prostate, and lung [9, 13-16]. Mechanistically, PPARγ agonists act to inhibit tumorigenesis through several pathways [17-27]. PPARγ inhibits cellular progression through the cell cycle by inducing upregulation of the cell cycle inhibitors, p18, p21, and p27 while concurrently downregulating the cell cycle mediator, cyclin D1. PPARγ agonists also inhibit angiogenesis, partly by reducing the expression of VEGF. PPARγ agonists also stimulate apoptosis. Finally, PPARγ agonists induce cellular differentiation. *In vivo*, PPARγ agonists slow the growth of tumors in rodents, both in carcinogen-induced tumor models, and from ectopically implanted cancer cell lines (breast, colon, prostate) [9, 28].

1.2.2 Classification and mechanisms of action

PPARs were first cloned from a Xenopus cDNA library in 1992[9, 10] . There are three main subtypes,α γ, and δ. They are typical nuclear hormone receptors that, when bound to a ligand, heterodimerize with members of the RXR family and bind to peroxisomal proliferator response elements (PPREs) in the promoter region of a number of genes. There they interact with several coactivators and corepressors and act to modulate expression of a variety of target genes. The expression pattern of the subtypes and their biological roles differ [12]. PPARα is expressed in several tissues including liver, kidney, heart, skeletal muscle, and adipose tissue. In general, PPARα is involved in fatty acid catabolism. PPARγ exists as two isoforms created by alternative splicing. PPARγ2 is highly expressed in adipocytes while PPARγ1 is expressed in lower levels in a variety of tissues including heart, skeletal muscle, colon, SI, kidney, pancreas, and spleen [12]. PPARγ is generally involved in adipocyte differentiation, lipid homeostasis, and regulation of blood glucose levels, though these effects may be predominately mediated by PPARγ2 [9, 12]. The effects of PPARγ1 are harder to elucidate, but PPARγ1 may play a larger role in the regulation of cellular differentiation and proliferation. Finally, PPARδ is expressed in a variety of tissues, but with particularly high levels in the brain, adipose, skin, and in the developing embryo. PPARδ is involved in embryonic development, myelogenesis, and may act to enhance tumorigenesis.

1.2.3 Ligands

The endogenous ligands of the PPARs include a number of fatty acids and eicosanoids [12]. Their role in normal biological function, however, is not well defined, particularly because most of the endogenous ligands identified so far are effective at micromolar concentrations, too high for true biological activity. There are, however, a number of synthetic ligands [9, 10]. The TZDs were found to be potent PPARγ agonists, and efatutazone in particular has a very high affinity for PPARγ. Aryl-tyrosine derivatives such as GW 1929 are also PPARγ specific. Fibric acid derivatives are weak PPARα agonists, and there are a variety of more potent experimental PPARα agonists. There are also PPARα and PPARγ dual receptor specific derivatives. Some NSAIDs have weak PPARα and PPARγ activity. Finally, there are no selective PPARδ inhibitors.

1.2.4 Biological Effects

The PPARs are involved in a wide variety of biologic pathways [9-12]. PPARα may be involved in fatty acid/cholesterol regulation. It is the target of the antihyperlipidemic fibrates, and it may have some role in cancer prevention and/or inflammation. PPARδ alternatively may play a role in tumorigenesis. PPARδ also appears to be involved in the maintenance of fertility by affecting embryonic implantation, as well as in myelogenesis in the CNS. Finally, PPARγ has the widest variety of effects including the inhibition of inflammation, induction of differentiation, enhancement of insulin sensitization, and anticancer effects, the last of which will be the focus below.

1.2.5 PPARs and Cancer

The interest in PPARγ as a potential cancer therapy target first developed with the observation that ectopic expression of PPARγ in a fibroblast cell line, in the presence of small amounts of ligand, could induce adipogenesis, essentially terminal differentiation [29]. Based on these observations, PPARγ agonists were tested in human liposarcoma cells, which normally express much higher levels of PPARγ. These cells underwent a dramatic

differentiation to adipocytes in response to PPARγ ligands [30, 31]. Since then PPARγ ligands have been shown to reduce cell growth and induce differentiation in a number of cancer cell lines including breast, colon, gastric, pancreatic, bladder, prostate, and lung. These effects are often additive to the effects of retinoids [13-15, 32]. Mechanistically, PPARγ agonists act to inhibit tumorigenesis through several pathways [17]. PPARγ inhibits cellular progression through the cell cycle by inducing upregulation of the cell cycle inhibitors, p18, p21, and p27 while concurrently downregulating the cell cycle mediator, cyclin D1[18-24]. PPARγ agonists also inhibit angiogenesis and inflammation via the COX-2 and PGE2 pathway, and partly by reducing the expression of VEGF [33]. PPARγ agonists also induce autophagy via the AMPK and mTORC1 pathwa y[34]. PPARγ agonists also stimulate apoptosis. They also reduce cytokine production such as interleukin (IL)-6 and IL-8 via NF-κB [35]. PPARγ agonists also disrupt tumor-stromal interactions required for metastasis through PTEN and pAKT [33, 35]. They prevent cell migration via the suppression of Snail and upregulation of E-cadherin [35] and exert several effects with the ERK cascade [36]. Finally, PPARγ agonists induce cellular differentiation, the exact mechanisms of which are not clear, but do include modulation of the cadherin-catenin system. Ohta*, et al*, demonstrated that use of a PPARγ agonist results in a dramatic increase in expression of E-cadherin, with a concomitant shift of β-catenin to the cell membrane [25, 26]. Furthermore, PPAR activity may directly affect the β-catenin/TCF pathway. Liu and Farmer have shown that a PPARγ agonist induces proteosome-mediated β-catenin degradation [37].

In vivo, PPARγ agonists slow the growth of tumors in rodents, both in carcinogen-induced tumor models, and from ectopically implanted cancer cell lines (breast, colon, prostate) [9, 28]. More limited data is available in humans. In a large (87,678 patient records) epidemiologic study, a statistically significant 33% reduction (relative risk = 0.67; 95% CI, 0.51 to 0.87; P = .0033) in lung cancer risk among thiazolidinedione users versus nonusers was observed [38]. Mueller, *et al* reported that Rosiglitazone led to either a decrease in or prolonged stabilization of PSA levels in patients with prostate cancer. One of 41 patients with androgen dependent prostate cancer had a decrease in PSA of greater than 50%. Less prominent declines in PSA were noted in both patients with androgen dependent (3/12) and androgen independent (4/29) prostate cancer [39]. The therapy was well tolerated, the majority of toxicities being mild to moderate. The only severe toxicities reported were one patient with reversible diarrhea, and another with transaminase elevation.

1.3 Myxoid Liposarcomas and PPARgamma

The potential role of PPARγ agonists as anticancer agents in liposarcoma was first described by Tontonoz, *et al*. They demonstrated the ability of a PPARγ agonist, troglitazone to induce terminal differentiation of liposarcoma cell lines [30]. Demetri, *et al*, were later able to demonstrate in patients with liposarcoma who underwent serial tumor biopsies, before and after treatment with troglitazone, the re-differentiation of liposarcoma tumors into adipocytic tissue [31]. Later, Eposti, *et al*, reported that three out of four patients with recurrent, metastatic liposarcoma treated with PPARγ agonist Pioglitazone had prolonged disease stabilization [40] Moreover, myxoid liposarcomas (MLS), which include round cell liposarcomas (RCL) may be particularly sensitive to treatment with a PPARγ agonist.

