UT SOUTHWESTERN
MEDICAL CENTER
HAROLD C. SIMMONS COMPREHENSIVE CANCER CENTER

A Phase II Study of Pioglitazone for patients with cancer of the pancreas

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II. **Abbreviations**

ALT – alanine amino transferase
AST – aspartate amino transferase
BUN – blood urea nitrogen
Ca - calcium
CBC – complete blood count
Cl - chloride
CO^2 - bicarbonate
CR - complete response
CRF – case report form
CRO – Clinical Research Office
CT – computed tomography
CTCAE - Common Terminology Criteria for Adverse Events
DSMC - Data and Safety Monitoring Committee
ECOG - Eastern Oncology Cooperative Group
IRB – institutional review board
K – potassium
LAT - lateral
Na - sodium
OR - objective response
PA – posterior to anterior
PI - principal investigator
PPARγ - peroxisome proliferator-activated receptor gamma
PR - partial response
RECIST - Response Evaluation Criteria in Solid Tumors
SCCC -Simmons Comprehensive Cancer Center
TDP - time to disease progression
TZDs - thiazolidinedione

III. Introduction

A. *Background*

Pancreatic cancer is a cause of significant morbidity and mortality and effective treatment strategies are lacking. The annual incidence of pancreas cancer in the United States is 9 cases per 100,000 people. In 2008 there will be approximately 37,680 new cases and 34,290 deaths from pancreas cancer in the United States [1]. Pancreas cancer is the fourth leading cause of cancer-related mortality in North America. Early systemic spread is seen in most patients with pancreas cancer. Eighty percent of patients with pancreas cancer present with clinical evidence of distant metastases. With currently available therapies, the 5-year overall survival of patients with pancreas cancer is less than 5%.Treatment of patients with unresectable or metastatic pancreas cancer and good performance with the pyrimidine anti- metabolite gemcitabine results in a median overall survival off less than 6 months and a clinical benefit response of 24%[2].

Cancer related cachexia is a cause of significant morbidity and no effective therapies exist. Cachexia, a syndrome characterized by significant loss of adipose and skeletal muscle tissue accounts for more than 50% of cancer related death. Patients with cancer and cachexia have a short overall survival and decreased response to chemotherapy [3]. Insulin resistance is a hallmark of cancer-associated cachexia [4] and is in part mediated by cytokines such as TNF-α [5]. Severe malnutrition and cachexia develops in 85% of patients with pancreas cancer during the course of their illness.

Pancreatic cancer provides an excellent model to study cancer associated cachexia and insulin resistance. Up to 85% of pancreatic cancer patients will experience cachexia in their lifetime. In addition type 2 diabetes mellitus occurs in 70 to 80% of patients with pancreas cancer. The development of diabetes in patients with pancreas cancer is likely secondary to a marked decline in pancreatic β cell function and profound peripheral insulin resistance. Patients with advanced pancreas cancer display many of the metabolic abnormalities seen in type 2 diabetes mellitus including glucose intolerance, increased hepatic glucose production, recycling, and insulin resistance.

Thiazolidinediones (TZD) lead to improved insulin sensitivity and weight gain, but effects on pancreatic cancer patients are unknown. Therapies that decrease cachexia-associated wasting, also result in increased peripheral tissue insulin sensitivity [6]. The thiazolidinediones (TZDs) are a class of medications that produce insulin sensitizing effects in animal models [6-9] and in insulin resistant human subjects [10-12]. The TZDs are high affinity ligands for the nuclear receptor, peroxisome proliferator-activated receptor gamma (PPARγ) which transactivates PPAR-responsive gene promoters[13]. Some of the insulin-sensitizing properties of PPARγ agonists are thought to be mediated through their anti-inflammatory activity. In peripheral monocytes, peritoneal macrophages, and adipocytes, PPARγ agonists are reported to inhibit the production of inflammatory cytokines. The anti-inflammatory activity of PPARγ agonists appears to be mediated through inhibition of the activation of transcription factors such as nuclear factor-κB (NF-κB), activator protein-1 (AP-1), and signal transducer and activator of transcription (STAT). Additionally, the insulin-sensitizing effects of PPARγ agonists may in part be related to a positive regulation and increase in serum levels of the adipocyte-specific secretory protein adiponectin, a mediator of systemic insulin sensitivity [14, 15]. Serum levels of adiponectin may serve as a marker for gain of insulin sensitivity in patients treated with PPARγ agonists. Intracellular lipid accumulation in myocytes and hepatocytes has been associated with decreased insulin sensitivity. Treatment with PPARγ agonists in humans and in

rodents results in significant weight gain primarily due to increased fat mass, despite improved insulin sensitivity. One possible mechanism of action of PPARγ agonists may rely on their ability to redistribute triglycerides from muscle and liver towards adipose tissue. The anabolic effects of PPARγ agonists would be highly desirable in patients with metastatic pancreas cancer. **PPARγ agonists increase systemic insulin sensitivity, adipose mass, and significantly decrease inflammation at the level of adipocytes and macrophages. The anti-inflammatory, insulin sensitizing, and anabolic effects of PPARγ agonists may offer an ideal approach to counter many of the symptoms associated with metastatic pancreas cancer**.

TZDs have been used in a number of cancer-related settings. In a retrospective study in type II diabetic patients there was a 33% decreased incidence of lung cancer among TZD users compared with nonusers after adjusting for confounder interactions. The risk for colorectal and prostate cancers was not significantly altered [16]. TZDs have been used in the context of liposarcomas. Several studies report a positive impact of a TZD regimen, demonstrating induction of solid tumor differentiation by TZDs in patients with liposarcoma . Other studies in contrast concluded that TZDs are not effective anti-tumoral drugs in the treatment of liposarcomas [17]. Of particular interest are the studies in breast cancer patients. Activation of PPARγ is associated with anti-proliferative effects on human breast cancer cells in preclinical studies. However, clinical trials using PPARγ ligands in patients with treatment-refractory metastatic breast cancer failed to show any clinical benefits [18]. In contrast to pancreatic cancers, PPARγ tends to be highly suppressed in breast cancer cells [19] and as such, these cells not offer high levels of PPARγ target for the TZDs to act upon. The commonly observed up- regulation of PPARγ in pancreatic ductal adenocarcinoma [20] may predispose these cells to a high level response to the TZDs.

Preliminary data from UT Southwestern in patients receiving pioglitazone as second line therapy for metastatic pancreatic cancer demonstrated significant TZD response. Among treated patients, the increase in adiponectin levels varied from 50% to three times the baseline. However this study was terminated due to poor accrual. Adequate follow up was not possible due to poor survival of patients, demonstrating selection of terminally ill patients to the protocol. Also the effect on other markers of insulin resistance is not known.

