CASE COMPREHENSIVE CANCER CENTER

STUDY NUMBER: **CASE 1212**

STUDY TITLE: **A Phase II Study of Metformin plus modified FOLFOX 6 in Patients with Metastatic Pancreatic Cancer**

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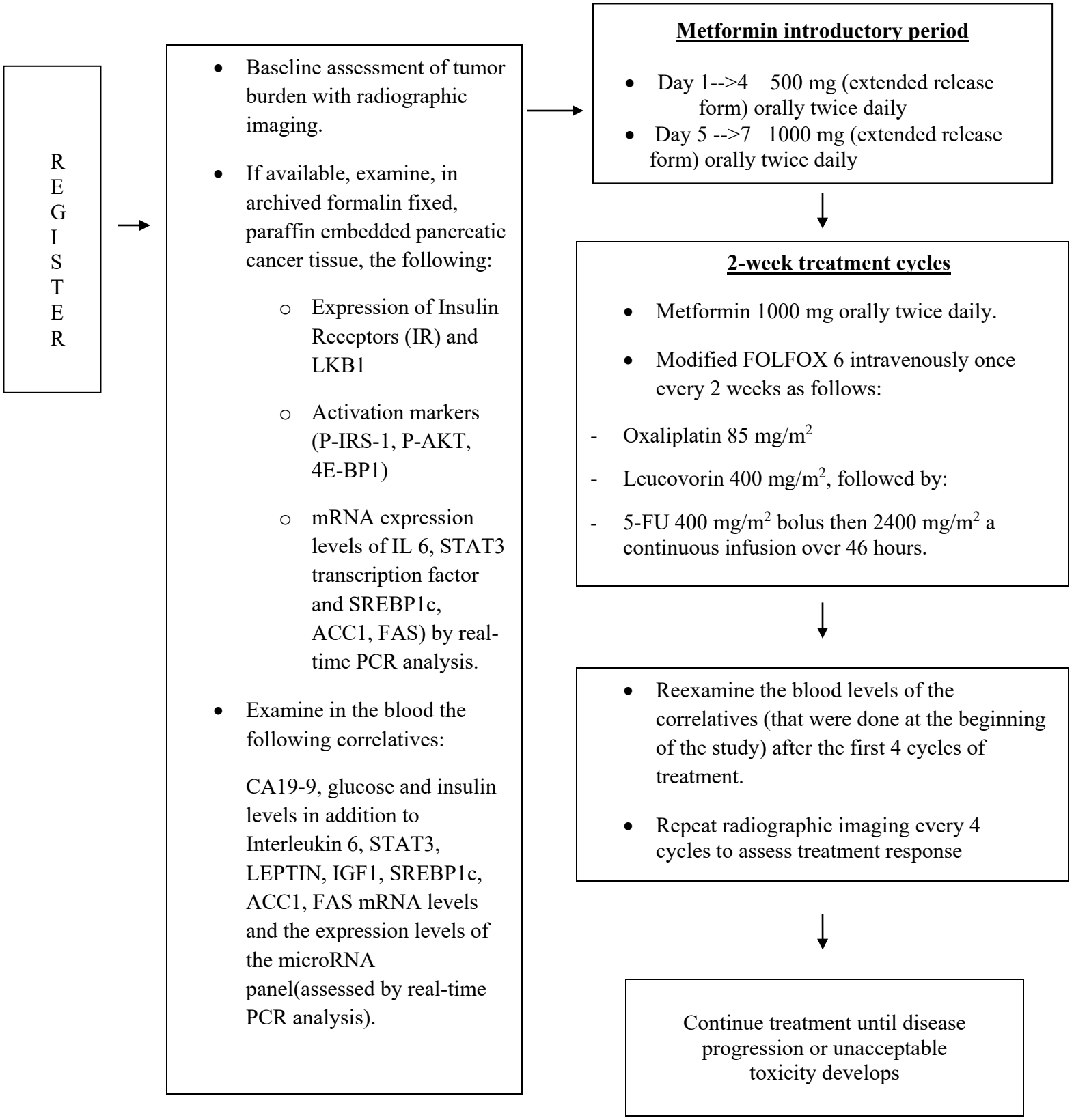
Study Schema



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1.0 INTRODUCTION/BACKGROUND

1.1 Pancreatic Cancer

Pancreatic adenocarcinoma is an aggressive gastrointestinal cancer with an estimated annual incidence of 44,030 cases in the United States, and is also expected to account for approximately 37,600 deaths in the United States in 2011 making it the fourth leading cause of cancer death for both men and women. Five-year survival rate is around 6 %. The incidence of diagnosis peaks in the seventh and eighth decade of life (1). Pancreatic adenocarcinoma is characterized by extensive local growth and early metastasis, making surgical control of disease uncommon.As a result, chemotherapeutic agents are often employed in an effort to control growth and spread of the cancer, as well as to prolong life and maximize function for patients with pancreatic cancer.

Currently, the most widely used first line regimens for metastatic pancreatic cancer in the US involves gemcitabine, which is a nucleoside analog, either alone or in combination with erlotinib, an inhibitor of epidermal growth factor receptor-associated tyrosine kinase. Median survival with gemcitabine based regimen ranges approximately between 5.2-7.2 months (2,3,4).

Recently, a new combination therapy consisting of 5-FU/LV plus oxaliplatin and irinotecan (FOLFIRINOX) was approved as a first line treatment for metastatic pancreatic cancerafter a large randomized phase 3 trial showed significant improvement in overall survival compared to gemcitabine monotherapy (11.1 vs 6.8 months, $p < 0.001$). There are, however, many concerns about the toxicity of the FOLFIRINOX regimen. The grade 3/4 toxicity rates were 12.3% for diarrhea, 15.6% for nausea, 17.2% for vomiting, 24% for fatigue, 47.9% for neutropenia, and 5.7% for febrile neutropenia. Patients who were enrolled in the study had an ECOG performance status of 0-1 (3). Therefore, this regimen has not been completely adapted by the medical oncology community.

Clearly, new therapies that could improve survival in patients with pancreatic adenocarcinoma and has an acceptable toxicity profileare urgently needed.

1.2Metformin

Metformin belongs to the biguanide class of oral hypoglycemic agents. It is the drug of choice forpatients with type 2 diabetes and is the most widely prescribed anti-diabetic drug (5). Recent evidence suggests that metformin may be active in the prevention and treatment of cancer. In a case control study of over 11,000 diabetic patients, metformin usage was associated with a 21% lower risk of developing cancers (6). In another study that included about 63000 diabetic patients, patients who used insulin or sulfonylureas had an increased risk of cancer (HR 1.36 and 1.42 respectively with $p < 0.001$) compared to those who used metformin monotherapy(7). A hospital-based case control study found that diabetic patients who used metformin had a significantly lower risk of developing pancreatic cancer with odds ratio of 0.38, 95% CI 0.22-0.69, $p= 0.001$ (8). Another retrospective study found that among diabetic patients with breast cancer receiving

neoadjuvant therapy, those on metformin were more likely to have a pathologic complete response rate (24% compared to 8% for diabetic patients not using metformin) (9).

Most recently, at ASCO 2011, several retrospective studies were presented that showed improved outcomes in cancer patients who were taking metformin (10, 11, 12). One study showed that the use of Metformin in type II noninsulin-dependent diabetes patients with colorectal cancer was associated with improved overall survival compared to patients not treated with metformin (76.9 months vs 56.9 months, p = 0.048) (10). A similar study showed that metformin appears to improve the overall survival rate of patients with colorectal cancer treated with chemotherapy compared to patients not treated with metformin with HR of 0.61(0.41-0.91;p=0.017) (11). A third study, suggested that metformin may improve the overall survival in diabetic patients with pancreatic cancer with HR of 0.67 (95% CI: 0.51-0.88, p=0.005) (12).

The mechanism by which metformin may act as an antineoplastic agent is not well defined. Metformin may exert its cell growth-inhibitory effects through two distinct mechanisms: a direct mechanism (insulin independent) through activation of adenosine monophosphate-activated protein kinase (AMPK) and an indirect mechanism depending on insulin/insulin-like growth factor 1(IGF-1) signaling. Both direct and indirect pathways lead to inhibition of mammalian target of rapamycin (mTOR) complex that plays a central role in cancer cell growth (13, 14). Of note, as an anti-diabetic agent it is believed that metformin inhibits the gluconeogenesis through activation of AMPK as well (15).

Two studies (16,17) demonstrated that metformin inhibits the growth of breast cancer cells through AMPK activation resulting in inhibition of mTOR. Another study (18) showed that metformin inhibits the cross-talk between insulin and G-protein coupled receptor signaling systems in pancreatic cancer cells by induction of AMPK, leading to inhibition of DNA synthesis and proliferation. In the same study metformin inhibited the growth of human pancreatic cancer cell xenografts. Similar studies reported inhibitory effects of metformin on growth of colon, lung, prostate and ovarian cancer cells (5).

Dr. Iliopoulos (a collaborator on this study) and colleagues conducted preclinical studies of metformin in combination with chemotherapy. They reported that the combination of doxorubicin with metformin suppressed tumor growth and prolonged remission in breast cancer mouse models, through inhibition of breast cancer stem cells (19). They have also reported in a separate study that inhibition of breast cancer stem cells is mediated via suppressing IL6 expression (20). Additional data (personal communication) showed that the combination of metformin and FOLFOX (5-FU, leucovorin and oxaliplatin) in two pancreatic cancer mouse models suppressed >90% tumor growth and inhibited metastasis. Antitumor activity was associated with reduced nuclear factor-kappa B (NF-κB) and IL6 expression. Metformin may reduce cardiovascular complications through suppression of NF-κBand IL6 in endothelial cells (21). Serum interleukin-6 levels were found to decrease following metformin treatment in women with polycystic ovary syndrome (22). Finally, the team also identified a panel of micro-RNAs (miR-200b, miR-145, miR-21, miR-210, let-7a, miR-20a, miR-34, miR-204, miR-214) that were highly associated with the survival of pancreatic cancer cells.

