Phase I/II Study Combining Tosedostat with Capecitabine in Patients with Advanced or Metastatic Pancreatic Adenocarcinoma

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SCHEMA

Eligible Patients

- Histologically or cytologically confirmed pancreatic adenocarcinoma
- Metastatic or inoperable pancreatic adenocarcinoma
- Previously received a gemcitabine-based regimen
- Radiographically measurable or evaluable disease
- Eastern Cooperative Oncology Group (ECOG) performance status 0-2

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Treatment Plan

Phase I
Tosedostat daily(dosing schedule below) Days 1-21 with capecitabine 1000 mg/m^2 PO BID Days 1-14 of each 21-day cycle

Phase II
Tosedostat PO daily (dose determined during Phase I) Days 1-21 with capecitabine 1000 mg/m^2 PO BID Days 1-14 of each 21-day cycle

Patients to continue on treatment as long as the regimen is tolerated and the patient does not meet discontinuation criteria. Patient will be assessed with CT scans after every 2 cycles.

Dose De-Escalation Schedule		
Dose Level	**Tosedostat (PO daily) Days 1-21**	**Capecitabine (PO BID) Days 1-14**
Level 0 (Starting dose)	120 mg	1000 mg/m^2
Level -1	60 mg	

Glossary of Abbreviations

AE	Adverse event
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
B-HCG	Beta human chorionic gonadotropin
BID	Bis in die (twice a day)
BSC	Best supportive care
CBC	Complete blood count
CFR	Code of Federal Regulations
CIVI	Continuous IV infusion
CMP	Complete metabolic panel
CR	Complete response
CRF	Case report form
CRP	C-reactive protein
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DLTs	Dose Limiting Toxicities
DNA	deoxyribonucleic acid
DPD	Dihydropyrimidine dehydrogenase
DSM	Data and Safety Monitoring
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FWA	Federal wide assurance
HIV	Human Immunodeficiency Virus
HRPO	Human Research Protection Office (IRB)
IND	Investigational New Drug
IRB	Institutional Review Board
IULN	Institutional upper limit of normal
IV	Intravenous
KPS	Karnofsky performance score
LVEF	Left ventricular ejection fraction
MM	Multiple myeloma
mOS	Median overall survival
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose

MUGA	Multi-gated acquisition scan
NCCN	National Cancer Center Network
NCI	National Cancer Institute
NIH	National Institutes of Health
NSCLC	Non-small cell lung cancer
OHRP	Office of Human Research Protections
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PI	Principal investigator
PK	Pharmacokinetic
PO	Per os (by mouth)
PR	Partial response
QASMC	Quality Assurance and Safety Monitoring Committee
RECIST	Response Evaluation Criteria in Solid Tumors (Committee)
RNA	Ribonucleic acid
RP2D	Recommended phase II dose
rt-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
SCC	Siteman Cancer Center
SD	Stable disease
TTP	Time to progression
UPN	Unique patient number

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1.0 BACKGROUND AND RATIONALE

1.1 Metastatic Pancreatic Adenocarcinoma

Metastatic pancreatic adenocarcinoma has a dismal prognosis, with a median overall survival of less than one year (1). According to the American Cancer Society, there were an estimated 45,220 new cases of pancreatic cancer in 2013 with 38,460 deaths (1). Despite comprising only 3% of all new cancer diagnoses, pancreatic cancer remains the fourth most common cause of cancer death, and it is expected to rise to the second most common cause of death by 2030. Unfortunately, pancreatic cancers are typically diagnosed at advanced stages when the only available treatments are palliative; around 40% of patients are found to have metastatic disease at the time of diagnosis. Recent advances using combination chemotherapies have extended the overall survival (OS) of patients with metastatic disease, but only by about 6 months (to one year) (2), still making pancreatic adenocarcinoma one of the most deadly solid malignancies.

1.2 First-Line Therapy for Inoperable or Metastatic Pancreatic Adenocarcinoma

For over 40 years, until the approval of gemcitabine in 1997, fluorouracil-based chemotherapy was the mainstay of treatment for pancreatic adenocarcinoma despite mean survival rates of less than 6 months (3). Gemcitabine was approved after it was shown to be superior to 5-FU in terms of clinical benefit. In a randomized controlled trial (4), 126 patients with advanced pancreatic cancer were randomized to receive either gemcitabine at 1000 mg/m^2 weekly for 7 weeks followed by one week off, then on Days 1, 8, and 15 of a 28-day cycle, or weekly 5-FU at 600 mg/m^2. The primary endpoint in this trial was clinical benefit, which was defined by pain score, Karnofsky performance score (KPS), and body weight. Not only did patients receiving gemcitabine have a better clinical benefit rate (23.8% vs. 4.2%; p=0.0022), but gemcitabine-treated patients had a statistically better median overall survival (mOS) (5.65 vs. 4.41 months; p=0.0025) and overall one year survival rate (18% vs. 2%; p=0.0025).

Combining gemcitabine with nab-paclitaxel (nanoparticle albumin bound paclitaxel) improved overall survival compared to gemcitabine alone. In a phase III randomized, open-label, multicenter trial (MPACT), 861 untreated patients with metastatic pancreatic cancer were randomized to receive gemcitabine plus nab-paclitaxel or gemcitabine alone (5). mOS, progression-free survival (PFS), and tumor response rates were significantly improved in the combination group compared to gemcitabine alone (8.5 vs. 6.7 months, p<0.001; 5.5 vs. 3.7 months, p<0.001; 23% vs 7%, p<0.001, respectively).