(MRI will be performed on UT Southwestern and PHHS patients ONLY) We propose to evaluate the use of MRI to quantitate changes in a) intratumoral fat deposition in pancreatic cancer and b) visceral/subcutaneous fat distribution in pancreatic cancer patients treated with pioglitazone in this phase II study. To determine intratumoral fat content, we will use a previously described advanced chemical shift-based gradient-echo MRI technique that measures the proton density fat fraction (PDFF) [21]. In addition, MRI will allow quantitative determination of body fat volume in the abdomen e.g. subcutaneous/visceral adipose tissue (SAT/VAT) depots, which have been shown to have an important role in insulin resistance [22, 23]. TZD therapy has shown to increase 'good' SAT and have a concomitant decrease in 'bad' VAT and liver fat in patients with diabetes but has not been studied in patients with pancreatic cancer related weight loss.
MRI examination will be performed on a clinical whole body system (Philips Achieva) at 3.0 Tesla at Rogers MRI Center equipped with a dedicated transmit/receive body coil and images will be interpreted by a dedicated study radiologist,(Department of Radiology). Scan protocol include a preliminary localizing sequence and a 3D multi-echo spoiled gradient echo sequence, with scan parameters optimized for fat quantification as previously described *[21].*

We propose this study to determine, what is the effect of PPARγ agonist therapy with pioglitazone on adiponectin levels and markers of insulin sensitivity (fasting glucose, OGTT 0, 2 hour, I/G ratio) in pancreatic cancer patients. In addition we will evaluate the effects of pioglitazone therapy on weight, ECOG functional status, quality of life and disease response.

In order to differentiate pioglitazone related effects from chemotherapy related effects we will enroll a cohort of pancreatic cancer patients for correlative analysis only and will serve as a control arm. These patients will meet all eligibility criteria as detailed above but will not receive pioglitazone. **Pioglitazone**

General: Pioglitazone is one of two currently available PPARγ agonists on the market. It is sold in the US under the name Actos™. The other drug in this class on the market is rosiglitazone (Avandia™).

Alternative Names and Clinical Structure: Actos™. Pioglitazone has been approved by the FDA as an oral anti-diabetic in 1999 and has been used widely since then with a good safety profile for long term use in type 2 diabetics. 10 million patients have been prescribed Actos™ in the US to date.

Presentation: Pioglitazone is dosed once daily orally without regard to meals. The suggested dose here is 45 mg per diem, a dose used in many clinical studies, including the recent PROactive study.

Mechanisms of Action: Pioglitazone is a transcriptional activator of the nuclear receptor PPARγ.

Preclinical Activity: Pioglitazone has a good preclinical safety profile. This is a drug that has been widely studied. We have shown that a significant portion of its insulin-sensitizing activity is mediated via induction of the adipokine adiponectin. However, there are additional PPARγ transcriptional targets involved as well.

Clinical Studies: Pioglitazone is an oral anti-diabetic agent that acts primarily by decreasing insulin resistance.

Pharmacokinetics: Serum concentrations of total pioglitazone (pioglitazone plus active metabolites) remain elevated 24 hours after once daily dosing. Steady- state serum concentrations of both pioglitazone and total pioglitazone are achieved within 7 days. At steady-state, two of the pharmacologically active metabolites of pioglitazone, Metabolites III (M-III) and IV (M-IV), reach serum concentrations equal to or greater than pioglitazone. In both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the peak total pioglitazone serum concentrations and 20% to 25% of the total area under the serum concentration-time curve (AUC).

Maximum serum concentration (C_{max}), AUC, and trough serum concentrations (C_{min}) for both pioglitazone and total pioglitazone increase proportionally at doses of 15 mg and 30 mg per day. There is a slightly less than proportional increase for pioglitazone and total pioglitazone at a dose of 60 mg per day.

The mean serum half-life of pioglitazone and total pioglitazone ranges from 3 to 7 hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be 5 to 7 L/hr.

Safety Profile: Systemic and hematologic: Pioglitazone may be associated with hypoglycemia, edema, anemia (lower hemoglobin levels and hematocrit due to edema), weight gain (increased fat cell differentiation), and/or ovulation in premenopausal, anovulatory women. The most common adverse events (≥5%) reported to date include upper respiratory tract infection, headache, sinusitis, myalgia, tooth disorder, aggravated diabetes mellitus, and pharyngitis.

Gastrointestinal (GI)/Liver*:* Reports of hepatitis and of hepatic enzyme elevations to three or more times the upper limit of normal (ULN) have been reported with pioglitazone. Very rarely, these reports have involved hepatic failure with or without fatal outcome, although causality has not been established. Liver enzymes, including serum ALT, need to be evaluated in all patients at initiation of therapy with pioglitazone, and periodically thereafter. If ALT >2.5X ULN at baseline or if the patient exhibits clinical evidence of active liver disease, pioglitazone will be discontinued.

Systemic*:* Like other thiazolidinediones (TZDs), pioglitazone can cause fluid retention when used alone or in combination with other anti-diabetic agents, including insulin. Fluid retention may lead to or exacerbate heart failure. However, in the context of pancreatic cancer, these potential issues seem relatively minor. Nevertheless, we will exclude patients with a history of previously existing cardiac disease.

Cardiovascular*:* The Endocrinologic and Metabolic Drugs and Drug Safety and Risk Management Advisory Committees to the FDA recently met jointly to review the cardiovascular ischemic/thrombotic risks of the thiazolidinediones (TZDs) class, with focus on rosiglitazone. At this stage, there were no concerns raised with respect to the cardiovascular safety of pioglitazone.

Pioglitazone has been prescribed in many patients with pancreas cancer who have a diagnosis of type 2 diabetes mellitus in routine clinical practice. To our knowledge, no unexpected serious adverse events have been reported in patients with pancreas cancer receiving treatment with pioglitazone.

Table 1: Adverse Effects of Pioglitazone

Placebo-Controlled Clinical Studies of ACTOS Monotherapy: Adverse Events Reported at a Frequency ≥ 5% of Patients Treated with ACTOS

(% of Patients)		
Adverse Effects	**Placebo N=259**	**ACTOS N=606**
Upper Respiratory Tract Infection	8.5	13.2
Headache	6.9	9.1
Sinusitis	4.6	6.3
Myalgia	2.7	5.4
Tooth Disorder	2.3	5.3

Diabetes Mellitus Aggravated	8.1	5.1
Pharyngitis	0.8	5.1

Rationale for the Selection of Dose and Schedule

We plan to prescribe pioglitazone 45 mg per mouth daily, which is the maximum U. S. Food and Drug Administration (FDA) approved dose for the treatment of type 2 diabetes mellitus. Pioglitazone has been extensively prescribed in humans at the planned doses for this study. The safety and toxicity profile of pioglitazone is well established. We do not expect a higher than usual toxicity in patients with pancreas cancer receiving pioglitazone.

IV. Schema

This is an open label, double arm Phase 2 study. We plan to enroll 15 patients with adenocarcinoma of the pancreas to this study of oral pioglitazone 45 mg daily. Patients are allowed to continue on antineoplastic therapy while on this study and this will be determined by the treating physician.

A control cohort of up to 10 patients will be enrolled for correlative (blood and radiological) testing alone. These patients will meet all criteria set forth for the study and follow the same study visits, but not be treated with pioglitazone.

V. Hypothesis

Prior studies have shown that a significant proportion of patients with metastatic pancreas cancer have metabolic changes consistent with insulin resistance. Treatment of insulin resistance in patients with metabolic disorders like type 2 diabetes mellitus is associated with improved outcomes and less morbidity. We propose an exploratory clinical trial to study as a primary aim, the effects of the oral inhibitor of the peroxisome proliferator- activated receptor gamma (PPARγ) pioglitazone in markers of insulin resistance in patients with pancreas cancer.