Metformin is a very safe and well-tolerated drug (5). Many cancer patients who have diabetes continue to use it while they are receiving chemotherapy. The most common side effects are gastrointestinal, such as diarrhea, nausea/vomiting and flatulence, which are reported to occur in less than 10 % of patients taking the extended-release form of metformin (23). Metformin rarely causes hypoglycemia and is associated with very low incidence of lactic acidosis (<1/10,000), predominantly in patients with poor renal function.

Currently, there are several phase 2 and 3 clinical trials exploring the effect of metformin on cancer outcome in different types of cancer (24).

1.3 Modified FOLFOX 6

FOLFOX (5-FU and oxaliplatin) is an approved second line regimen in metastatic pancreatic cancer. A study showed that it improves survival compared to 5-FU/Leucovorin when used as second line treatment (25). Also, there is some but limited data about its efficacy in first line regime with similar outcome to gemcitabine (26). The combination of FOLFOX plus irinotecan (FOLFIRINOX) also improves survival compared to gemcitabine as first-line treatment of metastatic pancreatic cancer (3).

1.4 Rationale

Based on the growing volume of preclinical and clinical evidences that metformin may have antineoplastic effect in different types of cancer, in particular, our disease of interest (pancreatic cancer), and based on the potential data that showed in vivo synergy between metformin and FOLFOX which is a known active regimen in pancreatic cancer, we propose a phase 2 clinical study to evaluate the effectiveness of metformin plus FOLFOX as first line therapy in patients with metastatic pancreatic cancer.

2.0 OBJECTIVES

2.1 Primary Objective

To determine if metformin when added to FOLFOX improves overall survival in patients with metastatic pancreatic cancer.

2.2 Secondary Objective(s)

1. To assess response rate (RR),
2. To assess progression free survival (PFS)
3. To assess toxicity in patients with metastatic pancreatic cancer receiving FOLFOX and metformin.
4. To identify tumor/serum correlative markers (see section 10.0)

3.0 STUDY DESIGN

3.1 Study design including dose escalation / cohorts

Patients with previously untreated histologically confirmed metastatic pancreatic cancer will be enrolled in this study.
Metformin will be administered alone for a one-week introductory period before the addition of FOLFOX according to the following schedule:

- Day 1-->4 500 mg twice daily
- Day 5 -->7 1000 mg twice daily
- Day 8 and beyond 1000 mg twice daily with chemotherapy

" Starting with a low dose metformin and increasing it gradually is a common practice when using metformin. It is believed to minimize the odds of gastroenterology side effects. Therefore, we have implemented this short introductory period".

FOLFOX will be administered intravenously once every 2 weeks as follows: Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, followed by 5-FU 400 mg/m^2 bolus then 2400 mg/m^2 a continuous infusion over 46 hours.
Radiographic imaging will be performed at baseline and after every 4 cycles. RECIST version 1.1 will be used to assess response to treatment.
Treatment will continue until disease progression, unacceptable toxicity or decision of patient/physician.

3.2 Number of Subjects

Estimated sample size is 43 patients(see section 14.0)

3.3 Replacement of Subjects

Subjects who receive less than 2 cycles of treatment and have to be withdrawn from the study will be replaced unless the withdrawal is secondary to progression or unacceptable toxicity.

3.4Expected Duration of Subject Participation

3.4.1 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment

- The investigator considers it, for safety reasons, to be in the best interest of the patient.
- Unacceptable adverse event(s) such as:

  -Unacceptable treatment related toxicity, NCI CTC AE version 4.0. Grade 3 or 4 that fails to recover to baseline or < Grade 3 in the absence of treatment within 4 weeks.

  -Any toxicity or other issue that causes a delay of study drug administration by more than 4 weeks.

- General or specific changes in the patient's condition rendering the patient unacceptable for further treatment in the judgment of the investigator.
- Patient decision to withdraw from treatment (partial consent) or from the study (full consent).
- Pregnancy during the course of the study for a child-bearing participant.
- Initiation of other anticancer therapy.
- Death

3.4.2 Duration of Follow Up

Patients will be followed until death. Patients who are removed from study will be followed every 6 months until death. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event, then every 6 months until death.

4.0 PATIENT SELECTION

4.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment:

4.1.1 Patients must have histologically or cytologically confirmed metastatic pancreatic adenocarcinoma(or any mixed pathology if adenocarcinoma is predominant).

4.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm with conventional techniques or as >10 mm with spiral CT scan.

4.1.3 Patients must have not received systemic chemotherapy for metastatic disease.

Prior chemotherapy, radiation therapy, concurrent chemoradiation are allowed if used for treatment of non-metastatic disease.

Prior palliative radiation for symptom management is allowed.
Any Chemotherapy must have been completed 4 weeks prior to enrollment.
Any Radiotherapy must have been completed 2 weeks prior to enrollment.

4.1.4 Age ≥18 years.

Because no dosing or adverse event data are currently available on the use of modified FOLFOX 6 in patients <18 years of age, children are excluded from this study.

4.1.5 ECOG performance status 0-2 (see Appendix A).

4.1.6 Patients must have adequate organs and marrow function as defined below.
Pre- study labs must be done within 1 week before starting treatment.

Absolute neutrophil count ≥ 1,500/dL

- Platelets ≥ 100,000/dL
- Hemoglobin ≥9g/dL
- Total bilirubin ≤ 2 mg/dL
- AST(SGOT)/ALT (SGPT) ≤ 2.5 × institutional upper limit of normal
- Creatinine ≤ 1.5

4.1.7 5-FU and/or oxaliplatin chemotherapy could cause fetal risk. Therefore, women of childbearing potential and men must agree to use adequate contraception (double barrier method of birth control or abstinence)prior to study entry and for the duration of study participation.

Should a woman become pregnant or suspect that she is pregnant while she or her partner is participating in this study, she should inform the treating physician immediately.

4.1.8 Subjects must have the ability to understand and the willingness to sign a written informed consent document.

4.1.9 Patients with diabetes are eligible for this trial All diabetic patients who are enrolled on this study should discuss the need to change their diabetes management regimen with their primary care physician

or endocrinologist prior to enrollment.

4.1.10 Diabetic patients who are on metformin are eligible as long as they have been on metformin for less than 6 months (estimated 6 months or less duration of metformin therapy from start of metformin to enrollment on study)

4.2 Exclusion Criteria

The presence of any of the following will exclude a patient from study enrollment.

4.2.1 Chemotherapy within 4 weeks prior to entering the study, radiotherapy within 2 weeks priorto entering the study or failure to recover from adverse events due to agents administered more than 4 weeks earlier.

4.2.2 Prior treatment toxicities must be resolved to ≤ Grade 1 according to NCI CTCAE Version 4.0.

4.2.3 Current use of metformin for more than 6 months prior to enrollment on study.

4.2.4 Use of any other investigational agents.

4.2.5 Patients with untreated brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

4.2.6 History of allergic reactions attributed to compounds of similar chemical or biologic composition to metformin or oxaliplatin or 5-FU.

4.2.7 Active second primary malignancy or history of second primary malignancy within the last 3 years, with the exception of basal cell skin cancers or carcinoma in situ that have been adequately treated.

4.2.8 Patients with uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

4.2.9 Pregnant or nursing women.

Note: Ineligibility is because 5-FU and or Oxaliplatinhave the potential for teratogenic or abortifacient effects. As for metformin, the potential for teratogenic or abortifacient effects is unknown.

4.2.10 HIV-positive patients. Note: Ineligibility is because of increased risk of lethal infections when treated with marrow suppressive therapy.

4.2.Chronic or planned acute alcohol use of 3 or more drinks per day.

4.2.12Metabolic acidosis, acute or chronic, including ketoacidosis.

4.3 Inclusion of Women *and* Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

5.0 REGISTRATION

5.1 Registration

All subjects who have been consented are to be registered in the OnCore Database. For those subjects who are consented, but not enrolled, the reason for exclusion must be recorded.

All subjects will be registered through Name of Lead site and will be provided a study number by calling telephone number of study coordinator**.**

6.0 TREATMENT PLAN

6.1 MetforminAdministration

Metformin will be administered alone for a 1-week introductory period before the addition of FOLFOX according to the following schedule:

- Day 1-->4 500 mg twice daily
- Day 5 -->7 1000 mg twice daily

After the introductory period, patient will be continued on metformin 1000 mg twice daily in 2-week (14 day) cycles.

"All patients will be taking an extended release form of metformin and will be instructed to take it with meals. This will minimize the odds of gastroenterology side effects"

Patients will be provided with a Patient Pill Diary (Appendix B) and instructed in its use to record each dose of oral medication. Patients will be asked to bring the diary with them to each appointment.

6.2FOLFOX6 Administration:

Patients will receive modified FOLFOX6 (mFOLFOX6) on an outpatient basis on Day 1 of each 2-week (14 day) cycle. First cycle to begin as soon as the metformin introductory period is over. This regimen consists of concurrent IV administration of 85 mg/m^{2}oxaliplatin and 400 mg/m^{2}leucovorin over 120 minutes, followed by 400 mg/m^2 5-fluorouracil (FU) bolus, then 2400 mg/m^2 5-FU as a 46 hour infusion. An ambulatory infusion pump may be used for the 5-FU infusion. All patients must have central intravenous access (e.g., mediport, PICC line) for the continuous infusion of 5-FU.