In 2011, combination chemotherapy with drugs other than gemcitabine in metastatic pancreatic cancer also showed a meaningful survival benefit over single agent gemcitabine (2). The ACCORD phase II/III trial studied 342 patients with previously untreated metastatic pancreatic cancer who were randomized to receive FOLFIRINOX (14-day cycles of 5-FU at 400 mg/m^2 on Day 1 followed by 2400 mg/m^2 CIVI over 46 hours, leucovorin at 400 mg/m^2 on Day 1, irinotecan at 180 mg/m^2 on Day 1, and

oxaliplatin at 85 mg/m^2 on Day 1) or gemcitabine alone (1000 mg/m^2 given weekly for 7 weeks followed by one week off, then on Days 1, 8, and 15 of a 28-day cycle). Patients treated with FOLFIRINOX had a significantly improved mOS of 11.1 months compared with 6.8 months in the gemcitabine arm ($p<0.001$), as well as an improved PFS of 6.4 months compared to 3.3 months ($p<0.001$). A higher tumor response rate was seen in the FOLFIRINOX arm as well (31.6% vs 9.4%; $p<0.001$). FOLFIRINOX is now considered one of the standard first-line regimens for patients with metastatic pancreatic cancer and good performance status.

1.3 Second-line Therapy for Inoperable or Metastatic Pancreatic Adenocarcinoma

Despite the aggressive nature of pancreatic cancer, nearly half of the patients who have progressed on front-line therapy are able to receive second-line therapy. A fluorouracil-based regimen is currently recommended for patients who progress through a gemcitabine-based regimen. In a phase III clinical trial, patients who had progressed on a gemcitabine-based chemotherapy were randomized to receive folinic acid at 200 mg/m^2 5-FU at 2000 mg/m^2 as a continuous 24 hour infusion on Days 1, 8, 15, and 22, and oxaliplatin at 850 mg/m^2 on Days 8 and 22 of a 42-day cycle (OFF regimen), or best supportive care (BSC) (6). The study was terminated early due to low recruitment, but despite this, the OFF regimen showed a median survival of 4.82 versus 2.30 months ($p=0.008$) and a mOS survival benefit of 9.09 versus 7.90 months ($p=0.031$) in patients treated with OFF compared to BSC. However, recently the results of the CONKO-003 trial were published, which was a randomized, open-label phase III trial in which 168 patients with advanced pancreatic cancer who had progressed on gemcitabine were randomized to folinic acid and fluorouracil (FF) or oxaliplatin and FF (OFF) (7). Median overall survival was significantly longer in the OFF group compared to FF alone (5.9 versus 3.3 months, $p=0.010$). PFS was also extended in the OFF treatment arm compared to the FF arm (2.9 versus 2.0 months, $p=0.019$). Based on these trials, the National Comprehensive Cancer Network (NCCN) recommends fluoropyrimidine plus oxaliplatin as one of the second-line treatment options.

However, for patients who performance status is poor, a fluoropyrimidine alone is often given, either as infusional 5-FU or capecitabine, and it is considered to be a reasonable second line option endorsed by the NCCN. 5-FU is a fluorinated pyrimidine that acts as an antimetabolite antineoplastic agent. Capecitabine is an orally administered prodrug of 5'-deoxy-5-fluorouridine which generates 5-FU selectively in tumor cells, and so is often used instead of 5-FU given its ease of administration. Both are frequently used as the control group in the second-line setting in clinical trials. For example, three recent phase II and phase III trials have used capecitabine or 5-fluorouracil in combination with an investigational drug compared with capecitabine or 5-fluorouracil alone. A phase II randomized, double-blind, placebo-controlled trial of ruxolitinib, a JAK1/JAK2 inhibitor, in combination with capecitabine in patients with recurrent or metastatic pancreatic cancer (RECAP trial) showed improved OS in patients with an elevated C-reactive protein (CRP). The hazard ratio (HR) for OS in the intent to treat population was 0.79 [95% CI, 0.53-1.18; *P*=0.25 (2-sided)] and in the pre-specified subgroup analysis in

patients with an elevated CRP, the HR for OS was 0.47 (95% CI: 0.26-0.85; *P*=0.01 (2-sided)), with 6-month survival in the ruxolitinib arm of 42% vs. 11% in the placebo arm (8). And, as mentioned above, 5-FU was used as the control arm in the CONKO-003 trial. Finally, in a phase III trial of MM-398 (NAPOLI-1 trial), patients were randomized to receive MM-398, 5-FU, or combination therapy (9). Median OS was 6.1 months in the combination arm compared to 4.2 months in the 5-FU arm (HR 0.67, p=0.012).

1.4 Tosedostat

[redacted]

1.4 Study Rationale

Unresectable advanced or metastatic pancreatic adenocarcinoma is an incurable disease, with a mean overall survival of less than one year despite current available treatments. The two most common first-line chemotherapies for pancreatic adenocarcinoma are FOLFIRINOX (2) or gemcitabine plus nab-paclitaxel (5). However, most patients will progress on these regimens. Many patients cannot tolerate FOLFIRINOX due to significant adverse side effects, making gemcitabine plus nab-paclitaxel a frequent first-line choice. And although 5-FU and capecitabine have activity in pancreatic cancer, their use as a single agent generally only gives an overall survival benefit of a few months. Therefore, one treatment strategy is to improve the efficacy of capecitabine with an additional chemotherapeutic agent.

APN/CD13 is a zinc metalloprotease and has been investigated in pancreatic cancer (19). Reverse transcriptase polymerase chain reaction (rt-PCR) was performed on 50 tumor samples in patients who underwent pancreatectomy between 1992 and 1999, to quantify the expression of this gene in pancreatic cancer. Of the 50 tumors tested, 24 (48%) were positive by immunohistochemistry and 25 (50%) were positive for gene expression of *APN/CD13* by rt-PCR. There was a correlation between *APN/CD13* expression and overall survival. Patients whose tumors were positive for *APN/CD13* expression had a shorter overall survival than in patients whose tumors were negative, 9.5 versus 13.2 months respectively, p=0.0009). Multivariate analysis of the 50 patients showed that *APN/CD13* expression was a significant independent prognostic factor (p=0.016).