MLS/RCL are defined by a chromosomal translocation: 90% of patients with MLS/RCL carry a t(12;16)(q13;p11) translocation resulting in the FUS-DDIT3 fusion gene (previously referred to as TLS-CHOP); while 10% carry a variant t(12;22) that results in an EWSR1-DDIT3 fusion gene [41-43]. The t(12;16)(q13;p11) fusion gene results in an mRNA fusion transcript that links the FUS gene on chromosome 12 with the DDIT3 gene on chromosome 16. FUS is an RNA

binding protein, while DDIT3 is a DNA-binding basic leucine zipper transcription factor. Therefore, the FUS-DDIT3 acts as an abnormal transcription factor only found in MLS/RCL. The FUS-DDIT3 transgene blocks terminal differentiation of preadipocytes *in vivo* and *in vitro*. FUS-DDIT3 transgenic mice developed MLS/RCL-like tumors in adipose tissue, and transfection of FUS-DDIT3 into HT-1080 fibrosarcoma cells induces the transformation into liposarcomas [44, 45]. PPARγ plays a critical role in regulating the maturation of pre-adipocytes into mature adipocytes, and the FUS-DDIT3 gene product blocks expression of PPARγ. However, the rescue of PPARγ expression or the addition of a PPARγ agonist can overcome the block in maturation, and induce terminal differentiation [44, 45]. Thus, PPARγ agonists may be particularly active as anti-cancer agents for patients with MLS. It should be noted, that Debrock, *et al* conducted a clinical trial of 12 patients with LPS treated with the second generation TZD, rosiglitazone. In that trial, which included six patients with MLS, the median progression free survival was only 5.5 months, and there were no responses. It is possible that a more potent, third generation TZD may be more effective in patients with MLS.

1.4 Efatutazone (CS-7017, Daiichi-Sankyo)

1.4.1 Pre-clinical Data

Efatutazone is a novel, third-generation thiazolidinedione that selectively activates PPARγ-mediated transcription, with little effect on other PPAR subtypes. Efatutazone is ≥ 50-times more potent than rosiglitazone and 500-times more potent than troglitazone at PPAR response element-activation and inhibition of cancer cell growth [46]. Efatutazone inhibits proliferation of human pancreatic and anaplastic thyroid tumor-cell cultures, as well as growth of human colorectal tumor xenografts in nude rodents [47]. The antitumor activity of efatutazone *in vivo* may be enhanced in combination with cytotoxic agents including gemcitabine, paclitaxel, and irinotecan [48].

1.4.2 Phase I Experience with Efatutazone

We completed a Phase I clinical trial of the PPARγ agonist, efatutazone in refractory patients with advanced malignancies [49]. 31 patients were treated at doses ranging from 0.10–1.15 mg twice a day (BID). While the maximally tolerated dose was not reached, based on pharmacodynamic and pharmacokinetic data, 0.5mg orally BID was selected as the RP2D. The drug was reasonably well tolerated. A majority of patients experienced peripheral edema (55%) often requiring diuretics, which was unrelated to the dose of therapy. Of 27 evaluable patients, one sustained partial response (690 days on therapy) was observed in a patient with myxoid liposarcoma. In addition, 12 patients had stable disease (SD), 7 for > 80 days (81–290 days).

1.4.3 Efatutazone Pharmacokinetics

Following oral administration of efatutazone, the drug gets converted to the active metabolite R-150033. In plasma, the peak concentrations (Cmax) of R-150033 were observed at 2 to 3 hours post-dose. The mean apparent half-life ranged from 5.7 to 14 hours and appeared to be similar across all dose levels. Following single and multiple doses of efatutazone, the increase in exposure (AUC and Cmax) of R-150033 appears to be dose proportional over the investigated dose range of 0.10 mg to 1.15 mg BID. Based on trough plasma concentrations, efatutazone BID appeared to reach steady-state levels by cycle 2, week 1. Accumulation with multiple dosing to steady state was approximately 140% to 180% across all doses, which is consistent with the half-life and dosing regimen.

1.4.4 Efatutazone Biomarker Analysis

Plasma adiponectin levels were increased 6- to 14-fold by efatutazone administration at all dose levels of 0.10 mg to 1.15 mg twice-daily. Although the increase in adiponectin appeared to be dose dependent, because of the small sample size (3 to 6 patients) and high inter-patient variability, a definitive conclusion was not possible, and statistical analysis revealed no significant dose-dependent effect on the efatutazone -mediated increase in plasma adiponectin levels.

Archived tumor tissue was available for 21 of the 31 study patients. Freshly cut slides were used to perform immunohistochemical analysis of several key proteins. Recognizing that the formation of a bimolecular complex of PPARγ and RXR requires both analytes to be present in the same cell, we compared the product of the expression frequencies (determined as the percentage positive cells) of PPARγ and RXR in tumor specimens (an indirect approximation to the percentage of cells actually expressing both receptors), in those who received clinical benefit (SD for ≥60 days or PR) versus those who did not. When comparing samples that demonstrated increased expression frequencies of both PPARγ and RXR, the difference in outcome was highly statistically significant (nonparametric version of O'Brien's test, 1-sided P = 0.0079). Finally, to provide a preliminary indication of the performance characteristics that such a comparison might have, we performed a receiver-operating curve (ROC) analysis of sensitivity versus specificity of the comparison, as a function of the cutoff value between predicted clinical benefit and lack of clinical benefit. Based on limited data, the optimal cutoff (closest distance to the point of 100% sensitivity and 100% specificity) is 10, corresponding to a sensitivity of 0.83 and a specificity of 0.91. The area under the ROC curve was 0.89 indicating a statistically significant difference from the null line (P = 0.0003). Thus, immunohistochemistry of archived specimens for PPARγ and retinoid-X receptor expression levels is a likely predictive biomarker of response to efatutazone.

Given the strong pre-clinical rational above, and based on the success of the Phase I trial of efatutazone, we now propose a Phase II trial of efatutazone for patients with advanced, unresectable or metastatic myxoid liposarcoma, whose disease has progressed on at least one prior systemic therapy.

1.5 Registration Quality of Life (QOL) Measurements

QOL measurements of fatigue and overall perception of QOL are routinely included in Alliance studies and will be assessed upon registration in this study. Evidence has arisen indicating that baseline single-item assessments of fatigue and overall QOL are strong prognostic indicators for survival in cancer patients, independent of performance status. This evidence was derived from two separate meta-analyses recently presented at ASCO, the first involving 23 NCCTG and Mayo Clinic Cancer Center oncology clinical trials, the second involving 43 clinical trials. Routine inclusion of these measures should be considered similar to that of including performance status, either as stratification or prognostic covariates [50, 51].

1.6 Design Change

Due to slow accrual to the trial, the decision was made to change the study design from a double blind, placebo controlled trial of efatutazone in myxoid liposarcoma, to single arm efatutazone in myxoid liposarcoma. The impact of the trial is critical as additional effective therapies are needed in this rare and aggressive malignancy, and the prior data is compelling that the agent may have activity.

2.0 OBJECTIVES

2.1 Primary objective

To determine the confirmed response rate for efatutazone in patients with advanced myxoid liposarcoma whose disease has progressed on at least one prior therapy.

2.2 Secondary objective

2.2.1 To assess the progression free survival (PFS), overall survival (OS), and adverse event rates for efatutazone treated patients with advanced myxoid liposarcoma whose disease has progressed on at least one prior therapy.

2.3 Correlative science objectives

2.3.1 To assess the following in patients with advanced unresectable or metastatic myxoid liposarcoma treated with efatutazone:

1) The predictive value of PPARg and RXR tumor expression from archived patient tumor samples
2) The predictive value of the expression of PPARγ-regulated markers of adipocyte differentiation.
3) The predictive value of the expression of PPARγ-regulated cell cycle proteins
4) The effects of efatutazone treatment on serum adiponectin levels

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Contact Information page. Please note that the Study Chair cannot grant waivers to eligibility requirements

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Although they will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for $\geq$ 3 years.
- Patients who cannot swallow oral formulations of the agent(s).
- Patients with a life expectancy < 12 weeks
- Diabetic patients using insulin therapy are excluded from enrollment unless they are able to discontinue insulin use (in exchange, for example, for non-insulin antihyperglycemic medications) due to the risk of dangerous and rapid fluid retention with the concurrent use of insulin and efatutazone (see Section 3.3.7)

In addition:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).
- Efatutazone is metabolized by CYP3A4/5, and inhibits CYP2C8, 2C9, 2C19, and 3A4, and is a substrate of PgP and BCRP. The clinical significance of any drug interactions is unknown to date.

3.2 Pre-Registration Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following pages.

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday four weeks later would be considered Day 28.