6.3General Concomitant Medications and Supportive Care Guidelines

Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, etc when appropriate.

6.3.1*Antiemetics*

5-FU and oxaliplatin may be emetogenic. Antiemetics such as ondansetron, dolasetron, or granisetron should be used prior to each cycle of therapy.

A recommended anti-emetic regimen is provided below:

Pre medications: Dexamethasone 16 mg IV 30 min prior to oxaliplatinandondansetron 16 mg IV 30 min prior to oxaliplatin

Take home medications: Dexamethasone 4 mg PO bid X 4 doses starting the day after oxaliplatin administration

Ondansetron 8mg orally q 8 hours prn nausea and Prochloroperazine (Compazine) 10mg orally q 8 hours prn nausea

6.3.2 *Growth Factors*

The American Association of Clinical Oncology (ASCO) guidelines will be followed for the prophylactic use of G-CSF.

6.3.3 *Oxaliplatin-Related Issues*

- Peripheralneuropathy:Oxaliplatin is consistently associated with 2 types of peripheral neuropathy, which includes paresthesias and dysesthesias of the hands, feet, and perioral region. Patients treated in this study will be counseled to avoid cold drinks and exposure to cold.

- Hypersensitivity:Oxaliplatin, as is the case with all platinum-containing compounds, is associated with a measurable (approximately 11%) incidence of hypersensitivity reactions, usually after multiple doses of treatment. This may present as bronchospasm, hypotension, and even hemolytic anemia. Pretreatment with glucocorticoids and antihistamines may be useful for some patients, but may not always prevent the development of anaphylactoid reactions, especially in patients with a prior history of hypersensitivity to this agent. For patients who have experienced a Grade 1 or 2 acute hypersensitivity reaction that is assessed as related to oxliplatinadministration, the following premedication is recommended prior to each subsequent dose of oxaliplatin (patients who have grade 3 or 4 acute hypersensitivity reactions should discontinue oxaliplatin therapy): Dexamethasone 20 mg PO or IV, 12 and 6 hours prior to the oxaliplatindose; Dexamethasone 20 mg PO or IV, as well as diphenhydramine 50 mg IV, and one of the following: cimetidine 300 mg IV, ranitidine 50 mg IV, or famotidine 20 mg IV 30-60 minutes prior to oxaliplatin administration. If these prophylactic measures

fail to prevent oxaliplatin-related hypersensitivity, therapy with oxaliplatinshould be discontinued.

- LaryngopharyngealDysesthesia: An unusual laryngopharyngealdysesthesia (LPD), a loss of sensation of breathing without any objective evidence of respiratory distress (laryngospasm, bronchospasm or hypoxia) has also been observed. This neurotoxicity may be induced or exacerbated upon exposure to cold and should be distinguished from a hypersensitivity reaction. If a patient develops LPD, the patient's oxygen saturation should be evaluated via a pulse oximeter and, if normal, reassurance, a benzodiazepine or other anxiolytic agent should be considered and the patient should be observed in the clinic until the episode has resolved. The oxaliplatin infusion may then be continued at a reduced rate, 33% of the original rate. Because this syndrome may be associated with the rapidity of oxaliplatin infusion, subsequent doses of oxaliplatin should be administered as 6-hour infusions. To minimize the risk of LPD, patients will be instructed to avoid ice and cold drinks the day of treatment.

- Oral cryotherapy: Patients on oxaliplatin should not receive oral cryotherapy on day 1 and 2 of each cycle as this may exacerbate laryngopharyngealdysesthesia caused by oxaliplatin.

- Pulmonary fibrosis: In the case of unexplained respiratory symptoms such as nonproductive cough, dyspnea or radiological pulmonary infiltrates, oxaliplatin should be discontinued until further investigation excludes interstitial pulmonary fibrosis. If interstitial pulmonary fibrosis is confirmed, oxaliplatin therapy should be terminated.

- Veno-occlusive disease (VOD) is estimated to occur in 1 in 5000 patients treated with oxaliplatin and 5-FU. All patients on and off therapy who develop signs and symptoms of VOD should be thoroughly evaluated, closely monitored, and supported as clinically indicated. Evaluation of VOD should include observation of liver and spleen size, assessment for ascites and jaundice, inquiry into and evaluation of any gastrointestinal bleeding, and ultrasound to evaluate for reversal of portal blood flow. Consider measuring serum procollagen type III, which can rise early in the course of VOD.

6.3.4 *Metformin-Related Issues*

- Use of iodinated contrast:Concurrent use of metformin is contraindicated in participants receiving intravascular iodinated contrast media due to an association with lactic acidosis and acute renal failure. If/when participants on study will be exposed to iodinated contrast (such as when they are getting a scan) the metformin must be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure.

- Hypoglycemia:Although it is very rare, hypoglycemia could occur. Some of the factors that could increase the risk of hypoglycemia are:

    - Diabetic patients who are taking other glucose lowering-agents (eg, sulfonylureas, insulin).

- Concomitant use of fluoroquinolones.

- Concomitant use of beta blocking agents.

- Diabetics patients will be asked to monitor their glucose at home through a glucometer twice weekly at least. Also, all diabetic patients should discuss the need to change their diabetes management regimen with their Primary care physician or endocrinologist.

If patients are on fluoroquinolones and/or beta blocking agents, it will be left at the discretion of their primary providerto decide on how often their glucose level needs to be checked, whether at home through a glucometer or throughlaboratory blood draw.

Vitamin B12: In controlled clinical trials of metformin hydrochloride tablets, a decrease to subnormal levels of previously normal serum Vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12 -intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin hydrochloride tablets or Vitamin B12 supple- mentation. Vitamin B12 levels need only to be checked in the case of unexplained/irreversible anemia. If Vitamin B12 level was found to be low, Vitamin B12 supplementation could be given orally.

6.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Disease progression

- Intercurrent illness that prevents further administration of treatment

- The investigator considers it, for safety reasons, to be in the best interest of the patient.

- Unacceptable adverse event(s) such as:

-Unacceptable treatment related toxicity, NCI CTC AE version 4.0.Grade 3 or 4 that fails to recover to baseline or < Grade 3 in the absence of treatment within 4 weeks

-Any toxicity or other issue that causes a delay of study drug administration by more than 4 weeks.

- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

- Patient decision to withdraw from treatment (partial consent) or from the study (full consent)

- Pregnancy during the course of the study for a child-bearing participant

- Initiation of other anticancer therapy
- Death

6.5 Duration of Follow Up

Patients will be followed for survival until death. Patients who are removed from study will be followed every 6 months until death. Patients removed from study for unacceptable adverse events will be followed every 6 months until resolution or stabilization of the adverse event, then until death.

Patients will be followed for toxicity for 30 days after treatment has been discontinued or until death, whichever occurs first.

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

6.6 Leucovorin shortage:

There is currently (as per April 2012) a shortage of leucovorin in the United States.
If this shortage continues when this study is open, patients may be treated with IV levo-leucovorin at 200mg/m^2 instead of leucovorin at 400 mg/m^2 . If levo-leucovorin is not an option, patients may be treated with low-dose leucovorin at 20mg/m^2 or may be treated without leucovorin.

7.0 DOSING DELAYS / DOSE MODIFICATIONS

7.1 Metformin dose modifications

Metformin will be administered alone for a 1 week introductory period before the addition of the " Folfox chemotherapy" according to the following schedule:
- Day 1-->4 500 mg twice daily
- Day 5 -->7 1000 mg twice daily
- Day 8 and beyond 1000 mg twice daily with chemotherapy

7.1.1 Gastrointestinaladverse events (except hepatic dysfunction)

Through the above titrating schedule, the use of the extended release form of metformin and the administration of metformin with meals, the odds of metformin related GI side effects will be much minimized.

Considering that most metformin related GI toxicity are transient, self-resolved with continuous use and usually managed individually with no universally adopted guidelines, GI side effects which are expected to be less than 10 %, will be managed on a case by case basis by the investigator.

The following points will be taken into consideration;

During the introductory period (before chemotherapy is started):
1) When/if GI side effects develop; patient should be encouraged to continue the medication since symptoms could very well self-resolve.
2) The investigator may delay the dose increase to 1000 mg twice daily for grade 3 or above GI toxicity that persist and doesn't respond to symptomatic management) until symptoms improve/resolve.
3) If GI symptoms occur and persist upon increasing the dose to 1000 mg twice daily, dose could be reduced again to 500 mg twice daily (if grade 3 or above GI toxicity persist) and chemotherapy will be initiated while on this dose.

After the introductory period (after chemotherapy is started):

1) When/if new onset GI side effects occur; it will be, most likely, due to chemotherapy (FOLFOX) rather than due to metformin. Therefore, the investigator will follow the FOLFOX dose modifications schedule.
2) In the rare events where GI symptoms are felt to be related to metformin, the case will be discussed among the investigators to decide on whether the metformin dose should be reduced or modified.
3) If patient is started on chemotherapy while taking 500 mg twice daily dose (rather than the 1000 mg twice daily), the investigators will continue to assess the symptoms and potentially consider increasing the dose to 1000 mg twice daily with cycle # 2 of chemo.

7.1.2Hepatic dysfunction:
- Metformin must be stopped If bilirubin increases to >2. Bilirubin levels will be checked weekly and metformin can be resumed once bili is <2.
- Metformin must be stopped if AST or ALT increase to > 2.5 ULN. AST/ALT levels will be checked weekly and metformin can be resumed only if levels go below 2.5 ULN.