Given the evidence of possible upregulation of metalloproteases and their potential prognostic values in pancreatic cancer, the study rationale is to combine tosedostat with capecitabine, a standard second-line chemotherapy. We chose tosedostat at 120 mg daily as the first dose level for the following reasons. In the phase I study using tosedostat as a single agent, the MTD was determined to be 240 mg in patients with solid tumors (17). However, in patients with acute myeloid leukemia or multiple myeloma (20), the MTD

was determined to be 180 mg daily due to two cases of Grade 4 thrombocytopenia in patients who received 180 mg/day, and 130 mg was declared the maxiumum administered dose for phase II dosing. However, there were a number of cardiac events reported across the investigator sponsored trials, including atrial fibrillation, cardiac dysfunction, cardiac arrest and edema. An expert cardiology review panel concluded that events assessed as related to tosedostat may have been dose-related, as a greater proportion of the cardiac events were reported at the 180 mg dose than at the 120 mg dose. However, the panel noted that the pattern and diversity of the reported cardiac events might suggest exacerbations of underlying vulnerability, rather than primary drug toxicity. Because of the potential risk of cardiac toxicity, the maximum tosedostat dose will be 120 mg po daily.

Capecitabine is typically administered in combination with other chemotherapeutic drugs at a dose of 2000mg/m^2/day to 2500mg/m^2/day, and its dose-limiting toxicity is diarrhea. Because there is no signfiicant overlapping toxicites, we feel that the combination of tosedostat 120 mg daily and the lower dose of 1000 mg/m^2 BID capecitabine is a safe level to start.

1.5 Correlative Studies Background

Please refer to Section 9.2.

2.0 OBJECTIVES

2.1 Primary Objectives

1. Phase I: To determine the recommended phase II dose (RP2D) and dose-limiting toxicities (DLTs) of tosedostat and capecitabine combination therapy in patients with advanced or metastatic pancreatic cancer.
2. Phase II: To determine progression-free survival (PFS) rate at 3 months of tosedostat and capecitabine combination therapy in patients with advanced or metastatic pancreatic cancer.

2.2 Secondary Objectives

1. To determine the overall response rate (ORR) of patients with advanced or metastatic pancreatic cancer being treated with tosedostat and capecitabine combination therapy.
2. To determine the time-to-progression (TTP) of patients with advanced or metastatic pancreatic cancer being treated with tosedostat and capecitabine combination therapy.
3. To determine overall survival (OS) of patients with advanced or metastatic pancreatic cancer being treated with tosedostat and capecitabine combination therapy.
4. To determine CA19-9 response of patients with advanced or metastatic pancreatic cancer being treated with tosedostat and capecitabine combination therapy.

2.3 Exploratory Objectives

1. To explore the predictive molecular biomarkers for treatment response in patients with advanced or metastatic pancreatic cancer being treated with tosedostat and capecitabine combination therapy.
2. To explore the prognostic biomarkers for patients with advanced or metastatic pancreatic cancer receiving tosedostat and capecitabine combination therapy.
3. To correlate genetic alterations with response to treatment with combination tosedostat and capecitabine in patients with advanced or metastatic pancreatic cancer.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. Histologically or cytologically proven metastatic or inoperable pancreatic adenocarcinoma.

2. Measurable disease defined as lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$10 mm with CT scan or MRI, as $\geq$20 mm by chest x-ray, or $\geq$10 mm with calipers by clinical exam.

3. Must have progressed on, been intolerant to, or refused gemcitabine-based therapy.

4. At least 18 years of age.

5. ECOG performance status $\leq$ 2 (see Appendix A).

6. Normal bone marrow and organ function as defined below:
   a. Absolute neutrophil count $\geq$ 1,000/mcl
   b. Platelets $\geq$ 100,000/mcl
   c. Total bilirubin $\leq$ 2.0 mg/dL
   d. Creatinine $\leq$ 2.0 mg/dL
   e. AST or ALT $\leq$2.5 IULN ($\leq$5X IULN if liver metastases are present)

7. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

8. Able to understand and willing to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable).

3.2 Exclusion Criteria

1. Chemotherapy < 2 weeks prior to the first planned dose of study treatment.

2. Radiotherapy < 3 weeks prior to the first planned dose of study treatment.

3. A history of other malignancy ≤ 2 years previous with the exception of basal cell or squamous cell carcinoma of the skin which were treated with local resection only or carcinoma *in situ* of the cervix.

4. Currently receiving any other investigational agents.

5. Known brain metastases. Patients with known brain metastases must 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.

6. A history of allergic reactions attributed to compounds of similar chemical or biologic composition to tosedostat or capecitabine or other agents used in the study.

7. Previous treatment with any aminopeptidase inhibitor.

8. Previous exposure to either 5-FU or capecitabine at a systemic dose except for use in concurrent chemoradiation.

9. Known dihydropyrimidine dehydrogenase (DPD) deficiency or severe renal impairment (creatinine clearance < 30 mL/min by Cockcroft-Gault formula), as this would preclude use of capecitabine.