___ **3.2.1 Central pathology review submission:**

Patients must have a FFPE tumor block **OR** 1 representative H&E and 20 unstained myxoid liposarcoma tissue slides available for submission to central pathology review. This review is mandatory prior to registration to confirm eligibility. See Section 4.4 for details on slide/block submission.

3.3 Registration/Randomization Eligibility Criteria

___ **3.3.1** Measurable disease **as defined in Section 11.0.**

___ **3.3.2 Prior Treatment:**

Progression on at least one prior systemic chemotherapy for advanced, unresectable or metastatic disease. Prior adjuvant or neoadjuvant therapy is not included as prior systemic chemotherapy unless treatment occurred within the 6 months prior to study enrollment.

- There is no limit to the number of prior lines of treatment a patient has received.
- No treatment with biologic therapy, immunotherapy, chemotherapy, investigational agent for malignancy, or radiation ≤ 28 days before study registration. No treatment with nitrosourea or mitomycin ≤ 42 days before study registration.
- Patients should have resolution of any toxic effects of prior therapy (except alopecia) to NCI CTCAE, Version 4.0, grade 1 or less.

___ **3.3.3 No history of the following:**

- Class III or IV congestive heart failure (CHF).
- Pericardial effusion ≤ 12 months (Grade 3 or 4).
- Pericardial involvement with tumor.
- Grade 2 or higher pleural effusion ≤ 6 months.

___ **3.3.4** No symptomatic, untreated, or uncontrolled brain metastases present.

___ **3.3.5** Not pregnant and not nursing, **because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown.** Therefore, for women of childbearing potential only, a negative pregnancy test done ≤ 7 days prior to registration is required. A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

___ **3.3.6 Concomitant medications:**

- Patients with diabetes mellitus requiring concurrent treatment with insulin or thiazolidinedione (TZD) oral agents are not eligible.
- Patients with known hypersensitivity to any TZD oral agents are not eligible.

___ **3.3.7 Age ≥ 18 years**

___ **3.3.8 ECOG Performance Status 0-2**

___ **3.3.9 Required Initial Laboratory Values:**

Absolute Neutrophil Count (ANC)	≥ 1,000/mm^3
Platelet Count	≥ 75,000/mm^3
Creatinine	≤ 1.5 mg/dL x upper limits of normal (ULN)
	OR
Calc. Creatinine Clearance	≥ 30 mL/min**
Bilirubin	≤ 1.5 x upper limits of normal (ULN)
SGOT (AST) and SGPT (ALT)	≤ 2.5 x upper limits of normal (ULN) *

*For subjects with liver metastases, SGOT (AST) and SGPT (ALT) < 5 X the upper normal limit of institution's normal range and bilirubin ≤ 3 x ULN are allowed

** To be calculated by the Cockcroft-Gault formula as follows:

$$\text{CrCl (ml/min)} = \frac{(140 - \text{age in years}) \times \text{actual wt (in kg)}}{72 \times \text{serum creatinine (mg/dl)}} \quad \text{x .85 (for female patients)}$$

___ **3.3.10 Documentation of Disease:**

Histologic Documentation: Eligible patients must have histopathologically confirmed myxoid liposarcoma with confirmation of DDIT3 rearrangement.

4.0 PATIENT REGISTRATION

4.1 CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR Help Desk by email at < [redacted] >.

4.2 CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.2.1 Downloading Site Registration Documents:

Site registration forms may be downloaded from the A091202 protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the Alliance folder to expand, then select trial protocol A091202
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided

4.2.2 Requirements for A091202 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

4.2.3 Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU

RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable original documents should be mailed to:

[redacted]

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at [redacted] in order to receive further instruction and support.

4.2.4 Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Enrollment

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at [redacted]

4.4 A091202 Pre-Registration and Registration Requirements

4.4.1 Pre-registration requirements

- **Informed consent:** the patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.
- **Pre-Registration eligibility criteria**: Patients who meet the pre-registration eligibility criteria will be pre-registered using the OPEN registration system as above. Once a patient is pre-registered, the FFPE tumor block **OR** 1 representative H&E and 20 unstained myxoid liposarcoma tissue slides from diagnostic biopsy should be sent to the Alliance Biorepository at Ohio State (OSU) along with the completed "Central Pathology Review Form," per Section 6.1. Failure to submit this form with the specimens will delay turnaround time for central pathology review. The specimen will be centrally reviewed to confirm the patient meets the pathology criteria for myxoid liposarcoma with confirmation of DDIT3 rearrangement. Once the site has received confirmation from the Alliance, and the Registration and Randomization Eligibility Criteria have been met, the patient can be registered to the study.

4.4.2 Registration requirements

- **Registration Procedures:** Sites will be notified via e-mail within **21 business days** of receipt, whether or not the patient is eligible based on the central pathology review. The results section of "Central Pathology Review Form" will be completed by the pathologist, scanned and sent via e-mail to the Responsible CRA listed on the form. After receiving the results form via e-mail, the institution must forward the form to the Alliance Patient Registration office at [redacted] in order to register the patient. Once the form is forwarded to the Alliance Patient Registration Office and the Registration and Randomization Eligibility Criteria have been met, the patient can then be registered using the OPEN system (registration will occur within 14 days of specimen submission). The CRA should enter the ID number obtained at pre-registration into the OPEN system to register the patients. The OPEN system will provide the institution with a printable confirmation of registration. Please print this confirmation for your records. Retain the "Central Pathology Review Form" confirming eligibility for your records and to upload via Rave.

Follow the OPEN enrollment procedures as detailed in Section 4.3.

4.5 Registration to Correlative Study

4.5.1 Registration to Substudy described in Section 14.0

There is one substudy within Alliance A091202. This correlative science study **must be offered to all patients** enrolled on Alliance A091202 (although patients may opt to not participate). This substudy does not require separate IRB approval. The substudy included within Alliance A091202 is:

- Analysis of Cell Cycle Regulated Proteins and Markers of Differentiation, Alliance A091202-ST1 (Section 14.2)

If a patient answers "yes" to "I agree to have my specimen collected and I agree that my specimen sample(s) and related information may be used for the laboratory study described above." Question #2 in the model consent, they have consented to participate in the substudy described in Section 14.0. The patient should be registered to Alliance A091202-ST1 at the same time they are registered to the treatment trial (A091202). Samples should be submitted per Section 6.0.

5.0 STUDY CALENDAR

Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

Pre-Study Testing Intervals

- To be completed ≤ 14 DAYS before registration: All laboratory studies, history and physical.
- To be completed ≤ 28 DAYS before registration: Any imaging modality which is utilized for tumor measurement per protocol.
- To be completed ≤ 42 DAYS before registration: Any baseline exams used for screening, or any imaging of any type which is not utilized for tumor measurement.

	Prior to Registration *	Days 1 (+/- 4 days) of each cycle through Cycle 4; then Day 1 (+/- 7 days) of every odd numbered cycle for Cycle 5 and beyond	Weeks 2 and 3 (+/- 2 days) of Cycle 1	Post treatment follow up***	At PD, withdrawal, or removal****
Tests & Observations					
History and physical, weight, PS	X	X	X	X	X
Height	X				
Pulse, Blood Pressure	X	X	X		
Adverse Event Assessment		X	X		X
Registration Fatigue/Uniscale Assessment	X(1)				
Laboratory Studies					
Complete Blood Count, Differential, Platelets	X	X			
Creatinine,	X	X			
Albumin, glucose	X	X			
AST, ALT, Alk. Phos., Bili	X	X			
Fasting Triglycerides, total cholesterol		X(5)			
Serum or Urine HCG	X(2)				
Staging					
Central pathology review for eligibility	X(3)				
Tumor Measurement	X	A		X	
CT/MRI chest/abdomen/pelvis	X(4)	A		A	
A091202-ST1 Correlative studies: For patients who consent to participate					
Archival block OR slides	X				

* Labs completed prior to registration may be used for day 1 of cycle 1 tests if obtained ≤ 14 days prior to treatment.

*** For patients who are removed from protocol therapy for reasons other than progression: Physical examination and staging scans are required every 12 weeks (+/- 7 days) (after the end of treatment) until disease progression. On completion of study treatment, all patients are followed for survival only every 6 months (+/- 30 days) until death or a maximum follow-up of 5 years. See also Section 12.0.