7.1.3
Renal dysfunction:
- Metformin must be stopped if creatinine increases to > 1.5. Creatinine level will be checked weekly and metformin can be resumed once creatincine is < 1.5

7.1.4 Others:
- If any other toxicity develop and felt that it is related to metformin, further treatment will be at the discretion of the investigator.

7.2 mFOLFOX 6 modifications

mFOLFOX dose levels

Dose Level	Oxaliplatin mg/m2	Leucovorin mg/m2	5-FU Bolus mg/m2	5-FU Infusion mg/m2
Starting dose	85	400	400	2400
Dose Level -1	71	400	334	2000
Dose Level -2	57	400	267	1600

mFOLFOX dose modifications:

Dose modifications will be required for AEs observed during the cycle and on day 1 of a cycle. Dose modifications will be based on the AE requiring the greater modification.		
NCI CTC v 4.0 Category/Grade	Modifications for AEs that occurred DURING A CYCLE but did not require a treatment delay	Modifications for AEs that required a TREATMENT DELAY (observed on day 1 of cycle) [a]. **Hold mFOLFOX6 for treatment-related toxicities listed in this table that are > grade 1 on day 1 of a cycle (except ANC).**
Blood/Bone Marrow		
Neutrophils/ Granulocytes [b]		
Grade 2	Maintain dose	Maintain dose
Grade 3	Maintain dose	5FU and oxaliplatin 1 dose level
Grade 4	↓ 5FU and oxaliplatin 1 dose level	↓ 5FU and oxaliplatin 2 dose levels
Platelets [c]		
Grade 2	Maintain dose	↓5FU and oxaliplatin 1 dose level
Grade 3	↓ 5FU and oxaliplatin 1 dose level	↓5FU and oxaliplatin 1 dose level
Grade 4	↓ 5FU and oxaliplatin 2 dose levels	↓ 5FU and oxaliplatin 2 dose levels
Diarrhea[d]		
Grade 2	Maintain dose	↓5FU by one dose level.
Grade 3	↓5FU 1 dose level	↓5FU 1 dose level

Grade 4	↓5FU by 2 dose levels and oxaliplatin by 1 dose level	↓5FU by 2 dose levels and oxaliplatin by 1 dose level
Hepatic Function [e]		
Total bilirubin, AST	Hold all study therapy until bilirubin returns to baseline grade and AST is ≤ grade 1.	
Grade 2	oxaliplatin one dose level	↓oxaliplatin 1 dose level
Grade 3	↓5FU and oxaliplatin one dose level.	↓5FU and oxaliplatin 2 dose levels
Grade 4	Stop all study therapy	Stop all study therapy

Infection		
Febrile Neutropenia		
Grade 3	↓5FU and oxaliplatin 1 dose level [f]	↓5FU and oxaliplatin 1 dose level [f]
Grade 4	↓5FU and oxaliplatin 2 dose levels [f]	↓5FU and oxaliplatin 2 dose levels [f]
Infection with Grade 3 or 4 ANC		
Grade 3	↓5FU and oxaliplatin 1 dose level [f]	↓5FU and oxaliplatin 1 dose level [f]
Grade 4	↓5FU and oxaliplatin 2 dose levels [f]	↓ 5FU and oxaliplatin 2 dose levels [f]
Infection with normal ANC		
Grade 3	Maintain dose	Maintain dose
Grade 4	↓5FU and oxaliplatin 1 dose level	↓5FU and oxaliplatin 1 dose level
Pulmonary Toxicity		
Cough ≥ grade 3	Hold all study therapy until interstitial lung disease is ruled out. If non-infectious interstitial lung disease is confirmed, discontinue all study therapy. If non-infectious interstitial lung disease is ruled-out and infection (if any) has resolved, patients with persistent grade 2 dyspnea or hypoxia may resume treatment at the discretion of the P.I.	
Dyspnea ≥ grade 2		
Hypoxia ≥ grade 2		
Pneumonitis/pulmonary infiltrates ≥ grade 2		
Pulmonary fibrosis ≥ grade 2		
Other clinically significant AEs[g] **Except oxaliplatin-Related Neurologic toxicity**		
Grade 2	Maintain dose	↓5FU and oxaliplatin 1 dose level
Grade 3	↓5FU and oxaliplatin1 dose level	↓5FU and oxaliplatin 2 dose levels
Grade 4	↓5FU and oxaliplatin2 dose levels	↓ 5FU and oxaliplatin 2 dose levels
Oxaliplatin-Related Neurologic Toxicity		
Paresthesias/Dysesthesias (may be cold-induced)	Resolved During the Cycle	Persistent Between Doses
Grade 1	Maintain dose	Maintain dose

Grade 2	Maintain dose	↓oxaliplatin 1 dose level
Grade 3	↓oxaliplatin 1 dose level	Discontinue oxaliplatin
Grade 4	Discontinue oxaliplatin	Discontinue oxaliplatin
Laryngeal Dysesthesias	See section 6.3.2	

a)Treatment may not proceed until treatment-related toxicity has resolved to ≤ grade 1, except for neutrophils which must be ≥ 1200/mm3 in order to treat. Hold study drugs and recheck weekly.
b)Neutrophils must be ≥ 1200/mm3 in order to treat.
c)Treat if platelets are ≥ 75,000/mm3. Consider hemolytic uremic syndrome/ thrombotic thrombocytopenic purpura for ≥ grade 2 thrombocytopenia. If confirmed, discontinue oxaliplatin.
d)Hold mFOLFOX6 for grade 3 or 4 diarrhea at any time during a cycle or for grade 2 diarrhea on day 1 of a cycle. Resume treatment as per table when diarrhea has resolved to ≤ grade 1.
e)Elevation of bilirubin or AST to ≥ grade 3 will require bilirubin and transaminases to be monitored weekly. If all elevations do not resolve to ≤ grade 1 after 4 weeks, discontinue study therapy. Then monitor bilirubin and transaminases q 2 weeks for 2 months, then q 4 weeks until 1 year from study entry or until all elevations resolve to ≤ grade 1. Hold all study therapy for suspected veno-occlusive disease (VOD) of the liver (manifestations include hyperbilirubinemia, ascites, weight gain due to fluid retention, hepatomegaly, splenomegaly, or other signs of portal hypertension). If VOD is diagnosed, discontinue all study therapy.
f) Administer G-CSF with subsequent cycles.
g)The determination of clinically significant is at the discretion of the treating physician.

8.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

The following is a list of AEs (Section 8.1) and the reporting requirements associated with observed AEs (Sections 8.3 and 8.4).

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

8.1 Adverse Events and Potential Risks

8.1.1 Metformin

>10%:

Gastrointestinal: Diarrhea, nausea/vomiting, flatulence (Note: With the extended release form, these symptoms are reported to occur in less than 10 % of patients).

Neuromuscular & skeletal: Weakness

1% to 10%:

Cardiovascular: Chest discomfort, flushing, palpitation

Central nervous system: Headache , chills, dizziness, lightheadedness

Dermatologic: Rash

Endocrine & metabolic: Hypoglycemia

Gastrointestinal: Indigestion , abdominal discomfort , abdominal distention, abnormal stools, constipation, dyspepsia/ heartburn, taste disorder

Neuromuscular & skeletal: Myalgia

Respiratory: Dyspnea, upper respiratory tract infection

Miscellaneous: Decreased vitamin B_{12}levels , increased diaphoresis, flu-like syndrome, nail disorder

<1% (Limited to important or life-threatening):

Lactic acidosis, leukocytoclasticvasculitis, megaloblastic anemia, pneumonitis

8.1.2 Oxaliplatin

> 10%

Central nervous system: Fatigue (61%), fever (25%), pain (14%), headache (13%), insomnia (11%)

Gastrointestinal: Nausea (64%), diarrhea (46%), vomiting (37%), abdominal pain (31%), constipation (31%), anorexia (20%), stomatitis (14%)

Hematologic: Anemia (64%; grades 3/4: 1%), thrombocytopenia (30%; grades 3/4: 3%), leukopenia (13%)

Hepatic: AST increased (54%; grades 3/4: 4%), ALT increased (36%; grades 3/4: 1%), total bilirubin increased (13%; grades 3/4: 5%)

Neuromuscular & skeletal: Peripheral neuropathy (may be dose limiting; 76%; acute 65%; grades 3/4: 5%; persistent 43%; grades 3/4: 3%), back pain (11%)

Respiratory: Dyspnea (13%), cough (11%)

1% to 10%:

Cardiovascular: Edema (10%), chest pain (5%), peripheral edema (5%), flushing (3%), thromboembolism (2%)

Central nervous system: Dizziness (7%)

Dermatologic: Rash (5%), alopecia (3%), hand-foot syndrome (1%)

Endocrine & metabolic: Dehydration (5%), hypokalemia (3%)

Gastrointestinal: Dyspepsia (7%), taste perversion (5%), flatulence (3%), mucositis (2%), gastroesophageal reflux (1%), dysphagia (acute 1% to 2%)

Genitourinary: Dysuria (1%)

Hematologic: Neutropenia (7%)

Local: Injection site reaction (9%; redness/swelling/pain)

Neuromuscular & skeletal: Rigors (9%), arthralgia (7%)

Ocular: Abnormal lacrimation (1%)

Renal: Serum creatinine increased (5% to 10%)

Respiratory: URI (7%), rhinitis (6%), epistaxis (2%), pharyngitis (2%), pharyngolaryngealdysesthesia (grades 3/4: 1% to 2%)

Miscellaneous: Allergic reactions (3%); hypersensitivity (includes urticaria, pruritus, facial flushing, shortness of breath, bronchospasm, diaphoresis, hypotension, syncope: grades 3/4: 2% to 3%); hiccup (2%).