10. Significant cardiovascular disease defined as:
    a. Myocardial infarction within 6 months of screening.
    b. Unstable angina pectoris
    c. Uncontrolled or clinically significant arrhythmia Grade ≥ 2
    d. LVEF below institutional limits at screening
    e. Congestive heart failure NYHA class III or IV
    f. Presence of clinically significant valvular heart disease

11. Baseline troponin I or T> IULN and b-type natriuretic peptide > IULN.

12. Prior exposure to cardiotoxic agent, such as anthracyclines, within 3 months of enrollment.

13. Patient must have a QTc interval on ECG ≤ 0.48 seconds by Bazett's calculation at screening.

14. Patient may not be taking any drugs that prolong the QT/QTc interval (see Appendix C). If patient is on any of these drugs, patient may enroll in the study if the drugs can be discontinued for at least 5 half-lives prior to the first dose of tosedostat and capecitabine.

15. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection or psychiatric illness/social situations that would limit compliance with study requirements.

16. Pregnant and/or breastfeeding. Patients that are of childbearing age must have a negative pregnancy test at screening and agree on using contraception during the duration of the study.

17. Known HIV-positivity on combination antiretroviral therapy because of the potential for pharmacokinetic interactions with tosedostat or capecitabine. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.3 Inclusion of Women and Minorities

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

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center OnCore database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

5.0 TREATMENT PLAN

This is a single institution phase I/II study combining tosedostat, an aminopeptidase inhibitor, with capecitabine. The study aims to determine the recommended phase 2 dose (RP2D) of tosedostat when given with a standard dose of capecitabine (1000 mg/m^2 BID) and to evaluate the preliminary efficacy of tosedostat and capecitabine combination therapy in advanced or metastatic pancreatic adenocarcinoma.

The phase I study will be conducted in a standard 6-patient-per-cohort dose de-escalation fashion. For the phase II part of the study, the primary endpoint of the study is to assess the progression-free survival (PFS) of the combination therapy. The dose of tosedostat used in phase II of this study will be determined during the phase I dose de-escalation portion.

5.1 Premedication Administration

No premedications are required for either capecitabine or tosedostat. Anti-nausea medications can be used as per the treating physician's discretion.

5.2 Agent Administration

Tosedostat is an oral drug which will be taken on an outpatient basis daily on a 21-day cycle. Patients should take tosedostat at approximately the same time every day (preferably morning) with a glass of water after food. If a patient misses a dose by more than 6 hours, the patient should be instructed not to take or make up that dose and to resume dosing with the next scheduled dose. Patients will be instructed to bring all unused drug and their medication diary (Appendix B) to each study visit for assessment of compliance. Dosing of tosedostat during phase I will be as described in Section 5.4. Dosing of tosedostat during phase II will be the dose determined during phase I.

Capecitabine is an oral drug which will be taken on an outpatient basis at a dose of 1000 mg/m^2 twice a day on Days 1 through 14 of a 21-day cycle. The tablets are to be swallowed with water and taken 30 minutes after the end of a meal. If the patient vomits or misses a dose by more than 2 hours, s/he must not take the missed dose and must not double the next dose. Instead, s/he should continue with the dosing as scheduled.

Patients will be instructed to bring all unused tablets and medication diary (Appendix B) to each study visit for assessment of compliance.

5.3 Dose De-Escalation Schema

Dose Escalation Schedule		
Dose Level	**Tosedostat (PO daily) Days 1-21**	**Capecitabine (PO BID) Days 1-14**
Level 0 (Starting dose)	120 mg	1000 mg/m^2
Level -1	60 mg	

5.4 Phase II Treatment Plan

Once the RP2D is determined, additional patients will be enrolled for a total of 36 evaluable patients (the patients from the RP2D level of phase I will be included in this group).

5.5 Definition of RP2D, DLT, Dose De-Escalation Criteria, and Toxicity, Response, and DLT Evaluations

5.5.1 Definition of Recommended Phase 2 Dose (RP2D)

The recommended phase 2 dose (RP2D) is defined as the dose level immediately below the dose level at which 2 patients of a cohort (of 2 to 6 patients) experience dose-limiting toxicity during the first cycle. If 0 or 1 of 6 patients in Dose Level 1 experience DLT during the first cycle, Dose Level 1 will be presumed to be the RP2D.

5.5.2 Dose Limiting Toxicities (DLTs)

Hematologic DLT is defined as any of the following that occur during the first cycle that are attributed as possibly, probably, or definitely related to the study treatment:

- Grade 4 neutropenia > 7 day duration
- Febrile neutropenia of any duration with temperature ≥ 38.5 °C
- Grade 4 anemia which requires transfusion therapy on more than two occasions in 7 days
- Grade 4 thrombocytopenia

Non-hematologic DLT is defined as any possibly, probably, or definitely related grade 3 or grade 4 non-hematologic toxicity that occurs during the first cycle with the following specific EXCEPTIONS:

- Grade 3 nausea, vomiting, diarrhea, or anorexia lasting no more than 72 hours that returns to Grade 1 prior to the start of Cycle 2
- Grade 3 hand-foot syndrome will only be considered a DLT for patients who have received one week of supportive care treatment with no

improvement
- Grade 3 fatigue that returns to Grade 1 prior to the start of Cycle 2
- Grade 3 flu-like symptoms lasting no more than 72 hours that returns to Grade 1 prior to start of Cycle 2
- Grade 3 arthralgia or myalgias lasting no more than 72 hours that return to Grade 1 prior to the start of Cycle 2
- Grade 3 potassium, phosphorus, or magnesium that is asymptomatic or of non-clinical significance lasting no more than 72 hours
- Grade 3 hypoalbuminemia

5.5.3 Dose De-Escalation Criteria

Dose de-escalations will proceed as follows after the occurrence of dose-limiting toxicity (DLT):

Number of Patients with DLT at a Given Dose Level	**De-Escalation Decision Rule**
0 or 1 out of 6	If Dose Level 0: If 0-1 patients experience a DLT move to the phase II portion at Dose Level 0. If Dose Level -1: If 0-1 patients experience a DLT, move to the phase II portion at Dose Level -1
≥ 2 out of 6	Dosing at this dose level will be stopped and 6 additional patients will be entered at the next lowest dose level, if available.