**** Visit and AE assessment should be completed 4 weeks (+/- 7 days) after completion of protocol therapy

1 To be completed after pre-registration and prior to registration, see Appendix I.

2 For women of childbearing potential (see Section 3.3). Must be done ≤ 7 days prior to registration and ≤ 7 days prior to re-registration at crossover.

3 See Sections 4.5 and 6.1.

4 Baseline scans can include either: 1) a CT, spiral CT, or MRI, or 2) an FDG-PET scan and diagnostic CT performed with both IV and oral contrast, and the CT acquired with 5 mm or less slice thickness. If a bone scan is used for baseline scan, please note in ECRF, but bone scans are not mandatory. Documentation (radiologic and pathology report and clinic note) of the diagnosis scan must be submitted.

5 Fasting triglycerides and total cholesterol will be done on Day 1 of Cycles 3 and 6 (+/- 7 days).

A Every 6 weeks (approximately every 2 cycles) through 24 weeks, and then every 12 weeks (approximately every 4 cycles) after week 24 until evidence of progression or relapse. Scans may be done up to 7 days prior to beginning a cycle. Confirmatory scans should also be obtained at least 4 weeks following documentation of objective response (see Section 11.0).
If the baseline scans were a CT or MRI and bone scan, follow-up bone scans are required only for patients with bone metastases as the only site of evaluable disease, and are optional for other patients. **Response assessment should include assessment of all sites of disease and use the same imaging method as was used at baseline.** Documentation (radiologic and clinic note) must be provided at progression of disease.

6.0 DATA AND SPECIMEN SUBMISSION

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at [redacted] or by e-mail at [redacted]

6.1 Specimen collection and submission

For all patients pre-registered to Alliance A091202: Real-time histopathology review will be conducted using the myxoid liposarcoma tissue from the diagnostic biopsies.

	≤ 3 days from pre-registration	Submit to:
Mandatory for all patients registered to A091202:		
Archival FFPE tumor block OR 1 representative H&E and 20 unstained myxoid liposarcoma tissue slides (if site does not have 20 slides, please send as many as possible, up to 20)	X	OSU

For patients registered to substudy A091202-ST1: All participating institutions must ask patients for their consent to participate in the correlative substudy planned for Alliance A091202-ST1, although patient participation is optional. Rationale and methods for the scientific components of these studies are described in Section 14.0. For patients who consent to participate, a portion of the archival FFPE tumor block OR tissue slides will be used to complete the correlative study.

6.1.1 Specimen submission using the Alliance Biospecimen Management System

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: http://bioms.allianceforclinicaltrialsinoncology.org using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS web page to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: [redacted]. For assistance in using the application or questions or problems related to specific specimen logging, please contact: [redacted]

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

All submitted specimens must be labeled with the protocol number (A091202), Alliance patient number, patient's initials and date and type of specimen collected (e.g., serum, whole blood).

A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens.

Instructions for the collection of samples are included below. Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

Shipment on Monday through Thursday by overnight service to assure receipt is encouraged. Do not ship specimens on a Friday or Saturday or the day before a federal holiday.

All specimens should be sent to the following address:

Alliance Biorepository at Ohio State (OSU)
The Ohio State University
[redacted]

6.1.2 Collection and processing for central pathology review

Consistent and accurate histologic grading is important for this study. A FFPE tumor block **OR** 1 representative H&E and 20 unstained tissue slides (thickness of 5-6 microns) from the diagnostic myxoid sarcoma biopsy must be submitted. The submission should be taken from the highest grade area as identified by your local pathologist/investigator.

A FFPE tumor block **OR** 1 representative H&E and 20 unstained tissue slides (thickness of 5-6 microns) of the patient's myxoid sarcoma cancer diagnosis should be retrieved from the surgical pathology department. Blocks which contain minimal amounts of tissue specimen or that are very thin should not be submitted unless the block is the only representative tissue for the case. A de-identified surgical pathology report should be sent with all specimens. Usually, this is generated by obscuring all PHI (names and dates) with white-out or a black

magic marker, labeling each page of the report with the Alliance patient ID, and photocopying the report.

In addition to the pathology report, the institution must complete and submit the "Central Pathology Review Form" with the tumor block or slides to the Alliance Biorepository at OSU. Failure to submit this form with the specimens will delay turnaround time for central pathology review. The top portion of the form must be completed by typing and cannot be handwritten. For Alliance members, the form may be found on the A091202 study page on the Alliance website under the "Supplemental Materials" tab. For non-Alliance institutions, the form can be found under the "LPO Documents" tab on the CTSU A091202 study page (www.ctsu.org).

When shipping blocks and /or FFPE slides, it is important to avoid extreme heat. If environmental conditions indicate, specimens may be shipped in containers containing cold packs. The diagnostic slides must be appropriately packed to prevent damage (e.g. slides should be placed in appropriate slide container) and placed in an individual plastic bag. It is also important that blocks are shipped in appropriately padded and secure containers to avoid physical damage. Do not wrap blocks or slides in tissue or paper toweling that is in direct contact with the paraffin.

The Alliance has instituted special considerations for the small percentage of hospitals whose policy prohibits long-term storage of blocks, and the smaller percentage of hospitals whose policies prohibit release of any block.

The goal of the Alliance is to provide investigators with quality histology sections for their research while maintaining the integrity of the tissue. All slides/blocks may be returned with written request by the site.

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 7 days from registration.

Patients are permitted to have a new cycle of treatment delayed up to 7 days for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. Documentation to justify this delay should be provided.

Patients will receive efatutazone, 0.5mg orally twice daily. Each cycle is 21 days (3 weeks).

If at reimaging there is no evidence of disease progression, and the patient is tolerating therapy, then the patient will continue to remain on treatment until progression.

A091202 dose table:

Agent	Dose	Route	Day	ReRx
Efatutazone	0.5 mg	PO	BID	Every 21 days*

*Taken continuously with no break between cycles

Efatutazone tablets are to be self-administered PO BID, with or without food. The intended dosing schedule for efatutazone dosing is every 12 hours. However, dosing may occur within ± 2 hours of the scheduled administration time.

Treatment is to continue until disease progression or unacceptable adverse event. After disease progression or unacceptable adverse event, patients will be followed for a maximum of 5 years, as in Section 5.0.

8.0 DOSE AND TREATMENT MODIFICATIONS, UNBLINDING

8.1 Ancillary therapy, concomitant medications, and supportive care

8.1.1 Patients should not receive any other agent which would be considered treatment for the primary neoplasm or impact the primary endpoint.

8.1.2 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

8.1.3 Treatment with hormones or other chemotherapeutic agents may not be administered except for steroids given for adrenal failure; hormones administered for non-disease-related conditions (e.g., non-TZD oral agents for diabetes).

8.1.4 Antiemetics may be used at the discretion of the attending physician.

8.1.5 Palliative radiation therapy: Patients who require radiation therapy during protocol treatment will be removed from protocol therapy due to disease progression.

8.1.6 Alliance Policy Concerning the Use of Growth Factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based, Clinical Practice Guideline. J Clin Oncol 24(19): 3187-3205, 2006.

Darbepoietin or Epoetin (EPO): Use of darbepoietin or epoetin in this protocol is permitted at the discretion of the treating physician.

Filgrastim (G-CSF) and sargramostim (GM-CSF)

Filgrastim/pegfilgrastim and sargramostim may not be used:

a. To avoid dose reductions or delays.
b. For the treatment of febrile neutropenia the use of CSFs should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSFs may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSFs in this setting. The use of CSF (filgrastim/pegfilgrastim or sargramostim) must be documented and reported.
c. If filgrastim/pegfilgrastim or sargramostim are used, they must be obtained from commercial sources.

8.1.7 Hyperlipidemia: Elevations of lipids is a known side effect of this medication. The use of medications for hyperlipidemia is permitted at the discretion of the treating physician.

8.1.8 Anemia: Patients have developed anemia associated with efatutazone. Full supportive care should be utilized at the discretion of the treating investigator.