Our primary hypothesis is that patients with pancreas cancer will have significant improvements in markers of insulin resistance when treated with pioglitazone.

As secondary aims, we will evaluate changes in cancer related symptoms, performance status, and weight. We will also evaluate the objective response of measurable lesions and the time to disease progression in patients with pancreas cancer. MRI will be used to assess for changes in body fat distribution and changes in intratumor fat content (UT Southwestern and PHHS patients ONLY). We will compare change in blood biomarkers and MRI between the pioglitazone and control arms.

VI. **Objectives**

Primary objective

1. Describe change in markers of insulin resistance, including in adiponectin levels standard glucose tolerance test, and serum levels of insulin and glucose in patients with pancreas cancer receiving pioglitazone.

Secondary Objectives

1. To determine the tumor response by RECIST in patients with pancreas cancer receiving pioglitazone.
2. To describe changes in weight in patients with pancreas cancer receiving pioglitazone.
3. To describe changes in ECOG performance status in patients with pancreas cancer receiving pioglitazone.

4. To describe changes in symptoms and quality of life using the FACT-Hep scale, version 4 (see Appendix 4).
5. Compare change in blood biomarkers and MRI between the pioglitazone and control arms.

VII. Endpoints

We will assess the primary and secondary endpoints of the study as follows:

Primary End point

The primary end point will be improvement in insulin resistance markers:

a. Change in serum adiponectin level. We will obtain serum levels of adiponectin at baseline and after 8 weeks of treatment with pioglitazone.
b. Changes in standard glucose tolerance test. We will perform the area under the oral glucose tolerance test at baseline and after 8 weeks of treatment with pioglitazone.
c. Fasting levels of serum glucose and insulin. We will obtain serum levels of fasting glucose and insulin every four weeks in all patients receiving pioglitazone

Secondary End points

a. Objective response (OR) is the proportion of patients with confirmed complete response (CR) or confirmed partial response (PR) according to the Response Evaluation Criteria in Solid Tumors (RECIST). Progression free survival (PFS) and overall survival (OS) of patients on treatment with pioglitazone.
b. Changes in weight in patients with pancreas cancer receiving pioglitazone.
c. Changes in ECOG performance status in patients with pancreas cancer receiving pioglitazone.
d. Changes in symptoms and quality of life using the FACT-Hep questionnaire, version 4 (see Appendix 4).
e. Characterize MRI determined changes in a) pancreatic intratumor fat; and b) body fast distribution in pancreatic cancer patients treated with pioglitazone (pilot study on 8-10 patients chosen by PI/investigator discretion) (UT Southwestern and PHHS patients ONLY).
f. Compare changes in serum and MRI end points between pioglitazone and control arms.

VIII. **Study Design**

Study Arm:

We plan to enroll fifteen patients with metastatic or locally advanced pancreas cancer into a double arm pilot exploratory study of oral pioglitazone 45 mg daily.

Treatment will be administered for 8 weeks and then stopped.

Control Arm:

Up to ten patients meeting eligibility criteria will be enrolled in the control arm. Patients will be treated per standard of care treatment at the discretion of the treating team and will not be treated with pioglitazone.

Treatment arm assignment:
Treatment arm will be assigned by the principal investigator or treating MD at their discretion. Given the exploratory nature of this study, randomization will not be performed.

Control arm patients can include the following examples:

- patient declines pioglitazone therapy but agrees to biomarker testing (Adiponectin, a hormone made by fat cells, will be measured). Additional assays may be performed
- Patient is enrolled in another clinical trial which does not allow experimental therapy (pioglitazone) to be given. The protocol of the patient's study will be reviewed to ensure biomarker testing (Adiponectin, a hormone made by fat cells, will be measured) as defined in this study is not specifically prohibited.

- Patients enrolled after completion of the 15 study arm patients
- Other patients as deemed appropriate by the PI or co-Is

A. ***Recruitment***

Eligible study patients will be screened, recruited, and enrolled at the following institutions:

1. University of Texas Southwestern Medical Center at Dallas:
    a. Harold C. Simmons Comprehensive Cancer Center
    b. University Hospital – Zale Lipshy
    c. University Hospital – Saint Paul
2. Parkland Health and Hospital System (PHHS)
3. VA North Texas (Dallas)

Study patients will be recruited from the practices of the PI and co- investigators. Potentially eligible patients will be approached by their health care providers who can refer them to the study coordinator for screening. All patients being considered for the study and eligible must sign an informed consent for the study prior to any study specific procedures.

IX. Eligibility Criteria

Inclusion Criteria

Inclusion Criteria	Reason
Signed informed consent	Document patient participation and understanding of study requirements
Histologically proven adenocarcinoma of the pancreas	Disease of interest
Radiologically measureable disease	Target lesion to follow response to therapy
ECOG functional status 0-2	Those with worse functional status may not have reasonable survival to demonstrate meaningful follow up

Exclusion Criteria	Reason
Prior radiation therapy for pancreatic cancer	Radiation effect can alter metabolic effects of the pancreas. If patient has measurable disease which has not been radiated, they may be enrolled.
If chemotherapy is planned, new chemotherapy regimen should have started no more than 21 days prior to enrollment	Start pioglitazone as close to the start of a chemotherapy regimen
Surgery or radiation planned within 8 weeks of starting therapy	Allow adequate exposure to TZD (minimum 8 weeks)

Prior exposure to Thiazolinedione (TZD) therapy in the past 12 months	Markers of interest will be altered by previous TZD exposure
Hypersensitivity of TZD	Contraindication to pioglitazone
New York heart association class III/IV heart failure.	Contraindication to pioglitazone
Known HIV positive	HIV/AIDS related cachexia may alter metabolic findings.
Pregnant or lactating women	Contraindication to pioglitazone. Pregnancy class C, not recommended in lactating women
History of, or active bladder cancer	Contraindication to pioglitazone
Inadequate hepatic function documented within 14 days of enrollment Total bilirubin level > 1.5 x ULN AST and ALT > 2.5 x ULN, unless there are liver metastases in which case AST and ALT or > 5 x ULN	TZD Clearance is significantly lower in hepatic impairment

X. Informed Consent Process

The research coordinator or the investigators will review the consent form with the subject page by page describing the purpose of the study, the research procedures, risks and alternatives. The subject will be given the opportunity to ask questions or voice concerns at this time. The informed consent counseling will take place in an area that provides privacy. The PI or co-investigator will describe all available options to potential patients, to answer questions, and to help the patients make participation decisions in a non-directive manner. The original signed informed consent document will be stored in a locked cabinet with the patient's case report forms (CRFs) in the Clinical Research Office (CRO), one copy will be given to the patient and one copy will be placed on the chart per institutional policy. Patients who are sedated or deemed emotionally or mentally unable to provide informed consent for any reason are not eligible for enrollment.