5.5.4 Toxicity, Response, and DLT Evaluations

All patients who receive any study treatment are evaluable for toxicity. Patients are evaluated from first receiving study treatment until a 30-day follow up after the conclusion of treatment or death.

All patients are evaluable for disease response unless they come off study due to treatment related adverse events(s) prior to completion of Cycle 2 and have not had any disease assessment.

A patient is evaluable for DLT assessment only if enrolled in the phase I portion and only during Cycle 1 of treatment. If the patient is not able to be treated on Day 1 of Cycle 2, then s/he is still considered in Cycle 1 active treatment and can experience a DLT. Once the patient has been treated in Cycle 2, s/he will no longer be evaluated for DLTs in all subsequent cycles.

5.6 General Concomitant Medication and Supportive Care Guidelines

Currently available *in vitro* data suggest that tosedostat may be a moderate inhibitor of selected catalytic activities of CYP3A4. Therefore, it may participate in or contribute to inhibitory drug-drug interactions *in vivo*, which are mediated by CYP3A4. Drugs that are known to be substrates for CYP3A4 include acetaminophen, carbamazepine, cyclosporin, digitoxin, diazepam, erythromycin, felodipine, fluoxetine, nifedipine, quinidine, saquinavir, triazolam, verapamil and warfarin. It is not expected, however, that tosedostat will reach sufficiently high, prolonged concentrations to significantly impact the metabolism of such drugs. Concomitant use of these drugs should be done with caution.

Due to the potential risk of cardiotoxicity, concomitant use of drugs that prolong the QT/QTc interval are prohibited (see Appendix C).

Due to the thrombocytopenic effects of capecitabine, an additive risk of bleeding may be seen in patients receiving concomitant anticoagulants and should be avoided. The manufacturer labeling for capecitabine includes a black box warning regarding concomitant use with warfarin. Administration of capecitabine concomitantly with Coumadin-derivative anticoagulants has resulted in prolonged coagulation parameters and/or bleeding; deaths have been reported. The interaction with warfarin is probably due to an inhibition of cytochrome P450 2C9 by capecitabine and/or its metabolites. If capecitabine is used with warfarin, close monitoring of the INR is necessary as dose adjustments may be necessary. If a patient is on enoxaparin or other anticoagulants, NSAIDs, or aspirin, use cautiously and discontinue with any bleeding episodes or if patient becomes thrombocytopenic.

Caution is advised when capecitabine is combined with phenytoin or fosphenytoin. Increased phenytoin plasma concentrations have been reported during concomitant use of phenytoin and capecitabine. Increased phenytoin plasma concentrations may be due to inhibition of cytochrome P450 2C9 by capecitabine and/or its metabolites. Patients taking phenytoin or fosphenytoin concurrently with capecitabine should be monitored for increased phenytoin plasma concentrations and associated clinical symptoms of phenytoin toxicity such as nystagmus, diplopia, ataxia, and confusion. A reduction in the phenytoin dosage may be required in some patients receiving concomitant capecitabine.

Patients should receive full supportive care during the study, including transfusion of blood and blood products, treatment with antibiotics, analgesics, erythropoietin, or bisphosphonates as appropriate. Anti-emetics (such as prochlorperazine, lorazepam, or other 5-HT3 antagonists) may be administered prophylactically in the event of nausea. Anti-diarrheals, such as loperamide, may be administered as needed in the event of diarrhea.

5.7 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with

amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative pregnancy test within 14 days prior to the first doses of tosedostat and capecitabine.

Female and male patients (along with their female partners) are required to use two forms of acceptable contraception, including one barrier method, during participation in the study and for 3 months following the last dose of either study drug.

If a patient is suspected to be pregnant, study treatment should be immediately discontinued. In addition a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a female patient or female partner of a male patient becomes pregnant during therapy or within 3 months after the last dose of either study drug, the investigator must be notified in order to facilitate outcome follow-up.

5.8 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

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

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious non-compliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will be followed as indicated in the study calendar.

5.9 Duration of Follow-up

Patients will be followed every 3 months for 1 year or until death, whichever occurs first.

Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

6.0 DOSE DELAYS/DOSE MODIFICATIONS

6.1 Tosedostat Dose Reduction Table

Starting Dose	120 mg po daily
Dose Level -1	60 mg po daily

Patients will be monitored for toxicity and the dose of tosedostat may be adjusted. Dose reduction by one dose level will be allowed. Patients requiring more than one dose reduction will be discontinued from the study.

Recommended dose reductions for tosedostat are to decrease the current dose by 60 mg. The lowest dose available is 60 mg. Doses may be held as needed for toxicity resolution during a cycle. Doses omitted for toxicity are not replaced or restored within the same cycle (meaning that the cycle remains 21 days regardless of the number of doses of taken). If a patient experiences toxicity which has not resolved to grade 2 or lower within two weeks, treatment with tosedostat should be permanently discontinued.

6.1.1 Cardiac Toxicity

Ejection Fraction Grade	**Occurrence**	**Tosedostat**
Grade 2*	1st	Hold Tosedostat and repeat ECHO. • Hold drug until LVEF is less than or equal to 9% points of baseline and resume at the current dose. • If LVEF is below institutional normal limit, please hold the study drug
	2nd	Hold Tosedostat and repeat ECHO. • Hold drug until LVEF is less than or equal to 9% points of baseline and resume at the next lower dose. • If LVEF is below institutional normal limit, please hold the study drug
	3rd and beyond	Hold Tosedostat and repeat ECHO. • If LVEF is above institutional normal limits: Hold drug until LVEF is less than or equal to 9% points of baseline and resume at the same dose. • If LVEF is below institutional normal limits: Discontinue
Grade 3	Any	Discontinue

*Per the PI's discretion, patients may be referred to Cardiology for a second opinion.