8.1.9 Edema: Edema/fluid retention is a common side effect of this medication. Patients should maintain the weight diary, and should be weighed with all visits. Patients should contact

their physician with a weight gain of over 5lb. for further management. The following is a suggested regimen for fluid retention but is NOT required:

- With weight gain of 5 lbs. or more, start furosemide 20mg daily and spironolactone 25mg daily
- For additional weight gain unresponsive to initial diuretics, increase dose of furosemide to 40mg daily and spironolactone to 50mg daily
- For patients allergic to sulfa-containing drugs where there may be concern over the use of furosemide, bumetanide may be used in place of furosemide at doses of 1mg daily, and increased to 2 mg daily, as needed for weight gain unresponsive to initial diuretics.

8.2 Dose Modifications

General rules for dose modification:

- If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.
- Efatutazone will not be re-escalated once reduced
- If dose reductions beyond dose level -2 is required or efatutazone is held for 21 days, efatutazone will be discontinued.

CTEP-AERS reporting may be required for some adverse events (See Section 9.0)

8.2.1 Dose Levels

Dose Level	Drug Name	Dose
0*	Efatutazone	0.5 mg BID
-1	Efatutazone	0.5 mg every morning, 0.25mg every evening
-2	Efatutazone	0.25 BID

*Dose level 0 refers to the starting dose.

8.2.2 Cardiac Toxicity

For **grade 3 or 4 pericardial effusion**, discontinue efatutazone

8.2.3 General disorders

- For **grade 2 edema**, omit efatutazone until grade < 2, then resume efatutazone at same dose with diuretic support
- For **grade 3 edema**, omit efatutazone until grade < 2, then resume efatutazone at one dose level decreased with diuretic support

8.2.4 Pulmonary Toxicity

- For **grade 2 pleural effusion**, omit efatutazone until grade ≤ 1, then resume efatutazone at one dose decreased with diuretic support
- For **grade 3 or 4 pleural effusion**, discontinue efatutazone with diuretic support

8.2.5 Metabolism and nutrition disorders

For **grade 3 or 4 hypertriglyceridemia** that has physiologic or life-threatening consequences, omit efatutazone until physiologic or life-threatening consequences have resolved, then resume at same dose. If grade 3 or 4 hypertriglyceridemia is based on the numeric value and there are no physiologic or life-threatening consequences, do not interrupt drug.

8.2.6 Non-hematologic Toxicities

For all other **grade 3 or 4 non-hematologic toxicities** likely related to efatutazone, omit efatutazone until resolved to ≤ grade 1, then resume efatutazone at one dose decreased

8.3 Unblinding Procedures (prior to update #02)

As of 10/01/16, the study was redesigned from a double-blind placebo controlled study to an open label single arm study of efatutazone, due to slow accrual to the trial. Therefore, on 10/01/16 the study was unblinded and all participants were placed on open label efatutazone.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. However, CTCAE v5.0 must be used for serious AE reporting through CTEP-AERS as of April 1, 2018. The CTCAE is available at http://ctep.cancer.gov/reporting/ctc.html. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms, using the codes provided.

9.1 Routine adverse event reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0. For this trial, Rave is used for routine AE reporting.

Solicited Adverse Events: The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment.

CTCAE v4.0 Term	CTCAE v4.0 System Organ Class (SOC)
Neutrophil count decreased	Investigations
Anemia	Investigations
Edema limbs	General Disorders
Weight gain	Investigations
Pleural Effusion	Respiratory disorders
Pericardial Effusion	Cardiac disorders
Cholesterol high	Investigations
Hypertriglyceridemia (See Section 5.0, Footnote "5").	Investigations
Fatigue	General Disorders

9.2 CTCAE Routine Study Reporting Requirements

***Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)**

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a

Possible		a	a, b	a, b	a, b
Probable		a	a, b	a, b	a, b
Definite		a	a, b	a, b	a, b

a) Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.

b) Adverse Events: Late CRF - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

9.3 Expedited adverse event reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined below. Alliance investigators are required to notify the Alliance Central Protocol Operations Program Office, the Study Chair, and their Institutional Review Board if a patient has an adverse event requiring expedited reporting. All such events must be reported in an expedited manner using the NCI Adverse Event Expedited Reporting System (CTEP-AERS). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

The Alliance requires investigators to route all expedited adverse events through the Alliance Central Protocol Operations Program Office for Alliance-coordinated studies. **Be sure to read this entire protocol section**, as requirements are described in both the table and bullet points following the table. The bullet points (additional instructions or exclusions) are protocol specific and in the case of a conflict, the additional instructions or exclusions supersede the table.

9.3.1 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND ≤ 30 Days of the Last Administration of the Investigational Agent/Intervention [1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour; 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted ≤ 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report ≤ 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

Additional Instructions or Exclusions:

- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB, according to local IRB policies.
- Alliance A091202 uses a drug under an Alliance IND. These reporting requirements apply for all agents (any arm) in this trial.
- Grade 3/4 myelosuppression or febrile neutropenia and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results via routine reporting.
- Treatment expected adverse events include those listed in Section 10.0, in the IB for efatutazone.
- All new malignancies must be reported through CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologoc malignancies, myelodysplasic syndrome/acute myelogenous leukemia, and in situ tumors. In CTCAE v5.0, secondary malignancies may be reported as one of the following three options: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment-related secondary malignancy. Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.
- All pregnancies and suspected pregnancies occurring in female patients during therapy or within 28 days after completion of treatment on A091302 must be reported via CTEP-AERS. In CTCAE version 5.0, pregnancy loss is defined as "Death in utero," and any pregnancy loss should be reported as "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC (grade 4).
    - CTEP-AERS reports should be amended upon completion of the pregnancy to report pregnancy outcome (e.g. normal, spontaneous abortion, therapeutic abortion, fetal death, congenital abnormalities). Fetal deaths should be reported as "Death neonatal" under the General disorders and administration SOC (grade 4).
    - The CTEP-AERS report should be amended for any neonatal deaths occurring within 28 days of birth considered at least possibly related to treatment. Use the event term "Death neonatal" under the General disorders and administration SOC (grade 4).
- Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.
- The reporting of adverse events described in the table above is in addition to and does not supplant the reporting of adverse events as part of the report of the results of the clinical trial, e.g. cooperative group data reporting.

10.0 DRUG INFORMATION

10.1 Efatutazone dihydrochloride monohydrate (CS-7017) (Alliance IND #121997)

Procurement

Efatutazone dihydrochloride monohydrate (efatutazone) will be provided by Daiichi Sanyko and distributed by Biologics, Inc. Use the order form on the A091202 CTSU webpage to order efatutazone.

Formulation

Efatutazone is supplied as 0.25 mg tablets. The strength of efatutazone is expressed as the anhydrous free base. Efatutazone is supplied as white uncoated tablets. The inactive ingredients are mannitol, low-substituted hydroxypropyl cellulose, silicon dioxide, and magnesium stearate.

The uncoated tablets are provided in 100 ct amber glass bottles.

Preparation, Storage and Stability

All drug supplies should be stored in a secure location, at room temperature, up to 25ºC (77ºF), with excursions permitted from up to 30ºC (86ºF). At the end of the trial, any expired or remaining supplies should be destroyed according to institutional procedure.

Administration

Efatutazone should be taken twice daily at the same time each day, approximately 12 hours apart with or without food.

Drug Interactions

CYP3A4/5 is involved in the metabolism of efatutazone. Efatutazone may inhibit CYP2C8, CYP2C9, CYP2C19, and CYP3A4. A drug-drug interaction study with CYP3A4 inhibitor ketoconazole has been evaluated in healthy subjects. With concurrent administration of ketoconazole, total exposure of efatutazone increased by approximately 71% without significantly affecting the peak exposure.

Food and gastric pH effect have been evaluated in healthy subjects receiving efatutazone. No clinically significant effect was observed on the oral bioavailability of efatutazone by either food or gastric pH. Therefore, efatutazone can be taken together with food or gastric pH modifiers.

In vitro studies indicate that efatutazone has an inhibitory potential on uptake transporters (OATP1B1, OATP1B3, OAT3, and OCT2) and efflux transporters (P-glycoprotein and BCRP) with IC_{50} values of 0.508 to 16μM. However, these levels of efatutazone are much higher than the exposure observed in humans; therefore drug-drug interaction on these transporters would be unlikely.