For more information on toxicities associated with oxaliplatin, please see the package insert.

8.1.3 5-FU

Hematologic: Leukopenia, thrombocytopenia, anemia, pancytopenia, thrombocytopenia, agranulocytosis; can also be dose limiting; less common with continuous infusion.

Dermatologic: Dermatitis, nail changes, hyperpigmentation, hand-foot syndrome with protracted infusions, alopecia, fissuring, photosensitivity as manifested by erytema or increased pigmentation of the skin, nail changes (including loss of nails).

Gastrointestinal: Nausea, vomiting, anorexia; diarrhea, can be dose limiting; mucositis, more common with 5-day infusion, occasionally dose limiting; severe, cholera-like diarrhea which can be fatal given with leucovorin; gastro- intestinal ulceration, bleeding, stomatitis, esophagopharyngitis.

Neurologic: Cerebellar syndrome (headache and cerebellar ataxia).

Cardiac: myocardial ischemia, angina, noted with continuous infusion, thrombophlebitis.

Ophthalmic: Eye irritation, nasal discharge, watering eyes, blurred vision.

Hepatic: Hepatitis with hepatic infusion.

Allergic reaction: anaphylaxis, generalized allergic reactions.

Psychiatric: disorientation, confusion, euphoria

Other: nose bleeds

For more information about 5-FU toxicity please see package insert.

8.1.4 Leucovorin

Hematologic: Thrombocytopenia, leukopenia.

Dermatologic: Skin rash, alopecia.

Gastrointestinal: Nausea, vomiting, diarrhea, stomatitis, constipation.

Allergic: Skin rash, hives, pruritis.

Pulmonary: Wheezing (possibly allergic origin).

Other: infection, lethargy, fatigue, anorexia, headache; may potentiate the toxic effects of fluoropyrimidine therapy, resulting in increased hematologic and gastrointestinal (diarrhea, stomatitis) adverse effects.

See Package Insert for additional information on leucovorin.

8.2 Definitions

8.2.1 Adverse Events

An **adverse event** (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the research study. The event does not necessarily have to have a causal relationship with the research, any risk associated with the research, the research intervention, or the research assessments.

Adverse events may be the result of the interventions and interactions used in the research; the collection of identifiable private information in the research; an underlying disease, disorder, or condition of the subject; and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject. In general, adverse events that are at least partially the result of (a) or (b) would be considered related to the research, whereas adverse events solely related to (c) or (d) would be considered unrelated to the research.

External adverse events are adverse events experienced by subjects enrolled in multicenter clinical trials at sites other than the site(s) over which the Institutional Review Board has jurisdiction.

Internal adverse events are adverse events experienced by subjects enrolled at the site(s) under the IRB's jurisdiction for either multicenter or single-center research projects.

8.2.2 The significance of an adverse event is used to describe the patient/event outcome or action criteria associated with events that pose a threat to a patient's life or functioning (i.e., moderate, severe or life threatening). Based on the National Cancer Institute Guidelines for the Cancer Therapy Evaluation Program, severity can be defined by the following grades of events:

Grades 1 are mild adverse events. (e.g., minor event requiring no specific medical intervention; asymptomatic laboratory findings only; marginal clinical relevance)

Grades 2 are moderate adverse events (e.g., minimal intervention; local intervention; non-invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation).

Grades 3 are severe and undesirable adverse events (e.g., significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation).

Grades 4 are life threatening or disabling adverse events (e.g., complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis; life–threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation).

Grades 5 are fatal adverse event resulting in death.

8.2.3 Serious Adverse Events

A **serious adverse event** (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

- Results in **death.**
- Is a **life-threatening** adverse experience. The term life-threatening in the definition of serious refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.
- Requires **inpatient hospitalization or prolongation of existing hospitalization**. Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following expectations is met:
    - The admission results in a hospital stay of less than 12 hours OR
    - The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study) OR
    - The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care.

  However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of "medically important" and as such may be reportable as a serious adverse event dependent on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.
- Results in **persistent or significant disability/incapacity**. The definition of disability is a substantial disruption of a person's ability to conduct normal life's functions.
- Is a **congenital anomaly/birth defect**.
- Is an **important medical event**. Important medical events that may not result death, be life-threatening, or require hospitalization may be considered a serious adverse

experience when, based upon appropriate 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood disease or disorders, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.2.4 Expectedness

Adverse Events can be Expected or Unexpected.

An expected adverse event is an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the Investigator Brochure, consent form or research protocol.

An unexpected adverse event is an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

8.2.5 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study drug. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study drug.
- Probable – The AE is likely related to the study drug.
- Possible – The AE may be related to the study drug.
- Unlikely – The AE is doubtfully related to the study drug.
- Unrelated – The AE is clearly NOT related to the study drug.

8.3 Reporting Procedures for All Adverse Events

All participating investigators will assess the occurrence of AEs throughout the subject's participation in the study. Subjects will be followed for toxicity for 30 days after treatment has been discontinued or until death, whichever occurs first. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject which occur after the subject has signed the informed consent are fully recorded in the subject's case report form, subject's medical records, and/or any other institutional requirement. Source documentation must be available to support all adverse events.

A laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the study), requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event.

The investigator will provide the following for all adverse events:

- Description of the event
- Date of onset and resolution
- Grade of toxicity

- Attribution of relatedness to the investigational agent
- Action taken as a result of the event
- Outcome of event

In this study, descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 available at http://ctep.cancer.govwill be utilized for AEreporting.

Investigative sites will report adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events.

8.4 Serious Adverse Event Reporting Procedures

Serious adverse events that occur beginning with the signing of the informed consent form, during treatment, or within 30 days of the last dose of treatment must be reported to the Principal Investigator.

Investigative sites will report serious adverse events to their respective IRB according to the local IRB's policies and procedures in reporting serious adverse events.

8.4.1 FDA Reporting

The principal investigator will be responsible for all communication with the FDA. In accordance with 21 CFR 312.32, the Principal Investigator is responsible for notifying the FDA of SAEs that are serious, unexpected (not listed in the Investigator Brochure) and judged to be related (i.e., possible, probable, definite) to the study drug.

8.5 Data Safety Toxicity Committee

It is the Case Comprehensive Cancer Center's Principal Investigator's responsibility to ensure that ALL serious adverse events are reported to the Case Comprehensive Cancer Center's Data Safety Toxicity Committee. This submission is simultaneous with their submission to the Sponsor or other Regulatory body.

9.0 PHARMACEUTICAL INFORMATION

9.1 Metformin

Chemical Name:*N*,*N*-dimethylimidodicarbonimidicdiamide hydrochloride

Classification: Biguanides

Molecular Formula:$C_4H_{11}N_5$

Mode of Action:
As a diabetic mediation, decreases hepatic glucose production and increases insulin sensitivity.
Refer to background for mechanism of potential antineoplastic effects.

Metabolism: Metformin is excretedunchanged in the urine and does not undergo hepatic metabolism (no metabolites have beenidentified in humans) nor biliary excretion. Renal clearance is approximately 3.5 timesgreater than creatinine clearance, which indicates that tubular secretion is the major route ofmetformin elimination.
Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life ofapproximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggestingthat the erythrocyte mass may be a compartment of distribution.

Route of administration: This is an oral drug that should be taken with food.

Availability:

Metformin is commercially available at the following doses:
500 mg, 850 mg, 1000 mg (fast release) tablets.
500 mg, 750 mg (extended release) tablets.
100 mg/ml (118 ml, 473 ml) oral solutions.

Storage: Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature.

Metformin Ordering:

Metformin Hydrochloride 500 mg (extended-release) tablets will be prescribed for each patient enrolled on this study using a special clinical trial prescription. The prescription will be filled through the institutions investigational pharmacy.

9.2 <u>Oxaliplatin</u>

Chemical name: cis-[(1 R,2R)-1,2-cyclohexanediamine-N,N'] [oxalato(2-)-O,O'] platinum.

Classification: Platinum Derivative

Molecular Formula: C8H14N2O

Approximate Solubility:

Slightly soluble in water (solubility in water at 20° C is 6 mg/mL). Very slightly soluble in methanol (solubility in methanol at 20° C is 0.125 mg/mL). Practically insoluble in ethanol and acetone. The pH of an aqueous solution of 2 mg/mL is between 4.8 and 5.7.

Mode of Action

Oxaliplatin is biotransformed to a reactive species which complex with (crosslink) DNA, amino acids, proteins, and other macromolecules and cause tumor cell death by preventing cellular replication and transcription and stimulating cells to undergo apoptosis.

How Supplied

Oxaliplatin is supplied in clear, glass, single-use vials with gray elastomeric stoppers and aluminum flip-off seals containing 50 mg or 100 mg of oxaliplatin as a sterile, preservative-free

lyophilized powder for reconstitution. Lactose monohydrate is also present as an inactive ingredient.

NDC 0024-0596-02: 50 mg single-use vial with green flip-off seal individually packaged in a carton.

NDC 0024-0597-04: 100 mg single-use vial with dark blue flip-off seal individually packaged in a carton.

RECONSTITUTION OR FINAL DILUTION MUST NEVER BE PERFORMED WITH A SODIUM CHLORIDE SOLUTION OR OTHER CHLORIDE- CONTAINING SOLUTIONS.

The lyophilized powder is reconstituted by adding 10 mL (for the 50 mg vial) or 20 mL (for the 100 mg vial) of Water for Injection, USP or 5% Dextrose Injection, USP. **Do not administer the reconstituted solution without further dilution.** The reconstituted solution must be further diluted in an infusion solution of 250-500 mL of 5% Dextrose Injection, USP.