6.1.2 Hematologic Toxicity

ANC must be ≥ 1,000 cells/µl and platelet count must be ≥75,000 cells/µl at the start of each cycle.

Grade	Occurrence	Tosedostat
Neutrophils		
Grade ≤2	Any	Current dose
Grade 3	Any	Hold till ANC≥1,000, resume the current dose
Grade 4	1st	Hold till ANC≥1,000, resume the next lower dose
Grade 4	2nd	Discontinue
Platelets		
Grade ≤1	Any	Current dose
Grade 2	Any	Hold till platelets ≥75,000, resume the current dose level
Grade 3	Any	Hold till platelets ≥75,000, resume the next lower dose
Grade 4	1st	Hold till platelets ≥75,000, resume the next lower dose
	2nd	Discontinue
Febrile neutropenia		
Grade 3	1st	Hold till ANC≥1,000, resume the next lower dose
	2nd	Discontinue

The patient will be taken off the trial if more dose reductions are called for than are allowed.

6.1.3 Other Nonhematologic Toxicities Reasonably Related to Treatment

Grade	Occurrence	Tosedostat
Grade 1	Any	Current dose
Grade 2*	1st	Hold until ≤ grade 1, then resume at the current dose
	2nd	Hold until ≤ grade 1, then resume at the next lower dose
	3rd	Discontinue
Grade 3*	1st	Hold until ≤ grade 1, then resume the next lower dose
	2nd	Hold until ≤ grade 1, then resume the next lower dose
	3rd	Discontinue
Grade 4*	1st	Hold until ≤ grade 1, then resume the next lower dose

	2nd	Discontinue

*Based off occurrence of the same repeating toxicity

Patients will be taken off the study if their treatment has to be held for more than 4 weeks for any reason.

6.2 Capecitabine Dose Reduction Table

Starting Dose	1000 mg/m^2 BID
Dose Level -1	750 mg/m^2 BID
Dose Level -2	500 mg/m^2 BID

Reductions table is for AE's that are deemed related to capecitabine. Once dosing for capecitabine has been reduced, it should not be increased at a later time. Doses of capecitabine that are omitted for toxicity should not be replaced or restored; the patient should simply resume his/her planned treatment cycle. If capecitabine is held for longer than 2 weeks within one cycle, treatment must be permanently discontinued and the patient should come off study. Dose modifications should be based on the same AE occurrence.

Grade	**Occurrence**	**Action During Course**	**Dose Adjustment for Next Treatment (% of starting dose)**
Grade 1	Any	Maintain dose level	Maintain dose level
Grade 2	1st	Interrupt until resolved to grade 0-1	100%
	2nd		75%
	3rd		50%
	4th	Discontinue permanently	--
Grade 3	1st	Interrupt until resolved to grade 0-1	75%
	2nd		50%
	3rd	Discontinue permanently	--
Grade 4	1st	Discontinue permanently OR if MD deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	50%

For grade 3 or 4 thromboembolic events which are related to capecitabine, hold capecitabine, start anticoagulation therapy Lovenox (preferred choice), and resume at the investigator's discretion.

Capecitabine or Tosedostat can be continued while the other drug is being held (if no hold criteria are met for the other drug).

6.3 Stopping Rule for Excess Toxicity

In the event of any deaths on study thought to be possibly, probably, or definitely related to study treatment, the study will be suspended, AEs will be assessed, and the study will be considered for revision or closure.

7.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outline below.

The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined in Section 7.6.

The FDA requires that all serious and unexpected adverse events be reported as outlined in Section 7.7. In addition, any fatal or life-threatening adverse experiences where there is a reasonable possibility of relationship to study intervention must be reported.

CTI BioPharma, Inc. requires that all SAEs, irrespective of causal relationship, be reported as outlined in Section 7.8.

7.1 Definitions

7.1.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.03 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

7.1.2 Serious Adverse Event (SAE)

Definition: any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

All unexpected SAEs must be reported to the FDA.

7.1.3 Unexpected Adverse Experience

Definition: any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

Events that are both serious AND unexpected must be reported to the FDA.

7.1.4 Life-Threatening Adverse Experience

Definition: any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Life-threatening adverse experiences must be reported to the FDA.

7.1.5 Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.1.6 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

7.1.7 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

7.1.8 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Pre-approval of all protocol exceptions must be obtained prior to the event.

7.2 Reporting to the Human Research Protection Office (HRPO) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

7.3 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as

reportable. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within 10 days of receipt of IRB acknowledgment via email to a QASMC auditor.

7.4 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It is the responsibility of the investigator to report any unanticipated problem to the FDA as follows:

- Report any unexpected fatal or life-threatening adverse experiences (Section 7.1.4) associated with use of the drug by telephone or fax no later than **7 calendar days** after initial receipt of the information.
- Report any serious, unexpected adverse experiences (Section 7.1.2), as well as results from animal studies that suggest significant clinical risk within **15 calendar days** after initial receipt of this information.

All MedWatch forms will be sent by the investigator or investigator's team to the FDA at the following address or by fax:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products
5901-B Ammendale Rd.
Beltsville, MD 20705-1266
FAX: 1-800-FDA-0178

7.5 Reporting to CTI BioPharma, Inc.

All SAEs, irrespective of causal relationship, must be reported to CTI using their SAE reporting form (Appendix D) within 24 hours of becoming aware of the event via either Fax or e-mail.