XI. Study Subject Identification Number

All subjects will be assigned a study number that is not linked to their personal identifiers to prevent loss of confidentiality. The number will be the IRB Protocol Number followed by a sequentially number starting with number 01. For example, the first subject enrolled will be assigned study subject number 072012-036-01; the next will be 072012-036-02, and so forth. This number will be assigned by the Clinical Research Manager (CRM) upon confirmation of subject eligibility during the subject registration process. Subject registration will be confirmed once the following documents have been received by the CRM:

- Signed copy of the Informed Consent signature page
- Inclusion/Exclusion worksheet signed by the coordinator and treating physician

XII. Subject Registration

All study subjects must be entered into the Velos database in a timely manner after obtaining the informed consent of the subject. Following completion of baseline assessments and confirmation of subject eligibility, patients will be registered and assigned a subject identification number by the CRM, Subject registration will be confirmed (within 24 hours) once the following documents have been received by the CRM:

- Signed copy of the Informed Consent signature page
- Inclusion/Exclusion worksheet signed by the coordinator and treating physician

Since this is a double arm, pilot study, randomization to different treatment arms is not required.

XIII. Study Procedures and Treatment Plan

A. *Screening Evaluations (for both treatment and control arms)*

The following Screening assessments must be performed within 28 days before the first treatment of study drug:

1. Signed Informed Consent
2. Complete medical history (Med Hx), including documentation of current medications (CM), and Adverse Event (AE) assessment;
3. ECOG Performance Status
4. Complete Physical Examination (PE);
5. Vital Signs - BP, HR, RR, and Temp (^{o}C)
6. Height (cm) and Weight (kg)(Record on weight log – see Appendix 2);
7. Laboratory requirements:
   - Hematology: CBC with differential and platelets
   - Serum Chemistry: Na, K, CL, Ca, CO_2, glucose, BUN, creatinine, AST, ALT, alkaline phosphatase, total bilirubin, total protein, albumin
   - Serum pregnancy test (women <60 years only)
8. Pathology report confirming adenocarcinoma histology
9. Staging work-up:
   a. Posterior to anterior (PA) and lateral (LAT) chest x ray (unless CT chest done)
   b. CT scan of abdomen and pelvis with IV and PO contrast

Following completion of the pretreatment assessments and confirmation of eligibility, patients will be registered, assign a subject identification number, evaluated and followed up according to the study procedures described below. Since this is a double arm, pilot study,

randomization to different treatment arms is not required.

B. Week 0 (**Baseline evaluation)**

The following baseline evaluations assessment will be performed on cycle 1 day 1 prior to the first dose of study drug: Control arm patients will have the same evaluation but will not receive study drug)

- Complete Physical Examination (PE)
- Vital Signs - BP, HR, RR, and Temp (°C)
- Weight (kg, record on weight log)
- ECOG Performance Status
- AE/Toxicity Assessment
- Laboratory assessments:
    - Hematology: CBC with differential and platelet count
    - Serum chemistry: Na, K, Cl, Ca, bicarbonate, BUN, creatinine, AST, ALT, alkaline phosphatase, total bilirubin, total protein, albumin
    - Pregnancy test (WOCBP ONLY)
    - CA19-9
    - C-reactive protein level
    - Serum fasting glucose (fasting for at least 8 hours)
- Exploratory Research Lab Evaluations
    - Glucose tolerance test (0 baseline and 2 hr ingestion)
    - Insulin level (0 hr baseline and 2 hr post ingestion)
    - Adiponectin (0 hr baseline)
    - MCP-1 level (0 hr baseline)
- FACT-Hep Questionnaire

- MRI abdomen noncontrast (Research)Should be done +/- 7 days of starting pioglitazone (7 days pre or 7 days after starting pioglitazone) MRI will be done on 8-10 patients chosen at PI/investigator discretion (UT Southwestern and PHHS patients ONLY).

C. ***Treatment Plan***

1. Prescription Information

How Supplied: Pioglitazone is available in 15 mg, 30 mg, and 45 mg tablets. The 15 mg tablets are white to off-white, round, convex, non- scored tablets with "ACTOS" on one side and "15" on the other side. The 30 mg and 45 mg tablets are white to off white, round, flat, non-scored tablets with "ACTOS" on one side and "30" or "45" (respectively) on the other side. Availability: Each (15 mg, 30 mg and 45 mg) are available in bottles of 30, 90 or 500.

Storage: Pioglitazone should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Keep the container closed tightly, and protect from moisture and humidity.

Ordering: The investigational drug pharmacist will purchase a bulk (cost efficient) supply of pioglitazone and dispense to study participants.

Cost Coverage: UT Southwestern Medical Center - Touchstone Diabetes Center is covering the costs of the pioglitazone for subjects enrolled onto this study. Invoices for reimbursement must be interoffice mailed to Judy Hollingsworth at mail code 8549. (Mailing Address: UT Southwestern Medical Center at Dallas, Touchstone Diabetes Center, Room L5.210, 5323 Harry Hines Boulevard, Dallas, TX, 75390-8549 Attn: Judy Hollingsworth)

Dispensation: Each subject should be given a one month (28-day) supply of pioglitazone per cycle.

Accountability: The investigator and investigator site are responsible for maintaining an accurate inventory and accountability logs for the study drug, pioglitazone, for patients enrolled on this study. The site is permitted to use their own drug accountability form to record study drug dispensation and patient returned tablets. These forms should be stored in the site's dispensing pharmacy. Use of standard pharmacy accountability logs is acceptable.

2. Administration schedule:

Patients will be instructed to take pioglitazone (45mg daily by mouth) and will be instructed on how to take the pioglitazone for the entire cycle (one cycle equals 28 days). Subjects will continue taking pioglitazone daily for two cycles (no more than 8 weeks) or until one of the following criteria mentioned in section XIII D. Subjects will record their daily drug administration on a dosing diary, supplied by the study coordinator, in order to verify subject dosing compliance.

See table below for treatment schedule (cycle one and subsequent cycles)

Study Drug	Cycle 1				Cycle 2			
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
Pioglitazone	daily	daily	daily	daily	daily	daily	daily	daily

D. ***Dose Modifications and Discontinuation***

- Patients developing a treatment-related CTCAE v4 Grade 1 or 2 adverse event will have their dose continued at the same level.
- Pioglitazone must be held for any grade 3 or 4 toxicity until the event resolves to at least grade 2. Following the resolution, the dose of pioglitazone must be reduced to level -1.
- The following table describes potential dose level modifications for pioglitazone. If a subject requires a dose reduction is beyond level -2, pioglitazone must be discontinued.
- Patients removed from treatment for intolerable toxicity must be followed for evaluation of their time to disease progression (TDP).

Agent	Initial Dose	Level -1	Level -2
Pioglitazone	45 mg /day	30 mg/day	15 mg/day

For all toxicities:

Standard symptomatic treatment will be offered by the treating physician.
There is no dose modification of pioglitazone for grade 1 or grade 2 toxicity

<u>Interruption in pioglitazone for greater than 14 days is not allowed. Subjects must discontinue treatment if this occurs.</u>

- <u>Hematologic Toxicities</u>
  There is no need to modify or discontinue pioglitazone due to hematologic toxicity.
- <u>Diarrhea</u>
  For grade 3 or 4 diarrhea, hold pioglitazone until diarrhea resolves to ≤ grade 2, then it may be resumed at one lower dose level.
- <u>Nausea and Vomiting</u>
  For grade 3 or 4 nausea or vomiting, hold pioglitazone until nausea and vomiting resolve to ≤ grade 2,

then it may be resumed at one lower dose level.