After reconstitution in the original vial, the solution may be stored up to 24 hours under refrigeration (2-8°C [36-46°F]). After final dilution with 250-500 mL of 5% Dextrose Injection, USP, the shelf life is **6 hours at room temperature (20-25°C [68-77°F]) or up to 24 hours under refrigeration (2-8°C [36-46°F]).** ELOXATIN is not light sensitive.

Incompatibilities

Oxaliplatinis incompatible in solution with alkaline medications or media (such as basic solutions of 5-FU) and must not be mixed with these or administered simultaneously through the same infusion line. The infusion line should be flushed with D5W prior to administration of any concomitant medication.

Do not use for the preparation or administration needles or intravenous infusion sets containing aluminum items (risk of degradation of oxaliplatin upon contact with aluminum).**Handling and Disposal**

As with other potentially toxic anticancer agents, care should be exercised in the handlingand preparation of infusion solutions prepared fromOxaliplatin. The use of gloves is recommended. If a solution of Oxaliplatin contacts the skin, wash the skin immediately and thoroughly with soap and water. If Oxaliplatincontacts the mucous membranes, flush thoroughly with water.

Procedures for the handling and disposal of anticancer drugs should be considered. Several guidelines on the subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Storage

Store the intact vials at controlled room temperature. Excursions permitted to 15°C to 30°C (59°F to 86°F), not exceeding 30°C.

Stability

The freeze-dried powder is stable for 3 years at room temperature protected from light.

Reconstituted solution: in 5% Dextrose or Water for Injection in the original vial, the solution may be stored for up to 24 hours between 2□C to 8□ C (36□F-46□F). Infusion solution: after dilution in 250-500 ml 5% Dextrose in Water, the shelf life is 24 hours at 2□C to 8□C (36□F-46□F) or 6 hours at room temperature (20-25 degrees Celsius).

Route of Administration

Intravenous.

Availability

Commercially available.

9.3 <u>5-Fluorouricil (5-FU)</u>

Classification: Antimetabolite

Molecular Formula: C4H3FN2O2

Mode Of Action

Fluorouracil is a pyrimidine antagonist that interferes with nucleic acid biosynthesis. The deoxyribonucleic acid of the drug inhibits thymidylatesynthetase, thus inhibiting the formation of the thymidylic acid form deoxyridylic acid, thus interfering in the synthesis in the synthesis of DNA. It also interferes with RNA synthesis.

Storage and Stability

Stable for prolonged periods of time (7 days at 37 °C, several weeks at 25 °C, at least 4 months at 0-4 °C) if protected from light. Inspect for precipitate; if apparent, agitate vial vigorously or gently heat to not greater than 140 □F in a water bath. Do not allow to freeze.

Handling and Disposal

Procedures for the handling and disposal of anticancer drugs should be considered. Several guidelines on the subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Route of Administration

Intravenous.

Warnings

The daily dose of fluorouracil is not to exceed 800 mg.

Fluorouracil should be used with extreme caution in poor risk patients with history of high-dose

pelvic irradiation or previous use of alkylating agents, those who have a widespread involvement of bone marrow by metastatic tumors or those with impaired hepatic or renal function.

Rarely, unexpected, severe toxicity (e.g., stomatitis, diarrhea, neutropenia and neurotoxicity) associated with 5-fluorouracil and despite 5-fluorouracil dose lowering, toxicity recurred and progressed with worse morbidity. Absence of the dihydropyrimidine dehydrogenase enzyme appears to result in prolonged clearance of 5-fluorouracil.

Availability

Commercially available in 500 mg/10 ml ampules and vials, and 1 gm/20 ml, 2.5 gm/50 ml, and 5 gm/100 ml vials.

9.4 <u>Leucovorin</u>

Classification

Tetrahydrofolic acid derivative

Molecular Formula: C20H23N7O7

Mode of Action

Leucovorin acts as a biochemical cofactor for 1-carbon transfer reactions in the synthesis of purines and pyrimidines. Leucovorin does not require the enzyme dihydrofolatereluctase (DHFR) for conversion to tetrahydrofolic acid. The effects of methotrexate and other DHFR-antagonists are inhibited by leucovorin.

Leucovorin can potentiate the cytotoxic effects of fluorinated polymerades (i.e., fluorouracil and floxuridine). After 5-FU is activated within the cell, it is accompanied by a folateconfactor, and inhibits the enzyme thymadylatesynthetase, thus inhibiting pyrimidine synthesis. Leucovorin increases the folste pool, thereby increasing the binding of folate cofactor and active 5-FU with thymidylatesynthetase.

Storage and Stability

All dosage forms are stored at room temperature. The reconstituted parenteral solution, 10 mg/ml, is stable for at least 7 days at room temperature. At concentrations of 0.5-0.9 mg/ml the drug is chemically stable for at least 24 hours at room temperature under normal laboratory light.

Preparation

The 50 and 100-mg vials for injection are reconstituted with 5 and 10 ml of sterile water or bacteriostatic water, respectively, resulting in a 10-mg/ml solution. The 350-mg vial is reconstituted with 17-ml sterile water resulting in a 20-mg/ml solution.

Administration

Intravenous

Compatibilities

Leucovorin (0.5-0.9 mg/ml) is chemically stable for at least 24 hours in normal saline, 5% dextrose, 10% dextrose, Ringer's injection or lactated Ringer's injection. Leucovorin (0.03, 0.24, and 0.96 mg/ml) is stable for 48 hours at room and refrigeration temperatures when admixed with floxuridine (FUDR, 1, 2 and 4 mg/ml) in normal saline. Leucovorin is also compatible with fluorouracil.

Availability

Commercially available as a tablet (5, 10, 15, 25 mg), cryodessicated powder for oral solution, and in parenteral formulations (3 and 5 mg ampule; 50 mg, 100 mg and 350 mg vial).

10.0 CORRELATIVE / SPECIAL STUDIES

10.1 Use of tumor blocks

Blocks of archived formalin fixed paraffin embedded pancreatic cancer tissues of each patient (if available) will be sent to Dr. Dimitrios Iliopoulos' Laboratory at the following address:

Dimitrios Iliopoulos Ph.D
Institute of Molecular Medicine (IMED)
David Geffen School of Medicine
UCLA
650 Charles E.Young Drive South
Los Angeles, CA 90025-7278

If paraffin block embedded is not available, unstained slides could be sent (preferably about 25 slides).
The following markers will be examined:

Insulin Receptor (IR):
We will examine expression of ***Insulin receptor(IR)***by Immunohistochemistry (IHC) in archived formalin fixed, paraffin embedded pancreatic cancer tissue. IR is believed to mediate insulin action on pancreatic tissue. The expression of IR will be indicative of the capacity of tumor cells to respond to indirect (insulin dependent) effects of metformin (Figure 1, page 55).

LKB1:
We will examine expression of LKB1 by IHC in archived formalin fixed, paraffin embedded pancreatic cancer tissue. LKB1 is a primary upstream kinase of AMPK. LKB1 expression is key to the ability of metformin to affect AMPK activity within tumors and to suppress the growth-promoting outputs of this signaling pathway. LKB1expression will be indicative of the capacity of tumor cells to respond to direct effects of metformin (Figure 1, page 55).

Phosphoantibody Markers of Activation of Key Signaling Pathways:
The expression of IR and LKB1willbe indicative of the capacity of tumor cells to respond to indirect and direct effects of metformin respectively. However, the expression of these factors cannot distinguish whether the downstream pathways are actually activated.

Therefore, we will also evaluate by IHC activation markers of these pathways **(P-IRS-1, P-AKT, 4E-BP1)** in the archived formalin fixed, paraffin embedded pancreatic cancer tissue as predictors of metformin benefit (Figure 1, page 55).

mRNA expression levels of inflammatory markers and lipid metabolism markers

RNA will be extracted from the archived formalin pancreatic cancer tissues and we will examine the mRNA expression levels of inflammatory markers ***(interleukin 6 and STAT3)***by real-time PCR analysis, in order to evaluate the activation of inflammatory signaling pathway. Furthermore, in the same tissues we will examine STAT3 phosphorylation status (Tyr705) by Immunohistochemistry.

Also,mRNA expression levels of Lipid metabolism markers ***(SREBP1c, ACC1, FAS)*** will be examined by real-time PCR analysis, in order to evaluate the activation of lipid metabolism signaling pathways (metformin was shown to inhibit some lipid metabolism factors that are implicated in the pathogenesis of insulin resistance, dyslipidemia and diabetes) (15).

10.2 Use of Blood Samples

The following blood samples will be drawn from patients on day 1 of treatment (or within 1 week prior to the metformin introductory period) and after the first 4 cycles of treatment (except for fasting glucose and CA 19-9 levels which will be drawn after every 4 cycles).

- 1 red yellow tube (4 ml) for fasting Glucose
- 1 red yellow tube (4 ml) for CA 19-9
- 1 lavender (EDTA) tube (4ml) for insulin and IGF-1
- 1 lavender (EDTA) tube (4ml) for inflammatory markers
- 1 lavender (EDTA) tube (4ml) for lipid metabolism markers
- 1 lavender (EDTA) tube (4 ml) for micro RNA panel

Blood from all lavender tubes will spun and the plasma will be stored in a freezer maintained at -80°C. Subsequently, the samples will be shipped frozen (in batches) on dry ice to Dr. Dimitrios Iliopoulos laboratory at the address mentioned in section 10.1.

The red yellow tubes (fasting glucose and CA 19-9) will be sent directly to the labs at University Hospitals or CCF.