Pharmacokinetics

Absorption: Well absorbed and has high oral bioavailability (59-101.8%). The rate of absorption is slightly slower in the fed state compared to the fasted state with respective median tmax values of 3 and 2 hours. The 90% CI for the ratio of Cmax for fed to fasted states was from 79.3% to 89.2% associated with a 15.9% decrease in mean Cmax. Efatutazone may be taken without regard to meals.

Distribution: V_d: 16.9 L at 0.5 mg dose

Protein binding in humans is 99.52% and low partitioning into red blood cells.

Metabolism: In rats and monkeys efatutazone was mainly metabolized by O-dearylation followed by sulfation and glucuronidation. *In vitro* correlation analyses conducted using human liver microsomes and specific antibodies for each P50 isoform suggest that efatutazone is mainly metabolized by CYP3A4/5.

Half-life elimination: 8.37 hours

Excretion: Feces (69.9%); urine (20.2%)

Clearance: 1.45 L/hour

Adverse Events

Final safety data are available from 10 completed studies as of December 8, 2011. Adverse drug reactions which have a reasonable causal relationship to treatment with efatutazone include: edema, facial edema, localized edema, peripheral edema, pitting edema, fluid retention, weight gain, joint swelling, facial swelling, pleural effusions, hypercholesterolemia, hypertriglyceridemia, fatigue, asthenia, dyspnea, nausea, pain in the extremities, and anemia. Neutropenia and febrile neutropenia has been observed when efatutazone was given with FOLFIRI.

10.1.1 Nursing Guidelines

1. Edema and fluid retention have been noted. Instruct patient to report any swelling or weight gain to the study team.
2. Lipid abnormalities have been reported. Monitor lipid panel as per protocol. Instruct patient on appropriate diet.
3. Monitor CBC w/diff. Instruct patients to report any signs/symptoms of infection or bleeding to the study team.
4. Eye toxicity was seen in animal models but thus far has not been noted in human subjects. Instruct patients to report any ocular symptoms immediately (i.e., sore or red eyes, difficulty with or changes in vision), as ulcerative keratitis has been seen in animal models and to a lesser extent, general eye irritation.
5. Agent may be taken with or without food.

11.0 MEASUREMENT OF EFFECT

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

11.1 Schedule of Evaluations:

For the purposes of this study, patients should be reevaluated every 6 weeks (approximately every 2 cycles) during treatment. Of note, scans should be performed according to the Study Calendar in Section 5.0. In addition to a baseline scan, confirmatory scans should also be obtained ≥ 4 weeks following initial documentation of objective response

11.2 Definitions of Measurable and Non-Measurable Disease

11.2.1 Measurable Disease

A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.

A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Tumor lesions in a previously irradiated area are not considered measurable disease.

11.2.2 Non-Measurable Disease

All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥ 1.0 to < 1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis < 1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.3.1 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.3.2 Acceptable Modalities for Measurable Disease:

- **Conventional CT and MRI:** This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

  As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.
- **PET-CT:** If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.
- **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 scans are preferable.
- **Physical Examination:** For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions,

documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

- **FDG-PET:** FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease (PD) and particularly possible 'new' disease. A 'positive' FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered 'negative.' New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

  a. Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

  b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

     1) If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

     2) If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.

     3) If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

11.3.3 Measurement at Follow-up Evaluation:

- A subsequent scan must be obtained ≥4 weeks following initial documentation of an objective status of either complete response (CR) or partial response (PR).
- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval 6 weeks (see Section 11.4.4).
- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.
- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases

11.4 Measurement of Treatment/Intervention Effect

11.4.1 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.2.1) up to a maximum of 5, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in 11.2.1), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

  Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- **Baseline Sum of Dimensions (BSD):** A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
- **Post-Baseline Sum of the Dimensions (PBSD):** A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.
- **The minimum sum of the dimensions (MSD)** is the minimum of the BSD and the PBSD.

11.4.2 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.2.2) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.4.3.3.

11.4.3 Response Criteria

11.4.3.1 All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.4.3.2 Evaluation of Target Lesions

- **Complete Response (CR):** All of the following must be true:
  a. Disappearance of all target lesions.
  b. Each target lymph node must have reduction in short axis to < 1.0 cm.
- **Partial Response (PR):** At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (see Section 11.4.1).

- **Progression (PD):** At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
  b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.4.1). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.
  c. See Section 11.3.2 for details in regards to the requirements for PD via FDG-PET imaging.
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.4.3.3 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- **Complete Response (CR):** All of the following must be true:
  a. Disappearance of all non-target lesions.
  b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.
- **Non-CR/Non-PD:** Persistence of one or more non-target lesions or non-target lymph nodes.
- **Progression (PD):** At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
  b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)
  c. See Section 11.3.2 for details in regards to the requirements for PD via FDG-PET imaging.

11.4.4 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following table:

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

* See Section 11.4.3.1

11.4.5 Symptomatic Deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration.

11.5 Definitions of analysis variables

Formal definitions of variables used in analyses can be found in the Statistical Considerations section of the protocol.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Treatment

12.1.1 CR, PR, or SD: Patients who are in CR, PR or SD will continue on therapy until disease progression/recurrence (or withdrawal of consent). After treatment is discontinued, patients will be followed per the study calendar in section 5.0.

12.1.2 Disease Progression: Patients will be evaluated per Section 11.0. Document details, including tumor measurements, on data forms.

After disease progression, patients should be followed for survival only per the study calendar (Section 5.0).

12.1.3 Discontinuation of study agent: If the patient discontinues efatutazone, patients should be followed for survival per the study calendar (Section 5.0).

12.2 Managing ineligible patients and registered patients who never receive protocol intervention

Definition of ineligible patients: A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible. Patients who are deemed ineligible may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Study participants who are registered to the trial but never receive study intervention (for a reason other than because they were deemed ineligible) must still complete follow-up requirements as specified below.

Baseline, on-study and off-treatment notice data submission required.

12.3 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Overview

This single arm Phase II trial will assess the confirmed response rate of efatutazone in patients with advanced, unresectable, or metastatic myxoid liposarcoma who have received at least one prior systemic therapy. Prior studies have shown that the confirmed response rate is generally around 5%. It is hoped that efatutazone can increase the confirmed response rate to at least 20%. In addition to the confirmed response rate, this trial will also estimate the progression-free survival (PFS), overall survival (OS), and adverse event rates for efatutazone.

13.2 Primary Endpoint and Study Design

The primary endpoint for this study will assess the confirmed response rate (by RECIST 1.1) of efatutazone in patients with advanced, unresectable, or metastatic myxoid liposarcoma who have received at least one prior systemic therapy. Any confirmed response that occurs during the first 8 cycles of treatment will count as a success (24 weeks). Per RECIST 1.1, responses need to be confirmed (2 consecutive responses at least 4 weeks apart) to count as a response (see Section 11). All eligible patients who are registered and start treatment will be evaluable for response. A Simon's optimal two-stage design will be utilized (see below). This design has 80% power to detect an improvement in the confirmed response rate from 5% to 20%, with a significance level of 0.10. See design details below:

Interim Analysis: Enroll 9 eligible patients (need 6 additional patients after design change to single arm trial). If at least 1 confirmed response is observed in the first 9 eligible patients, we will continue the study to a full accrual of 24 eligible patients. Otherwise, the study will be permanently closed due to lack of efficacy. The study will remain open during the interim analysis phase due to slow projected accrual rate and minimal expected toxicity.

Final Analysis: If the trial is a success during the interim analysis, we will enroll another 15 eligible patients (24 eligible total). If at least 3 confirmed responses are observed in the first 24 eligible patients (13%), the treatment will be considered worthy of further investigation. Otherwise, the study will be permanently closed due to lack of efficacy.

13.3 Secondary Endpoints

The following endpoints will be assessed: progression-free survival, overall survival, and adverse events. All patients who meet the eligibility criteria, and sign the consent form will be considered evaluable for these endpoints.