- Liver Function Tests
  For grade 3 or 4 elevation of the liver function tests, hold pioglitazone until elevation of the liver function tests resolve to ≤ grade 2, then gemcitabine and pioglitazone may be resumed at one lower dose level.
- Weight Gain
  For grade 3 or 4 weight gain, hold pioglitazone until peripheral edema resolves to grade 2, then it may be resumed at one lower dose level.

E: Concomitant medication/Treatments:

Pioglitazone is metabolized through the cytochrome P450 2C8/9 and 3A4 pathways. The metabolic pathway of concomitant medications will be checked prior to prescribing with pioglitazone. According to the pioglitazone prescribing information, co administration of pioglitazone and gemfibrozil, a strong CYP2C8 inhibitor, increases pioglitazone exposure approximately 3-fold. Therefore, the maximum recommended dose of pioglitazone is 15 mg daily when used in combination with gemfibrozil or other strong CYP2C8 inhibitors.
Other strong CYP2C8 inhibitors include fluconazole, ketoconazole, nicardipine, sulfonamides, and some NSAIDS.
Concomitant medications that are inhibitors of CYP 3A4 are likely to increase pioglitazone exposure as well and CYP 3A4 inducers may decrease pioglitazone concentrations.
Concomitant administration of pioglitazone with thioridazine is contraindicated

F. ***Treatment Evaluations***
Same procedure will be followed for pioglitazone (treatment) and control arms except the control arm will not receive study drug (pioglitazone) and therefore will not have a pill diary

2-week visit (+/- 7 days)

- Symptom Driven Physical Examination (PE)
- Vital Signs - BP, HR, RR, and Temp (^{o}C)
- Weight (kg, record on weight log)
- ECOG performance status
- AE/Toxicity assessment
- Laboratory assessments:
  - Hematology: CBC with differential and platelet count
  - Serum chemistry: Na, K, Cl, Ca, bicarbonate, BUN, creatinine, AST, ALT, alkaline phosphatase, total bilirubin, total protein, albumin
  - C-reactive protein level
  - Serum fasting glucose (fasting for at least 8 hours)
- Exploratory Research Lab Evaluations
  - Insulin level (0 hr baseline)
  - Adiponectin (0 hr baseline)
  - MCP-1 level (0 hr baseline)

4 Week Visit (+/- 7 days)

- Symptom Driven Physical Examination (PE)
- Vital Signs - BP, HR, RR, and Temp (^{o}C)
- Weight (kg, record on weight log)
- ECOG Performance Status
- AE/Toxicity assessment

- Laboratory assessments:
  - Hematology: CBC with differential and platelet count
  - Serum chemistry: Na, K, Cl, Ca, bicarbonate, BUN, creatinine, AST, ALT, alkaline phosphatase, total bilirubin, total protein, albumin
  - CA19-9
  - C-reactive protein level
  - Serum fasting glucose (fasting for at least 8 hours)
- Exploratory Research Lab Evaluations
  - Glucose tolerance test (0 baseline and 2 hr post ingestion)
  - Insulin level (0 hr baseline and 2 hr post ingestion)
  - Adiponectin (0 hr baseline)
  - MCP-1 level (0 hr baseline)
- FACT-Hep Questionnaire
- Review of Patient Pill Diary
- Patient will receive 4 week refill of Pioglitazone

6-week visit (+/- 7 days)

- Symptom Driven Physical Examination (PE)
- Vital Signs - BP, HR, RR, and Temp ($^{\circ}$C)
- Weight (kg, record on weight log)
- ECOG Performance Status
- AE/Toxicity assessment
- Laboratory assessments:
  - Hematology: CBC with differential and platelet count
  - Serum chemistry: Na, K, Cl, Ca, bicarbonate, BUN, creatinine, AST, ALT, alkaline phosphatase, total bilirubin, total protein, Albumin
  - C-reactive protein level
  - Serum fasting glucose (fasting for at least 8 hours)

- Exploratory Research Lab Evaluations
  - Insulin level (0 hr baseline)
  - Adiponectin (0 hr baseline)
  - MCP-1 level (0 hr baseline)

8 week visit (+/- 7 days)

- Symptom Physical Examination (PE)
- Vital Signs - BP, HR, RR, and Temp ($^{\circ}$C)
- Weight measurement (kg, record on weight log)
- ECOG performance status
- AE/Toxicity Assessment
- Laboratory assessments:
  - Hematology: CBC with differential and platelet count
  - Serum chemistry: Na, K, Cl, Ca, bicarbonate, BUN, creatinine, AST, ALT, alkaline phosphatase, total bilirubin, total protein, albumin
  - CA19-9
  - C-reactive protein level
  - Serum fasting glucose (fasting for at least 8 hours)
- Exploratory Research Lab Evaluations
  - Glucose tolerance test (0 hr baseline and 2 hr post ingestion)
  - Insulin level (0 hr baseline and 2 hr post ingestion)
  - Adiponectin (0 hr baseline)

    - MCP-1 level (0 hr baseline)
- FACT-Hep Questionnaire
- Disease Assessment
- Chest x-ray or CT scan of the chest
- CT scan of the abdomen and pelvis
- Review of Patient Pill Diary
- MRI Abdomen non-contrast (research study) (UT Southwestern and PHHS patients ONLY)

Early-Term or End of treatment visit (ET/EOT) (Early-Term, if patient discontinues treatment before 8 weeks for any reason) (+/-7 days)

- Complete physical examination
- Vital Signs - BP, HR, RR, and Temp (°C)
- Weight (kg on weight log)
- ECOG Performance Status e
- AE/Toxicity assessment
- Laboratory assessments:
    - Hematology: CBC with differential and platelet count
    - Serum chemistry: Na, K, Cl, Ca, bicarbonate, BUN, creatinine, AST, ALT, alkaline phosphatase, total bilirubin, total protein, albumin
    - CA19-9
    - C-reactive protein level
    - Serum fasting glucose (fasting for at least 8 hours)
- Exploratory Research Lab Evaluations
    - Glucose tolerance test (0 hr baseline and 2 hr post ingestion)
    - Insulin level (0 hr baseline and 2 hr post ingestion)
    - Adiponectin (0 hr baseline)
    - MCP-1 level (0 hr baseline)
- FACT-Hep Questionnaire

MRI Abdomen non-contrast (research study) (UT Southwestern and PHHS patients ONLY)

Follow up (2 weeks after completing treatment or last treatment date if Early-term (ET)) (+/- 7 days) (this corresponds to week 10 of control arm patients)

- Complete physical examination
- Vital Signs - BP, HR, RR, and Temp (°C)
- Weight (kg, record on weight log)

- ECOG Performance Status
- Laboratory assessments:
    - Hematology: CBC with differential and platelet count
    - Serum chemistry: Na, K, Cl, Ca, bicarbonate, BUN, creatinine, AST, ALT, alkaline phosphatase, total bilirubin, total protein, albumin
    - CA19-9
    - C-reactive protein level
    - Serum fasting glucose (fasting for at least 8 hours)
- Exploratory Research Lab Evaluations
    - Glucose tolerance test (0 hr baseline and 2 hr post ingestion)
    - Insulin level (0 hr baseline and 2 hr post ingestion)
    - Adiponectin (0 hr baseline)
    - MCP-1 level (0 hr baseline)
- FACT-Hep Questionnaire