Fax: (866) 660-8967
Email: pv@ctiseattle.com

Special Considerations:

- SAEs considered to be related (ie, assessed as possibly, probably or definitely related) to study drug or study procedure by the investigator shall be followed until the event resolves, stabilizes or the patient is lost to follow up.

- SAEs assessed as unrelated to study drug or study procedures shall be followed for 30 days after last dose of study treatment, or until the event resolves, returns to baseline, stabilizes or the patient is lost to follow-up, whichever comes first.
- An SAE form should be completed for any event for which doubt exists regarding its seriousness. If an ongoing SAE changes in intensity, relationship to study drug, or as new information becomes available and/or known for the event, a follow-up SAE Report form should be completed and sent to the CTI within 24 hours of the change in SAE assessment.
- Any SAE that occurs after study completion and is considered by the investigator to be related to Tosedostat should be reported to CTI.

A narrative outlining the details of the SAE and treatment and outcome are to be included on the SAE form. The narrative must state whether there is a reasonable possibility that study drug caused the event. Follow-up information, such as laboratory reports, discharge summaries, autopsy reports, and information concerning outcome of the event, should be submitted as soon as the information becomes available.

7.6 Timeframe for Reporting Required Events

Reportable adverse events will be tracked for 30 days following the last day of study treatment.

8.0 PHARMACEUTICAL INFORMATION

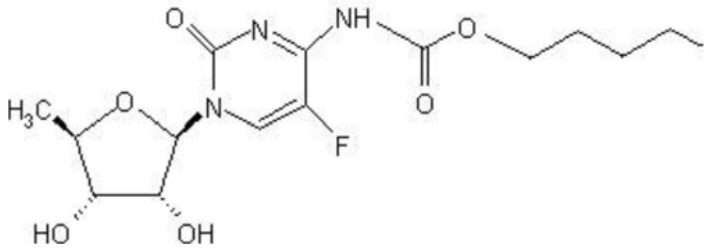
[redacted]

8.2 Capecitabine (Xeloda)

8.2.1 Capecitabine Description

Capecitabine is a fluoropyrimidine carbamate with antineoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is converted to 5-fluorouracil.

The chemical name for capecitabine is 5'-deoxy-5-fluoro-N-[(pentyloxy) carbonyl]-cytidine and has a molecular weight of 359.35. Capecitabine has the following structural formula:



8.2.2 Clinical Pharmacology

Enzymes convert capecitabine to 5-fluorouracil (5-FU) *in vivo*. Both normal and tumor cells metabolize 5-FU to 5-fluoro-2'-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). These metabolites cause cell injury by two different mechanisms. First, FdUMP and the folate cofactor, N^{5-10}-methylenetetrahydrofolate, bind to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate from 2'-deoxyuridylate. Thymidylate is the necessary precursor of thymidine triphosphate, which is essential for the synthesis of DNA, so that a deficiency of

this compound can inhibit cell division. Second, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA processing and protein synthesis.

8.2.3 Pharmacokinetics and Drug Metabolism

Following oral administration, capecitabine reached peak blood levels in about 1.5 hours (Tmax) with peak 5-FU levels occurring slightly later, at 2 hours.

Capecitabine and its metabolites are predominantly excreted in urine.

8.2.4 Supplier(s)

Capecitabine is commercially available and will not be provided for by this study. Expenses associated with this drug will be billed to a third party payer as part of standard of care.

8.2.5 Dosage Form and Preparation

Capecitabine is supplied as bioconvex, oblong film-covered tablets for oral administration. It is available in 150 mg and 500 mg tablets.

8.2.6 Storage and Stability

Store at 25ºC; excursions permitted to 15-30ºC. Keep tightly closed.

8.2.7 Administration

Capecitabine is an oral drug to be taken twice daily within 30 minutes after the end of a meal.

8.2.8 Special Handling Instructions

Care should be exercised in the handling of capecitabine. Capecitabine tablets should not be cut or crushed. The use of gloves and safety glasses is recommended to avoid exposure in case of breakage of tablets. If powder from broken capecitabine tablets contacts the skin, wash the skin immediately and thoroughly with soap and water. If capecitabine contacts the mucous membranes, flush thoroughly with water.

9.0 CORRELATIVE STUDIES

9.1 Proteomic samples

Samples will be collected for consideration of proteomic evaluation. Serum and plasma samples will be collected at the following time points:

- Baseline
- Day 1 of each cycle beginning on Cycle 2 before dosing capecitabine and tosedostat

All samples will be taken to Dr. Wang-Gillam's laboratory after they are drawn. For the plasma proteomic studies, collect 10 mL of blood in a lavender top K_2EDTA tube with a Hemogard stopper. After collection of whole blood into the EDTA tube, gently invert the tube 10 times. Centrifuge the blood samples immediately under refrigerated conditions (2-6°C) at 1300 x g for 10 minutes. Remove plasma into a 40 mL conical tube and leave approximately 1 mL of plasma overlaying the cells. Centrifuge the sample at 2400 x g for 15 minutes. Transfer aliquots (0.5 mL) to the cryovials and store at -70°C until analysis

For the serum proteomic studies, collect 10 mL of blood in a red top silica clot activator serum tube with a conventional stopper. The blood sample is allowed to sit upright for 30 minutes at room temperature. Centrifuge blood samples under refrigerated conditions at 1300 x g for 10 minutes. Remove the serum into a 40 mL conical tube and leave the residual serum so as not to disturb the clot. Centrifuge the sample at 2400 x g for 15 minutes. Transfer aliquots (0.5 mL) to the cryovials and store at -70°C until analysis.