Progression-Free Survival: Progression-free survival (PFS) is defined as the time from study entry to the first of either disease progression or death from any cause, where disease progression will be determined based on RECIST 1.1 criteria. PFS will be estimated using the Kaplan-Meier method.

Overall Survival: Overall survival (OS) is defined as the time from study entry to death from any cause. OS will be estimated using the Kaplan-Meier method.

Adverse events: The maximum grade for each type of adverse event will be summarized using CTCAE version 4.0. The frequency and percentage of grade 3+ adverse events will be estimated.

13.4 Statistical Analysis for Translational Studies

Due to the limited sample size in this study, the proposed translational studies are considered exploratory and hypothesis generating. We plan to estimate the effects of efatutazone treatment on the following translational endpoints:

1) PPARg and RXR tumor expression from archived patient tumor samples
2) PPARg-regulated markers of adipocyte differentiation.
3) PPARg-regulated cell cycle proteins

We will also correlate the tumor marker data with clinical endpoints (i.e. response, PFS, OS, and adverse events). Statistical and graphical techniques will be used to explore these relationships. For time-to-event endpoints, we will use Cox proportional hazards models, and for response/toxicity we will use Logistic regression models. In addition, we will use the Fisher's exact tests to test the association between categorical marker data and response/toxicity.

13.5 Total Sample Size, Accrual Duration, and Anticipated Time to Study Completion

A maximum of 24 evaluable patients (21 new efatutazone treated patients + 3 already randomized previously) will be accrued onto this randomized phase II study unless the study is closed early for excessive toxicity or lack of efficacy. We anticipate accruing an additional 20% of patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, maximum accrual is about 30 patients (up to 28 treated with efatutazone (25 new, 3 already enrolled) + 2 placebo treated patients (already enrolled from prior randomized study)). With an expected accrual rate of 1 patient per month, we anticipate that it will take about 3 years to reach full accrual. We anticipate that the study will take approximately 4 years to complete. This allows a 6-month follow-up for the final patient enrolled, along with data entry and analysis.

13.6 AE Stopping Rule

The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual after any temporary suspension or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may also choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as "possible", "probable", or "definite") that satisfy any of the following criteria:

- If at any time, 3 of the initial 9 treated patients or 33% or more of all patients (i.e. when accrual is greater than 9 patients) have experienced a grade 4 adverse event.
- If at any time, 2 patients have experienced a grade 5 adverse event (not due to progressive disease).

13.7 Accrual Monitoring Stopping Rule

Given the expected accrual rate is around 1 patient per month, it is expected that the study will take around 3 years to fully accrue. We plan to monitor the accrual continually and if we only end up accruing 3 patients or less in the first year (after study activation), we will consider stopping the trial for slow accrual.

13.8 Primary Endpoint Completion Time Estimation (For clinicaltrails.gov reporting)

The primary endpoint is to determine the confirmed response rate, as discussed in detail in section 13.2. The final analysis is expected to take place around 4 years after the study begins, so we expect that the primary endpoint completion time to be around 4 years after study activation.

13.9 Descriptive Factors

- Progression prior to starting treatment: Within 1 month vs. within 2-6 months
- Tumor characteristics:
  - RXR expression: high vs. low
- Number of prior lines of therapy: 1 vs. 2 or more
- Prior anthracycline: yes of no
- Prior trabectedin: yes or no

13.10 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin. There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	1	1	2
Not Hispanic or Latino	14	14	28
Ethnic Category: Total of all subjects	15	15	30
Racial Category			
American Indian or Alaskan Native	1	1	2
Asian	1	1	2
Black or African American	1	1	2
Native Hawaiian or other Pacific Islander	1	1	2
White	11	11	22
Racial Category: Total of all subjects	15	15	30

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

14.0 CORRELATIVE STUDIES

There is one substudy within Alliance A091202. This correlative science study **must be offered to all patients** enrolled on Alliance A091202 (although patients may opt to not participate). This substudy does not require separate IRB approval. The substudy included within Alliance A091202 is:

Analysis of Cell Cycle Regulated Proteins and Markers of Differentiation, Alliance A091202-ST1

14.1 Background

PPARγ binds to Retinoic acid receptor RXR-beta as a heterodimer, and a ligand of either receptor can stimulate target gene transcription including *Pyruvate dehydrogenase kinase isozyme 4 (Pdhk4), Adipose differentiation related protein (Adfp),* and *Fatty acid binding protein 4 (Fabp4) [10, 53]*. PPARγ agonists have been shown to reduce cell growth and induce differentiation in a number of cancer cell lines including breast, colon, gastric, pancreatic, bladder, prostate, and lung [9, 13-16]. Mechanistically, PPARγ agonists act to inhibit tumorigenesis through several pathways [17-26, 37]. PPARγ inhibits cellular progression through the cell cycle by inducing upregulation of the cell cycle inhibitors, p18, p21, and p27 while concurrently downregulating the cell cycle mediator, cyclin D1. PPARγ agonists also inhibit angiogenesis, partly by reducing the expression of VEGF [33]. PPARγ agonists also stimulate apoptosis [34]. Finally, PPARγ agonists induce cellular differentiation, and adipocyte differentiation, as evidenced by FABP4, adipsin, and adiponectin expression, as well as demonstrated by Oil-red O staining [29, 30].

Efatutazone specifically restrains growth of human anaplastic thyroid and colon cancer cells in xenograft mouse models [46, 48, 54], and inhibits formation and progression of azoxymethane induced colonic adenomas in mice [55]. In the anaplastic thyroid cancer cells, efatutazone reduces cell proliferation through a PPARγ-dependent mechanism impacting activation of Rho-related GTP-binding protein RhoB and Cyclin-dependent kinase inhibitor 1 signaling pathways [46, 54].

We demonstrated in a mouse model of *Brca1* mutation induced mammary cancer that efatutazone-induced reductions in AKT phosphorylation, and increased expression in the PPARγ-regulated genes *Adfp*, *Fabp4* and *Pdhk4 [56]*. In this model, which is deficient in two cell cycle regulatory proteins BRCA1 and p53, there were no consistent changes in cell cycle pRB, RB, Cyclin D1, Cyclin E, CDK4, CDK6, p21, and E2F1 either in malignant or preneoplastic mammary tissue.

To determine if pre-treatment expression levels of PPARγ and RXR are correlated with response, expression levels will be assessed by immunohistochemistry (IHC) and graded by a combined intensity and proportion of cells staining score as we have done previously [56]. We hypothesize that evaluation of PPARγ and RXR expression levels by IHC could be a significant predictor of response because in the Phase I trial of efatutazone, we performed immunohistochemistry on pre-treatment tumor specimens in 21/31 patients. We found that PPARγ and RXR protein tumor expression levels in patients with clinical benefit (defined as SD ≥60 days or PR) were significantly greater than in patients with no clinical benefit (defined as SD <60 or disease progression), p=0.0079, suggesting a possible predictive biomarker of response to efatutazone.

In an effort to identify predictive markers of response to efatutazone, we will assess the expression of PPARγ-regulated genes in archived tumor samples, as well as the predictive value of the expression of PPARγ and RXR itself. These studies are aimed to demonstrate:

1) The basal state of PPARγ-regulated genes in the patient tumors. This will provide a surrogate understanding of how active (or inactive) PPARγ is as a transcription factor in each patient's tumor, presumably as a result of the degree of *FUS-DDIT3* expression and presumably the timing of the development of the *FUS-DDIT3* translocation during adipocyte differentiation
2) The degree to which the tumor sample would be "receptive" to a PPARγ agonist, based on expression of the target of efatutazone, PPARγ itself, as well as its obligate heterodimeric partner, RXR

Therefore, we will assess archived tumor samples for the expression of known PPARγ–regulated target genes and markers of differentiation including the expression products (i.e. the protein product) of *Adfp*, *Fabp4, Pdhk4,* as well as the expression of PPARγ–regulated cellular proteins regulating cell proliferation, survival and adhesion (including but not limited to p18, p21, p27, Cyclin D1, E-cadherin, β-catenin, and Snail). The assessment of the expression of these proteins will be performed by IHC [20, 34-36].