- Toxicity/AE assessment

Long term Follow-up
Patient's chart will be reviewed intermittently by the study team to assess:
  - **Disease status**
  - **Vital status**

G. ***Imaging Procedures***

- Chest, abdomen and pelvic CT scans will be performed at the treating physicians' discretion. The respective institution's imaging protocols will be followed. Contrast exams will be preferred if there is no contraindication to contrast.
- Baseline CT Scans will be performed and then again every 8 weeks thereafter until disease progression or 2 years – whichever comes first.
- If CT Scans are performed within four (4) weeks after discontinuing pioglitazone, then they do not have to be repeated if the investigator's deems it unnecessary.
- (UT Southwestern and PHHS patients ONLY) MRI Abdomen non-contrast will be performed at the Roger's MRI (Department of Radiology) at baseline (7 days before starting therapy with pioglitazone or within 7 days of starting pioglitazone) and a second scan after the end of treatment at week 8 (to be done within 2 weeks of ending pioglitazone).If a patient is unable to complete 8 weeks of pioglitazone but has completed 6-8 weeks of therapy, a follow up MRI will be ordered (also to be done within 2 weeks of ending pioglitazone)

H. Routine and Exploratory Lab Assessments

- Blood for routine CBC, chemistry will be drawn per the laboratory protocol and performed in the clinical laboratory of the respective institutions. Results will be recorded as reported in the electronic medical record.
- A Standard 75 gram oral glucose tolerance test will be performed and blood collection for glucose levels will be obtained prior to the ingestion of the solution (pre-dose (0 hr) and at 2 hours following ingestion). Insulin levels at 0 hr (fasting at least 8 hours) and 2 hours post ingestion will be used to calculate insulin resistance . Record the date of collection, time of collection, and subject ID, on the blood collection source document for exploratory labs. All samples should be labeled for each time point for each patient per study visit. Specimen labels will be provided to each site for each patient.
- The following exploratory labs will be collected in a serum separator tube and sent to Dr. Scherer's laboratory for evaluation:
  - **Adiponectin Levels** : performed at the UT Southwestern Metabolic core as described previously [1]
  - **Insulin level** at 0 and 2 hours: Analysis will be performed at the UT Southwestern Metabolic Phenotypic core as described previously [1]
  - **Monocyte Chemoattractant Protein-1 (MCP-1)** performed at the MagPix multiplexing matching housed at the UT Southwestern Metabolic Core [2]
  - **PAI-1** performed at the MagPix multiplexing matching housed at the UT Southwestern Metabolic Core [2]
- Prior to shipment, complete the sample inventory logs for each patient so that specimen chain of custody can be established. Include in each batch shipment copies of; 1) the blood collection source documents for each patient; and 2) copies of each subjects specimen inventory form. Keep originals of these documents in the patient chart. Please see appendix XX, Specimen Processing and Shipment Instructions for further details.

Patients accrued at VA North Texas will have sample collected at the respective sites, frozen at -20 to -80 C and shipped on dry ice in batches to the UTSW Metabolic Core via overnight courier FedEx (FedEx number:370843180) to the following address

Scherer Laboratory
Touchstone Diabetes Center
Department of Internal Medicine
The University of Texas Southwestern Medical Center
L5.210
5323 Harry Hines Boulevard
Dallas, TX 75390-8549
Phone: (214) 648-8715
Fax: (214) 648-8720

H. ***Schedule of Events***

Procedures	Screening[1]	Baseline	2-Weeks	4-weeks	6-Weeks	8-Weeks	End of Treatment or Early-Term (EOT/ET)	14 –Day Follow-up[3]
Informed Consent	X							
I/E & Medical History	X							
Concomitant Medications Review / AE Assessment	X	X	X	X	X	X		
Physical Exam	X		X	X	X	X	X	X
Height (cm)[2] and Weight Measurement (Kg)	X		X	X	X	X	X	X
Performance status (ECOG)	X	X	X	X	X	X	X	X
Hematology[4]		X	X	X	X	X	X	X
Serum Chemistry[5]		X	X	X	X	X	X	X
Serum pregnancy test	X	X						
CA 19-9		X		X		X	X	X
C-reactive protein		X	X	X	X	X	X	X
Serum fasting glucose		X		X		X	X	X
Glucose tolerance		X		X		X	X	X
Adiponectin		X	X	X	X	X	X	X
Insulin level		X[6]	X	X[6]	X	X[6]	X	X
2 hour insulin level		X		X		X	X	X
MCP-1		X	X	X	X	X	X	X
Chest x-ray or Chest CT scan	X					X	X[7]	X
CT scan of abdomen and pelvis	X					X	X[7]	X
Toxicity Assessment		X	X	X	X	X	X	
FACT-Hep Questionnaire		X		X		X	X	X
MRI abdomen noncontrast		X[9]					X[10]	

1. Within 28 days before starting pioglitazone/Day 1 for control arm
2. Height performed at screening only
3. Within 14 days after discontinuing pioglitazone/week 8 for control arm

4. Hematology: CBC with differential and platelet count
5. Serum chemistry: Na, K, Cl, Ca, bicarbonate, BUN, creatinine, AST, ALT, alkaline phosphatase, total bilirubin, total protein, albumin
6. To be performed in conjunction with glucose tolerance test at 0 hr baseline and 2 hr post ingestion.
7. Chest x-ray must be posterior to anterior (PA) and lateral (LAT) plain chest x-ray.
9. 8. If performed within four (4) weeks of discontinuing pioglitazone, then not required to be completed (at the discretion of the investigator).. MRI will be done at Roger's MRI. Baseline MRI to be done before start of pioglitazone or within the first 7 days of starting pioglitazone (UT Southwesten and PHHS patients ONLY)
10. Follow up MRI can be done within 14 days of end of treatment. If patient does not complete 8 weeks but has completed 6-8 weeks of therapy, a follow up MRI should be done as if completed 8 weeks. MRI will be done on 8-10 patients chosen at PI/investigator discretion. (UT Southwestern and PHHS patients ONLY).

XIV. Treatment Duration (N/A for control arm)

Treatment will be continued for no more than **8 weeks** of therapy or unless the following events take place:

1. Patient withdraws consent.
2. Intercurrent illness that prevents further administration of pioglitazone
3. Unmanageable adverse events related to pioglitazone
4. General or specific changes in the patient's condition that in the judgment of the physician renders the patient unacceptable for further treatment with pioglitazone
5. Patient is lost to follow-up. Patient refuses to complete study procedures and scheduled appointments.
6. Patient requires more than two dose reductions
7. Interruption in study drug administration for greater than 14 days
8. Closure of the trial as deemed necessary by the principal investigator (PI), the UT Southwestern Institutional Review Board (IRB), the Simmons Comprehensive Cancer Center Data and Safety Monitoring Committee (DSMC) or the U. S. Food and Drug Administration (FDA).

XV. Withdrawal of Subjects

Patients can withdraw voluntarily if they are unable to continue with the treatment or for any other reasons. Patients will be encouraged to discuss withdrawal with their physician and the study team.

Patient who withdraw voluntarily will not be followed.