Glucose, Insulin and IGF1:

Levels of glucose, insulin and IGF1 will be measured in blood on day 1 of treatment (or within 1 week prior to the metformin introductory period) and afterthe first 4 cycles of treatment (fasting glucose will be measured every 4 cycles).

The purpose of these tests is to assess if baseline glucose, insulin and IGF1 levels predict metformin benefit and if the change in these levels after treatment correlate with any metformin benefit.

Inflammatory markers and lipid metabolism markers:

Levels of Interleukin 6, STAT3, LEPTIN, SREBP1c, ACC1 and FAS mRNA levelswill be assessed by real-time PCR analysis in blood samples derived from day 1 of treatment (or within 1 week prior to the metformin introductory period) and after the first 4 cycles of mFOLFOX6.

The purpose of these tests is to assess if baseline levels predict metformin benefit and if the change in these levels after treatment correlate with any metformin benefit.

microRNA panel
As mentioned in section 1.2, Dr. Iliopoulos and his team identified a microRNA panel that was highly associated with pancreatic cancel cells survival. Therefore, we are planning to assess the expression levels of the microRNA panel by real-time PCR analysis in blood samples derived from day 1 of treatment (or within 1 week prior to the metformin introductory period) and after the first 4 cycles of treatment.

CA 19-9
CA 19-9 Level will be measured in blood on day 1 of treatment (or within 1 week prior to the metformin introductory period) and then every 4 cycles of treatment.
CA 19-9 is a tumor marker that is usually elevated in patients with pancreatic cancer.
The purpose of this test is to assess if CA 19-9 levels at baseline and after treatment correlate with metformin benefit.

10.3 All specimens' information will be logged into the OnCore database, then de-identified using a code specific for this trial.

10.4 The above biomarkers will be compared between patients who respond and do not respond using an exact Wilcoxon rank-sum test. Their relationship to time to-event outcomes (OS and PFS) will be examined using the Cox proportional hazards model. Due to small sample sizes, these analyses will be exploratory.

11.0 STUDY PARAMETERS AND CALENDAR

11.1 Study Parameters

11.1.1 Screening(baseline) Evaluation

Screening studies and evaluations will be used to determine the eligibility of each subject for study inclusion.Screening evaluations are to be conducted within 1 week prior to administration of protocol therapy. Scans, x-rays, EKG and echo must be done within 4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

The followings should be obtained at baseline:

- Informed Consent
- Demographics
- Medical History
- Complete physical examination
- Height
- Weight
- Vital signs
- Concomitant Medications Assessment

- **ECOG** Performance Status
- Baseline Symptoms Assessment
- Laboratory Studies:
    - Complete Blood Count (CBC) with differentialand platelets
    - Comprehensive metabolic panel
    - Calculated creatinine clearance will be done if creatinine and/or BUN are abnormal.
    - ß-HCG for women of childbearing potential
- ECG
- Radiographic tumor assessment.

11.1.2 Treatment Period

Within 1 week prior to "metformin introductory period" or on day 1 of this period:

- **Correlative Studies:**
  CA19-9, fasting glucose and insulin levels in addition to Interleukin 6, STAT3, LEPTIN, IGF1, SREBP1c, ACC1, FAS mRNA levels and the expression levels of the microRNA panel (in blood).

The followings need to be repeated only if screening evaluations were conducted > 1 week prior to administration of protocol therapy (prior to the metformin introductory period).

- Physical Examination (may be performed up to 6 days prior to day 1)
- Weight
- Vital signs
- Concomitant Medications Assessment
- ECOG Performance Status
- Baseline Symptoms Assessment
- Complete Blood Count (CBC) with differential and platelets
- Comprehensive metabolic panel
- Calculated creatinine clearance will be done if creatinine and/or BUN are abnormal.

After the " metformin introductory period" (see section 6.1), treatment will begin in 2-week cycles.

Cycle 1, Day 1

- mFOLFOX 6 administration
- Continue metformin administration

Cycle 1, Day 2-14

- Metformin administration

Day 1 of every following cycle

- Physical Examination
- Weight
- Vital signs
- Concomitant medications assessment
- Toxicity assessment
- **Laboratory Studies (could be done one day prior to treatment):**
    - Complete Blood Count (CBC) with differential and platelets
    - Comprehensive metabolic panel
    - Calculated creatinine clearance will be done if creatinine and/or BUN are abnormal.
- mFOLFOX 6 administration
- Metformin administration

Day 2-14 of every following cycle

- Metformin administration

Every 4 cycles:

- Radiographic tumor assessment.
- Correlatives (Insluin, Interleukin 6, STAT3, LEPTIN, IGF1, SREBP1c, ACC1, FAS mRNA levels and the expression levels of the microRNA panel) will be sent once after the first 4 cycles (day 1 of cycle 5).
- Fasting glucose levels and CA 19-9 levels will be sent every 4 cycles.

<u>End of treatment:</u>

- Physical exam.
- Weight and vital signs including blood pressure, pulse, respiratory rate, and temperature.
- ECOG Performance Status
- Toxicity Evaluation. Treatment-related AEs will be followed until resolved.
- Documentation of all concomitant medications and procedures.
- CBC and comprehensive metabolic panel
- Radiographic tumor assessment (if not done within the last 4 weeks)
- If patient went off study before 4 cycles of mFOLFOX6 but received at least 2 cycles, the following correlatives (CA19-9, glucose and insulin levels in addition to Interleukin 6, STAT3, LEPTIN, IGF1, SREBP1c, ACC1, FAS mRNA levels and the expression levels of the microRNA panel) will be sent .

11.2 Calendar

Study Days	Pre-Study	Metformin introductory period	Cycle 1 Day 1	Cycle 1 Day 2-14	Cycle 2 + ongoing Cycles, Day 1	Cycle 2 + ongoing cycles Day 2-14	End of treatment
REQUIRED ASSESSMENTS							
Informed Consent	X						
Demographics	X						
Medical History	X						
Height	X						
Weight		X[1]	X		X		X
Vitals		X[1]	X		X		X
Physical Examination		X[1]	X		X		X
Concomitant Med Assessment		X[1]	X		X		X
ECOG PS		X[1]	X		X		X
Baseline Symptoms		X[1]	X				
Adverse Event Assessment		X[1]	X	X	X	X	X
ECG	X[2]						
CBC / diff / platelets		X[1]			X		X
Serum CMP[3]		X[1]			X		X
ß-HCG (women of childbearing potential)	X[2]						
DISEASE ASSESSMENT							
Tumor Measurements by radiologic evaluation (metformin must be discontinued at the time of or prior to any contrast scan and withheld for 48 hours subsequent to the scan.	X[2]				Tumor measurements are repeated every 4 cycles. Documentation (radiologic) must be provided for patient removed from study for progressive disease.		
TREATMENT							
mFOLFOX6 administration			X		X		
Metformin		X	X	X	X	X	
CORRELATIVES							
Correlative studies on archived formalin fixed, paraffin embedded pancreatic cancer tissue: 1) Examine the expression of (IR)and LKB1 2) Evaluate the expression of (P-IRS-1, P-AKT, 4E-BP1) 3) Examine the mRNA expression levels of interleukin 6 and STAT3 transcription factor by real-time PCR analysis.	X[4]						
Correlative studies from the blood: CA19-9, fasting glucose and insulin levels in addition to Interleukin 6,					Day 1 of cycle 5 and		

STAT3, LEPTIN, IGF1, SREBP1c, ACC1, FAS mRNA levels and the expression levels of the microRNA panel	X[4,5]				then for CA19-9 and glucose only every 4 cycles.		
MISC ITEMS							
Pill diary		X	X	X	X	X	

1 Within 1 week of starting treatment (if done prior to 1 week of starting treatment, they need to be repeated within 1 week of or day 1 of metformin introductory period).

2 Within4 weeks prior to first treatment

3 Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.

4 These should be done on day 1 of metformin introductory period or before starting treatment once patient is deemed eligible for the study and officially enrolled.

5 Diabetics patients will be asked to monitor their glucose at home through a glucometer twice weekly at least.

6 Physical examination may be performed up to 6 days before day 1 of each cycle.

12.0 MEASUREMENT OF EFFECT

12.1 Antitumor Effect

For the purposes of this study, patients should be re-evaluated for response every4 cycles of treatment..

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) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria. For primary brain tumors, response and progression will be evaluated using the RANO criteria [*J ClinOncol* 28: 1963-1972.2010].

12.1.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment.

Evaluable for objective response:Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable, but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

12.1.2 Disease Parameters

Measurable Disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter for non-nodal lesions and short axis for nodal lesions to be recorded) as $\geq$ 20 mm by chest x-ray, as $\geq$ 10 mm with CT scan, or $\geq$ 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be $\geq$ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no grater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI) are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'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.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance; the next largest lesion, which can be measured reproducible, should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.1.3 **Methods for Evaluation of Measurable Disease**

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged, but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

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

Conventional CT and MRI:These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. 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. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. 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-holding techniques, if possible.

UltrasoundUltrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J ClinOncol* 17, 3461-3467, 1999; *J ClinOncol* 26: 1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors where known residual benign tumors can remain).

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.

12.1.4 Response Criteria

12.1.4.1 *Evaluation of Target lesions*

Response	Evaluation of Target Lesions
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. **Note**: the appearance of one or more new lesions is also considered progression.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

12.1.4.2 Evaluation of Non-Target lesions

Response	Evaluation of Non-Target Lesions
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis). **Note:** If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

[Incompleteresponse/ StableDisease (SD)]	
Progressive Disease (PD)	Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Although a clear progression of 'non-target' lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.1.4.2 *Evaluation of Best Overall Response*

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

For Patients with Measurable Disease (i.e., Target Disease)

Target lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥ 4 wks. Confirmation **
CR	Non-CR/Non-PD	No	PR	≥ 4 wks. Confirmation **
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥ 4 wks from baseline **
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD ***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesion	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD *
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.		