The correlative aims are designed to build upon the phase I trial described above that demonstrated presence of a biomarker, and further demonstrate the mechanisms by which efatutazone exerts an anti-cancer effect on patient tumors.

Specific hypotheses include:

- We hypothesize that the PFS will be greatest in patients with high tumor levels of PPARγ and RXR expression
- We hypothesize that an evaluation of cell cycle regulatory proteins, markers of differentiation, and PPARγ-regulated genes will reveal additional predictive markers of response to, and potentially resistance to efatutazone.

14.2 Objectives

We will examine the expression of a number of correlative markers that reflect the state of PPARγ-trasncriptional activity in archived tumor samples, and may serve as predictive markers of response to therapy.

14.3 Methods

Upon receipt at OSU, archived tumor FFPE block or slides will be stored at room temperature.

Batched samples will be requested from the Alliance Biorepository to be shipped in preparation for the correlative assays to:

[redacted]

Upon receipt at [redacted] lab, FFPE blocks will be submitted to the Histopathology and Tissue Shared Resource (HTSR) in the LCCC for serial sectioning.

14.3.1 IHC Analysis of Integrated Biomarkers (PPARγ and RXRα)

Analytes

- PPARγ - The target of efatutazone and a nuclear hormone receptor that functions as a transcription factor

- RXRα – An obligate heterodimeric partner of PPARγ, RXRα is also a nuclear hormone receptor that functions as a transcription factor

Antibody staining will be performed on a DAKO Autostainer Plus Universal Staining System (Model LV-1) on 5 micron sections of formalin fixed paraffin embedded tissue.

PPARγ – will be detected using PPARγ (H-100) (sc7196, Santa Cruz Biotechnology, Inc., Dallas, TX), a rabbit polyclonal antibody raised against amino acids 8-106 of PPARγ of human origin at a concentration of 1:20. Slides will be incubated at room temperature for 1 hour with the primary antibody. Primary antibody detection will be performed using a biotinylated secondary antibody using the Peroxidase Vectastain Avidin Biotin Complex (ABC) "Rabbit IgG" system coupled with the DAKO Liquid DAB+ Substrate Chromagen system (DAKO Carpinteria CA).

RXRα – will be detected using RXRα (D-20) (sc-553, Santa Cruz Biotechnology, Inc., Dallas, TX), an affinity purified rabbit polyclonal antibody raised against a peptide mapping at the N-terminus of RXRα of human origin at a concentration of 1:300. Slides will be incubated at room temperature for 1 hour with the primary antibody. Primary antibody detection will be performed using a biotinylated secondary antibody using the Peroxidase Vectastain Avidin Biotin Complex (ABC) "Rabbit IgG" system coupled with the DAKO Liquid DAB+ Substrate Chromagen system (DAKO Carpinteria CA). .

Positive controls that are expected to demonstrate different levels of PPARγ and RXRα will include formalin-fixed paraffin embedded human liposarcoma, breast and colon cancers, normal breast, liver and fat tissue obtained from the tissue bank at Georgetown University Medical Center. All samples will be processed in parallel with a no-primary-antibody control to evaluate possible artifactual staining from the secondary antibody.

Sources of Assay Components

PPARγ - Santa Cruz Biotechnology Inc.; sc-7196; dilution1:20

RXRα – Santa Cruz Biotechnology, Inc.; sc-553; dilution 1:300

Scoring System

Scoring will include three components:

- Evaluation and comparison of staining on sections exposed to the primary and secondary antibodies as compared to negative control sections that were not exposed to the primary antibody (omitting primary antibody. Tissues will be scored as positively stained only if they exhibit a staining pattern with the primary antibody that is significantly different than that found with omitting the primary antibody. Those that do not demonstrate a significant difference between primary and omitting primary staining will be graded as 0+no stain and 0% cells stained (see below). Tissues that demonstrate a significant difference between the two conditions will be graded as described below.
- IHC staining will be evaluated and scored for intensity (1 = weak, 2 = moderate, 3 = strong) and distribution (1 = focal, 2 = moderate, 3 = diffuse). The 2 independent scores are multiplied by each other to reach a final score that ranges from 1 (weak and focal) to 9 (strong and diffuse).
- Two separate and independent scores will be provided for PPARγ and RXRα expression

An important application of the raw data will be the determination of the product of the percent positive cells for PPARγ and RXRα for each sample (as performed in our Phase I trial [49].

Scoring will be performed on batched samples in a blinded fashion by two board certified human pathologists, independently.

Molecular Analyses and Corresponding Biostatistics of Additional Biomarkers

Immunohistochemical Analysis of PPARγ-regulated Cell Cycle Regulated Proteins and Markers of Differentiation

20 slides, 4μm each will be cut from the FFPE block. These slides will be used for IHC following either manufacturers' instructions or as previously published [20, 56-61].

Detection of protein expression by IHC will be performed with the Vectastain ABC kit (Vector Laboratories, Burlingame,CA) for:

- p18
- p21
- P27
- Cyclin D1(1:50, SP4, RM-9104-S, Neomarkers, ThermoScientific, Fremont, CA)
- aP2 (Fatty Acid Binding Protein 4, FABP4) (HPA002188, Sigma)
- Adipsin) (1:100, sc-47683, Santa Cruz)
- Pyruvate dehydrogenase kinase isozyme 4 (Pdhk4)
- Adipose differentiation related protein (Adfp)
- E-cadherin
- β-Catenin
- Snail

Qualitative scoring of the IHC will be as follows: 0 (no stain), 1 (weak), 2 (intermediate) and 3 (strong). The proportion of cells with staining was scored 1 (≤1/3 positive cells), 2 (1/3 to 2/3 positive cells) and 3 (≥2/3 positive cells). The average of the proportion and intensity score will be used to determine a final IHC score: 0 (none), 1 (low), 2 (medium) and 3 (high). A board certified academic pathologist blinded to the identity and treatment group of the samples will read the pathology.

15.0 GENERAL REGULATORY CONSIDERATIONS AND CREDENTIALING

There are no credentialing requirements for A091202.

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APPENDIX I REGISTRATION FATIGUE/UNISCALE ASSESSMENTS

Registration Fatigue/Uniscale Assessments

At patient registration, this form is to be administered by a nurse/CRA, completed by the patient, and recorded on the Registration Fatigue/Uniscale Assessments Form (see Forms Packet).

If needed, this appendix can be adapted to use as a source document. A booklet containing this assessment does not exist – please do not order this booklet.

How would you describe:

your level of fatigue, on the average in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
No Fatigue										Fatigue as bad as it can be

your overall quality of life in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

APPENDIX II PATIENT DIARIES

Patient Medication Diary

A091202- A phase II study of the Peroxisome Proliferator-Activated Receptor Gamma Agonist, Efatutazone in Patients with Previously Treated, Unresectable Myxoid Liposarcoma

Medication: Efatutazone

PLEASE FILL OUT AND BRING THIS SHEET **AND** EFATUTAZONE BOTTLES TO ALL VISITS.

SPECIAL INSTRUCTIONS

Efatutazone should be taken by mouth, twice daily at the same time each day, approximately 12 hours apart. Efatutazone should be taken with or without food, for 21 days with no break between cycles. If a dose is missed, it should be skipped, and the tablets should be taken at the next dose time.

Cycle number _____

Date	AM Time	Number of tablets	PM Time	Number of Tablets	Comments

(To be completed by research staff)

Number of Pills Given:_____ Pill Bottle(s) returned: Circle Yes or No
Total Daily Dose:_____
Number of Pills returned:_____
Research Staff signature:_____
Date:_____

Patient Weight Diary

A091202- A phase II study of the Peroxisome Proliferator-Activated Receptor Gamma Agonist, Efatutazone in Patients with Previously Treated, Unresectable Myxoid Liposarcoma

PLEASE FILL OUT AND BRING THIS SHEET TO ALL VISITS.

SPECIAL INSTRUCTIONS: Weigh yourself daily and record weight in this diary. If you gain more than 5 lbs, call your treating doctor for instructions.

Cycle number _____

Date	Weight (in pounds)	Comments

(To be completed by research staff)

Research Staff signature:_____
Date:_____