XVI. Efficacy Assessments

The following outcome measures are required to evaluate the safety and efficacy of pioglitazone:

1. Measurement of insulin resistance biomarkers: serum adiponectin level, oral glucose tolerance test, and fasting serum levels of glucose and insulin every four weeks.

2. The oral glucose tolerance test will be performed on the initial visit and every four weeks, in fasting state (at least 8 hrs). Patients will be asked to drink a standard glucose solution containing 75 g of carbohydrate. Blood glucose will be obtained prior to the ingestion (0 hr baseline) of the solution, and at 120 min (2 hr) following the ingestion.
   Blood samples are
   collected for glucose levels.

3. Documentation of weight. We will measure weight every week in all patients receiving pioglitazone. (See Appendix 2)

4. Documentation Eastern Oncology Cooperative Group (ECOG) performance status. We will determine the ECOG performance status every week in all patients receiving pioglitazone. (See Appendix 1)

5. Measurement of changes in symptoms and quality of life using the FACT-Hep Scale, version 4. (See Appendix 4).

6. RECIST Criteria will be used to determine response. At the time of every tumor assessment and at the time of study discontinuation, assignment of response to one of three categories will be made; complete response (CR), partial response (PR) or progressive disease (PD). Evaluation of measurable and non-measurable lesions in relationship to the baseline tumor assessment will be used to determine response as follows.
7. *MRI will quantitate changes in a) intratumoral fat deposition in pancreatic cancer and b) visceral/subcutaneous fat distribution in pancreatic cancer patients treated with pioglitazone in this phase II study. To determine intratumoral fat content, we will use a previously described advanced chemical shift-based gradient-echo MRI technique that measures the proton density fat fraction (PDFF) [21]. In addition, MRI will allow quantitative determination of body fat volume in the abdomen e.g. subcutaneous/visceral adipose tissue (SAT/VAT) depots, which have been shown to have an important role in insulin resistance [22, 23].*

XVII. **Response Criteria**

Evaluation of Target Measurable Lesions

Complete Response (CR): Disappearance of all target lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Evaluation of Non-Measurable Lesions

Complete Response (CR): Disappearance of all non-target lesions and

normalization of tumor marker level

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

All CR or PR cases must be confirmed with follow-up tumor assessments done more than 4 weeks from the assessments that formed the basis for a response. The follow-up assessment must also meet the criteria for CR or PR in relation to baseline assessments.

Time to disease progression (TDP) is a secondary endpoint of this study. All patients should be followed for disease progression every month for the first six (6) months, then every three (3) months thereafter, following discontinuation of study treatment until at least two (2) years after discontinuation of pioglitazone.

XVIII. **Data handling and record keeping**

The principal investigator will maintain adequate records so that the conduct of the study can be fully documented and monitored. Copies of protocols, case report forms (CRFs), test result originals, all product accountability records, correspondence, subject informed consent, and any other documents relevant to the conduct of the study will be kept on file in the Simmons Clinical Research Office for at least two (2) years after all investigational use of product is discontinued. Study documents must not be destroyed. A record will be kept of all subjects considered and screened for the study and subsequently deemed ineligible. The reason for ineligibility must be recorded.

Case Report Forms (CRFs) will be utilized for each subject entered into the study. Study participants will not be identified by name on any study documents. Subjects will be identified by a subject identification number (see Section XI). The clinical research coordinator will keep the subject code list in a secured locked file cabinet in the Simmons Clinical Research Office. Additionally, all paper documents will be stored in a locked filing cabinet in the Clinical Research Office and all electronic records must be stored on a HIPAA Security Rule-compliant institutional server.

XIX. **Safety Monitoring**

A. ***Adverse Event Definition***

Adverse Events: Definitions and Reporting

Adverse Events will be reported as indicated by the appropriate following table (see below).

1.1.1 Definition

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, clinical event, or disease, that occurs during the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) and version number specified in the protocol. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring overnight hospitalization would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

1.1.2 Unanticipated Problems:

The term "unanticipated problem" is found, but not defined in the regulations for the Protection of Human Subjects at 45 CFR 46, and the FDA regulations at 21 CFR 56. Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ***each*** of the following criteria:

- unexpected; ***and***
- related *or possibly related* to participation in the research; ***and***
- suggests that the research *places subjects or others at a greater risk of harm* (including physical, psychological, economic, or social harm) *than was previously known or recognized.*

Follow-up

All adverse events will be followed up according to good medical practices.

1.1.3 **Reporting**

Local events requiring expedited reporting, are submitted to the UTSW IRB through the UTSW eIRB and to the SCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB report; the NCI ADEERS, FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be forwarded to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE documentation that is available are also submitted to the DSMC Chair who determines if further action is required.

If the event occurs on a multi-institutional clinical trial coordinated by the Cancer Center, the DOT Manager or lead coordinator ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all serious adverse events within upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

Telephone reports to: (Investigator: Insert names and phone numbers for required notifications) UTSW SCC Data Safety Monitoring Committee Coordinator (if fax report is not available) within 1 working day to 214-648-7097.
Written reports to: (Investigator: Insert names, fax numbers, an addresses for required notifications) UTSW SCC Data Safety Monitoring Committee Coordinator Email: SCCDSMC@utsouthwestern.edu Fax: 214-648-7018 or deliver to NB 2.418

1. **Unexpected Adverse Events**

   Non-serious adverse events which are classified as both unexpected (in terms of nature, severity and frequency) and possibly related require reporting to the UTSW IRB within 10 working days of PI awareness.

2. **SAEs**
   Local serious adverse events (SAEs) require reporting within 2 working days of PI awareness, or as described in the protocol.

3. **Unanticipated Problems**

   Unanticipated problems, including those that occur as non-local events, require reporting to the UTSW IRB within 10 working days of PI awareness of the event.

For further guidance for Investigators regarding safety reporting requirements for INDs and BA/BE studies, refer to FDA Draft Guidance document:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

G. ***Follow-up***

All adverse events will be followed up according to Good Clinical Practices.

H. ***Data and Safety Monitoring Plan***

The UTSW Simmons Cancer Center (SCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCC clinical trials. As part of that responsibility, the DSMC reviews all local serious adverse events in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance.

A detailed description of the Data and Safety Monitoring Plan is available in section X of the Clinical Research Office Operations Manual.

The SCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The QAC works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the patient population to be studied; adequacy of the data management system; and procedures to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles. The following examples can be used to begin developing DSMC plans for individual protocols.

- **High risk** examples include Phase 1 studies; Phase II or III studies where the SCC is the DSMC; gene therapy or recombinant DNA studies; and studies in which the investigator holds the IND.

- **Moderate risk** examples include pilot studies and other Phase II or III studies where the SCC DSMC is not the DSMC of record and which involve a non-FDA approved drug.

- **Low risk** examples include Phase II or III studies involving FDA-approved drugs where the SCC DSMC is not the DSMC of record, or trials, which involve non-therapeutic interventions.

- **Exempt** examples include non-interventional studies, which are exempt from audit requirements outlined above.

Multisite Monitoring

Monitoring for multi-institutional studies conducted with SCC as the primary site and coordinating center are the responsibility of the DOT Clinical Research Manager (CRM). The CRM or designee monitors all sub-sites for safety and data quality. The purpose of ongoing data monitoring at sub-sites is to ensure regulatory compliance, adherence to protocol requirements, and patient safety.