12.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started)
The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

13.0 RECORDS TO BE KEPT /REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

13.1 Data Reporting

The OnCore Database will be utilized, as required by the Case Comprehensive Cancer Center, to provide data collection for both accrual entry and trial data management. OnCore is a Clinical Trials Management System housed on secure servers maintained at Case Western Reserve University. OnCore properly used is compliant with Title 21 CFR Part 11. Access to data through OnCoreis restricted by user accounts and assigned roles. Once logged into the OnCore system with a user ID and password, OnCore defines roles for each user, which limits access to appropriate data. User information and password can be obtained by contacting the OnCore Administrator at oncore-registration@case.edu.

OnCore is designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. This study will utilize electronic Case Report Form completion in the OnCore database. A calendar of events and required forms are available in OnCore.

13.2 **Regulatory Considerations**

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

13.2.1 Written Informed consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject.

13.2.2 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

13.2.3 Accessing Electronic Medical Records for University Hospitals Health System and Cleveland Clinic Foundation

This study will access electronic medical records systems to obtain medical information for the subjects enrolled to this study.

In order to insure patient safety, investigators and study personnel must have up-to-the-minute health information for subjects enrolled to this study. Therefore, electronic medical records must be utilized to obtain medical information in a timely manner.

The following electronic systems will be used: IDX program to access scheduling information; UH Physician Portal to access lab results and physician notes;; COPATH to locate archived pathology records; PACS to access radiological imaging results; and MySecureCare (Sunrise Clinical Manager) to access some or all of the above information when this application is fully functional.
At the Cleveland Clinic Foundation, the EPIC EMR system will be used to access all required information.

Access to these systems is required for the life of this research study.

Information obtained from electronic systems will be copied into the SeidmanCancer Center Clinical Trials Unit research chart and/or printed (lab results, physician notes, etc.) and stored in the research chart. Research charts are kept secure and destroyed according to UH policy.

Study data will be obtained by the PI, co-investigators, study coordinator, and/or data manager for this study via password-protected login. The PI,Rami Manochakian, MD is a Case Western Reserve University employee with a University Hospitals email address and IT&S log on ID and Password. All study personnel involved in this research will adhere to the UH policies regarding confidentiality and Protected Health Information.

13.2.4 Retention of records

The Principal Investigator of The Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

13.2.5 Audits and inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the Center to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements.

13.2.6 Data Safety and Monitoring Plan

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI regulations.

14.0 STATISTICAL CONSIDERATIONS

14.1 Study design/Endpoints:

Primary endpoint: is the median overall survival (OS) defined by the time from first day of treatment to death from any cause. We hypothesize that metformin plus FOLFOX will result in a median overall survival of 10.2 months which is a 50% improvement compared to 6.8 months which is the median overall survival of patients with metastatic pancreatic cancer treated with gemcitabine (3).

Secondary endpoints:

1. Response rate (RR) Objective tumor response (partial response, complete response, stable disease or progressive disease) based on CT scans or MRI scans if patient is allergic to contrast agent or has some other contraindication to a CT scan. These will be evaluated according to RECIST criteria.

2. Progression free survival (PFS) defined by the time from first day of treatment received to the earlier documented disease progression or death from any cause. PFS will be determined by the investigator using RECIST 1.1 criteria
3. Toxicity evaluated through number of grade 3 and 4 toxicities according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE; Version 4.0) that occur after Cycle 1, day 1 in addition to the incidence, nature and severity of all adverse events that occur on or after Cycle 1, Day 1
4. Correlative studies (mentioned above)which will be exploratory.

14.2 Sample size/Accrual rate:

For a 1-sided test with type I error 0.10 assuming exponential distribution of survival to have 85% power to detect a difference of 6.8 vs. 10.2 months in median survival, 43 patients are required (27). Based on a projected accrual rate of 3-4 patients per month, we expect a 12-month accrual period.

14.3 Stratification factors:

N/A

14.4Statistical analysis of endpoints:

Overall survival (OS) will be calculated using Kaplan Meier methods and the median will be estimated assuming an exponential distribution (28).

Progression free survival (PFS) will also be calculated using Kaplan Meier methods and the median will be estimated assuming an exponential distribution (28).

The true response rate of the combination therapy for this patient population will be estimated based on the number of responses using a binomial distribution and its confidence intervals will be estimated using Wilson's method.

The toxicity profile of the combination therapy will be tabulated.

The correlative studies will be compared between patients who respond and do not respond using an exact Wilcoxon rank-sum test. Their relationship to time to-event outcomes (OS and PFS) will be examined using the Cox proportional hazards model. Due to small sample sizes, these analyses will be exploratory.

14.5 Reporting and exclusion:

14.5.1 **Evaluation of toxicity.**

All patients will be evaluable for toxicity from the time of their first treatment.

14.5.2 **Evaluation of response.**

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early

death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

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APPENDIX A

PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B
PATIENT PILL DIARY

Patient Name _____Patient Study ID _____Date ___/___/___
Drug ____Metformin_____Cycle #:_____

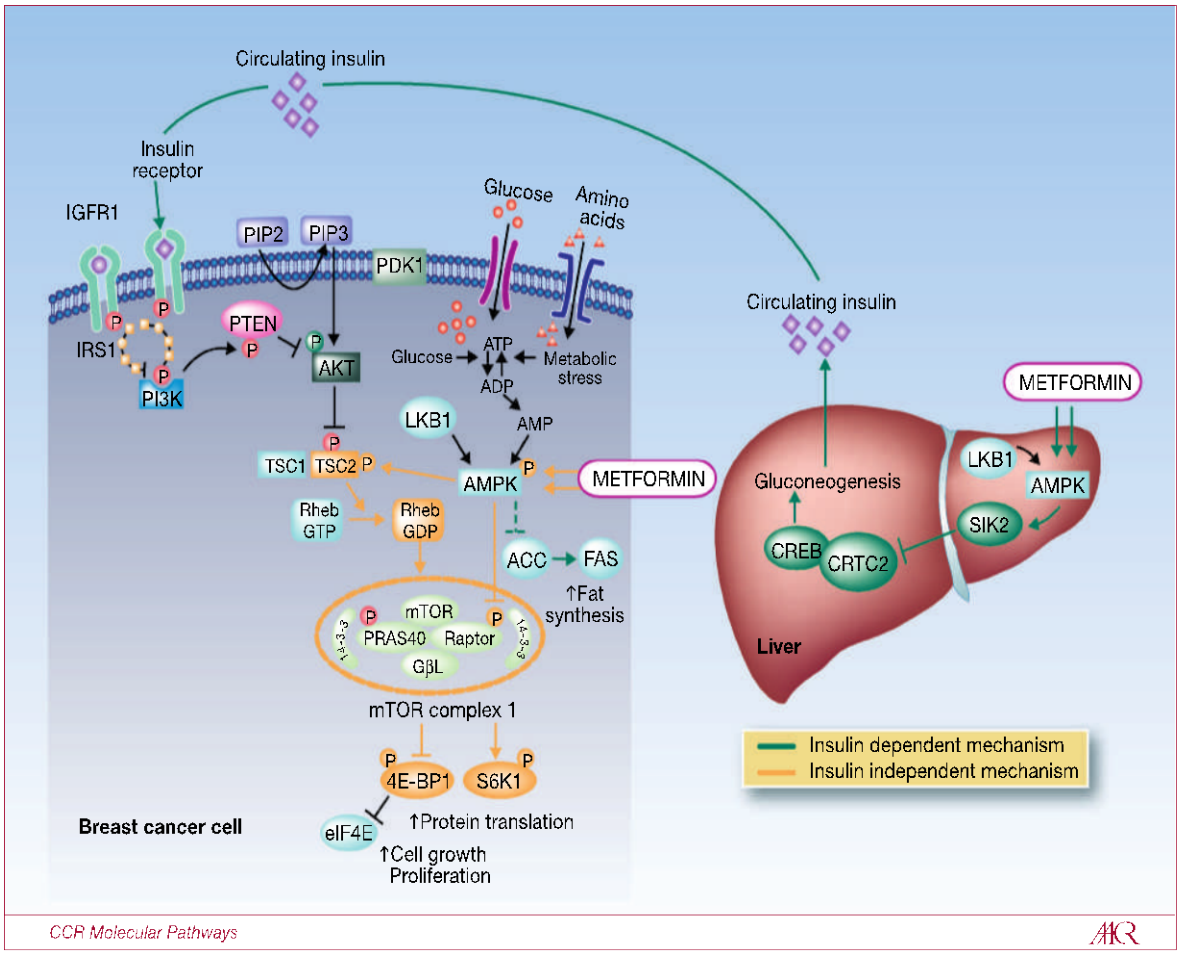
INSTRUCTIONS FOR THE PATIENT:
1. Days 1-4, take one 500 mg tablet twice daily, 12 hours apart
2. Days 5 – 7, take two 500 mg tablet twice daily, 12 hours apart.
3. From day 7 and forward take _____ tablet(s) twice daily with food, 12 hours apart.
4. Record the date, he time and the number of tablets that were taken.
5. Record any comments or side effects experienced in the comment column.
6. Bring medication and this pill diary to each appointment.

Day	Date	Time of AM dose	# of tablets <u>500 mg tablets</u>	Time of PM dose	# of tablets 500 mg tablets	Comments
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						

Patient signature_____Printed name_____
RN signature_____

Date_____

Figure 1



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