Sub-sites will be monitored no less than annually. Monitoring on site is preferred; however, remote monitoring is acceptable where there is not adequate funding for travel. The research documentation for at least 5 subjects is reviewed each time a study is monitored.

Monitoring will include verification of source documentation regarding consent, patient eligibility, investigational treatment, drug accountability, serious adverse events, toxicities, and treatment response. Results of data monitoring of sub-sites will be documented and the results will be made available to the QAC, during trial audit.

SAE's and reportable AE's must be reported to the IRB of the institution in which they occurred, the SCC lead investigators, and the SCC DSMC. The DOT Manager or lead coordinator ensures that the PIs at all of the participating sites and the respective IRBs are notified of the events and resulting action for events which modify the risk of the protocol or which otherwise meet FDA requirements for expedited reporting.

XX. **Data analysis and Statistical Methods**

A. ***Study Design and Sample Size***

This is a double arm, open label, Phase II study of pioglitazone in patients with pancreatic cancer. The primary endpoint for the sample size calculation is the adiponectin serum levels change after the pioglitazone treatment, which is the main indicator for insulin response improvement. We are interested in testing the hypothesis that pioglitazone can increase adiponectin by 40% from baseline. The change of adiponectin from baseline was defined as $c=(x1-x0)/x0$, where x1 is the adiponectin level after treatment, and x0 is the baseline adiponectin level. So the adiponectin

change is a continuous variable. The null hypothesis is that there is no change of adiponectin level. (H0: c=0). The alternative hypothesis is that the treatment will lead to 40% change of adiponectin from baseline (H1: c=0.4). Assuming that the standard deviation of the change is 0.5, (i.e the standard deviation of c values across population is 0.5), that a sample of 15 patients will provide a power of 82% at a significance level of 0.05 to detect 40% changes from baseline. This sample size calculation was implemented using SAS, and was reproduced using Power and Sample Size (PS) software.

B. ***Statistical Analysis Plan***

Biomarkers analyses

Statistical graphical tools will be used to illustrate the biomarker changes over time. Mean and median changes of results for glucose tolerance test, serum adiponectin level test, weight changes, and ECOG performance status will be summarized. Pre-defined cut-offs will be used to dichotomize the patients into with or without insulin response improvement which consists changes in serum adiponectin levels and standard glucose tolerance test. The insulin response improvement rate and 95% exact confidence interval will be calculated.

Tumor response analyses

Complete response rate, partial response rate, objective response rate and progression rate after week 8 with the exact 95% confidence intervals will be provided.

Time to progression

For a given patient, time to progression will be defined as the number of days from the day of registration to the day the patient experiences an event of disease progression (or death). If a patient has not experienced an event of disease progression (or death) at the time of analysis, then the patient's data will be censored at the date of the last available evaluation. Progression-free survival will be summarized using the point estimate of the median time to progression, and the associated 90% confidence interval. Moreover, the proportion of patients who are progression free at 24 months (after entering the study) will be calculated and the 90% confidence interval for this proportion will be constructed. The data will be presented graphically using Kaplan-Meier plots. Additionally, exploratory analysis may be performed including multivariate Cox regression analysis with appropriate baseline characteristics as covariates.

Overall survival

For a given patient, overall survival will be defined as the number of days from the day of registration to the day of the patient's death. Patients who have not

died at the time of analysis will be censored at the time they were last known to be alive. Overall survival will be summarized using the point estimate of the median overall survival time, and the associated 90% confidence interval. Moreover, the proportion of patients who are still alive at 24 months (after entering the study) will be calculated and the 90% confidence interval for this proportion will be constructed. The data will be presented graphically using Kaplan-Meier plots. Additionally, exploratory analysis may be performed including multivariate Cox regression analysis with appropriate baseline characteristics as covariates.

Correlative Analyses

Logistic regression on response and Cox regression on progression-free survival will be explored with multiple exploratory variables including the glucose tolerance level, serum adiponectin level, fasting serum glucose and insulin level, weight changes and ECOG performance. The association of response with other demographic baseline characteristics will be explored.

MRI assessment is exploratory.
Comparison of treatment (pioglitazone) and control arm will be exploratory.

Toxicity

Toxicities will be categorized using the NCI-CTCAE (version 4.0). The number and severity of toxicity and side effects incidents will be analyzed descriptively and summarized in tabular format.

XXI. References

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4. Tayek, J.A., *A review of cancer cachexia and abnormal glucose metabolism in humans with cancer.* J Am Coll Nutr, 1992. **11**(4): p. 445-56.
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Appendix 1

ECOG Performance Status Scale

Grade	Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Appendix 2

Weight Log

Subject ID: 072012-036 __ _

	Weight (kg)
Screening	
Cycle 1, Day 1 (Baseline)	**x 1.1**

If the weight of the subject becomes more than _____kg, then the dose should be modified according to section XIV-D of the protocol.

Study Visit	**Weight (KG)**
Week 2	
Week 4	
Week 6	
Week 8	
ET or EOS	
FU 2 WK Post ET or EOS	

Appendix 3 **Pill Diary**

Subject ID: _____ __ _ **Cycle: ___**

Take one (1) tablet of pioglitazone by mouth one time every day. If you forget to take a dose, but remember that same day, take the missed dose as soon as your remember to take it. However, if you do not remember until the next day, skip the missed dose and continue your regular dosing schedule. Do not take more than one dose in one day and do not take a double dose to make up for a missed one.

Day	Date	Did you take your tablet? Yes or No?
1	/	
2	/	
3	/	
4	/	
5	/	
6	/	
7	/	
8	/	
9	/	
10	/	
11	/	
12	/	
13	/	
14	/	
15	/	
16	/	
17	/	
18	/	
19	/	
20	/	
21	/	
22	/	
23	/	
24	/	
25	/	
26	/	
27	/	
28	/	

Appendix 4

FACT-Hep Questionnaire

Version 4

FACT-Hep (Version 4)

Pt. ID#: 072012-036- ____
Week #:_____
Date:_____

Below is a list of statements that other people with your illness have said are important. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box ☐ and go to the next section.					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Hep (Version 4)

Pt. ID#: 072012-036- ____
Week #:_____
Date:_____

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Hep (Version 4)

Pt. ID#: 072012-036- ____
Week #:_____
Date:_____

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C1	I have swelling or cramps in my stomach area	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
C4	I can digest my food well	0	1	2	3	4
C5	I have diarrhea	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
Hep 1	I am unhappy about a change in my appearance	0	1	2	3	4
CNS 7	I have pain in my back	0	1	2	3	4
Cx6	I am bothered by constipation	0	1	2	3	4
H17	I feel fatigued	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
Hep 2	I am bothered by jaundice or yellow color to my skin	0	1	2	3	4
Hep 3	I have had fevers	0	1	2	3	4
Hep 4	I have had itching	0	1	2	3	4
Hep 5	I have had a change in the way food tastes	0	1	2	3	4
Hep 6	I have had chills	0	1	2	3	4
HN 2	My mouth is dry	0	1	2	3	4
Hep 8	I have discomfort or pain in my stomach area	0	1	2	3	4