9.2 Tumor Specimen Collection

9.2.1 Archived Formalin Fixed Paraffin Embedded Tissue Samples

Formalin fixed paraffin embedded (FFPE) samples from previous diagnostic or therapeutic procedures for the tumors will be requested. Tissue blocks are preferable; however, if the tissue block cannot be obtained, 20 unstained slides sectioned at 5 microns will be required. Tumor samples must be from one FFPE block containing viable tumor with tumor cells from the primary pancreatic tumor. Tumor cells must account for at least 10% of cell nuclei in the tumor-containing regions of the block. Unacceptable specimens include specimens processed using acid decalcification (EDTA is acceptable); tumor cellularity less than 10% in tumor involved regions of the specimen; and frozen specimens. Minimum sample volume is 3-1mm punches (cores); 5-5µm scrolls; or 10-5µm slides. Storage/transport conditions: FFPE blocks: ambient /room temperature. Place in a sealed container (bag).

Next generation sequencing is performed on all coding regions of ABL1, AKT1, ALK, APC, ASXL1, ATM, BRAF, CEBPA, CTNNB1, DNMT3A, ERBB2, EGFR, ESR1, FGFR4, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MAPK1(ERK), MAP2K2(MEK), MET, KMT2A(MLL), MPL, MYC, MYD88, NOTCH1, NPM1, NRAS, PDGFRA, PIK3CA, PTEN, PTPN11, RB1, RET, RUNX1, STK11, TET2, TP53, VHL and WT1 to detect single nucleotide variants and small insertions and deletions; selected introns of ALK and KMT2A(MLL) to

detect rearrangements. Next generation sequencing will be performed on initial tumor biopsies.

A GPS requisition form is obtained and completed from the Washington University Genomics and Pathology Services.

9.2.2 Tumor Biopsy (optional)

After Cycle 2, patients will have the option of having another biopsy of the pancreatic tumor or metastatic site to correlate with treatment response. Patients who have a PR will be required to undergo biopsy if deemed safe for the patient and tissue is feasible to obtain.

Fresh tumor samples will be obtained where feasible by CT or ultrasound-guided core biopsy. The samples will be snap frozen for future comprehensive genomic analysis. All biopsy samples will be processed and stored in the PI's lab.

9.2.3 Evaluation of genetic alternations that potentially associated with treatment response

Pancreatic cancer, as all human malignancies, is caused by genetic mutations. Mutations in *KRAS*, *P16*, *TP53* and *SMAD4* genes are common (1821). With the advent of improved sequencing techniques, the identification of several key genetic alterations has led to the development of targeted therapies, such as imatinib and numerous EGFR-targeted therapies (cetuximab, erlotinib). Identifying the key genetic alterations in pancreatic cancer may lead to a better understanding of carcinogenesis and the development of more effective therapies. It is also important to analyze the somatic mutations and correlate them with treatment response and overall survival as there may be certain genetic alterations that prove to be more chemosensitive to certain drugs than others.

The Genomics and Pathology Service at Washington University (GPS@WU) offers next-generation sequencing of tumor somatic mutations in 42 oncogenes, tumor suppressors, and other cancer genes. The rationale for performing next generation sequencing is to identify the key genetic alterations in each patient's tumor. This information can then be used to compare patients' clinical information to see if there is a correlation between response rates, overall survival, and specific genetic mutations.

Next generation sequencing is performed on all coding regions of ABL1, AKT1, ALK, APC, ASXL1, ATM, BRAF, CEBPA, CTNNB1, DNMT3A, ERBB2, EGFR, ESR1, FGFR4, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MAPK1(ERK), MAP2K2(MEK), MET, KMT2A(MLL), MPL, MYC, MYD88, NOTCH1, NPM1, NRAS, PDGFRA, PIK3CA, PTEN, PTPN11, RB1, RET, RUNX1, STK11, TET2, TP53, VHL and WT1 to detect single nucleotide variants and small insertions and deletions; selected introns of ALK and KMT2A(MLL) to

detect rearrangements. Next generation sequencing will be performed on initial tumor biopsies.

A GPS requisition form is obtained and completed from the Washington University Genomics and Pathology Services

9.2.4 Assessment of Amino Acid Deprivation Response

Tosedostat's proposed mechanism of action is to deplete amino acids to limit production of new proteins and to stimulate a stress response (amino acid deprivation response), which leads to increased apoptosis. Autophagy is the process by which cells deliver cellular materials to lysosomes for digestion and autophagy is proposed to be increased in cells with nutrient deprivation (24). The kinase mTOR is a critical regulator of autophagy induction and autophagyrelated (Atg) genes help control autophagosome formation. Numerous gene products involved in autophagy, such as ATG5, ATG8, and Beclin-1 can be assessed by immunohistochemistry. The slides will be stained for metalloproteases such as APN/CD13 and autophagy markers, which may include but are not to limited to, ATG 8, ATG 5, and Becline.

9.3 Pharmacokinetic Studies

Serum will be collected from the patients in the phase I portion of the study at baseline and on Cycle 2 Day 1 in the event of unexpected toxicities to evaluate the pharmacokinetics.

10.0 STUDY CALENDAR

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy. Scans and x-rays must be done no more than 3 weeks prior to the start of the protocol therapy. Cycles are 21 days. All study visits must occur with in +/-3 days of the time indicated on the calendar (with the exception of ECHOs which must be resulted 7 days prior to Day 1 treatment).

	Screening	**Baseline**	**D1 of each cycle**	**End of C2**	**End of each even-numbered cycle**	**F/U[A]**
Informed consent	X					
H&P, VS, wt, ECOG PS	X		X			
CBC[I]	X		X[I]			
CMP[I]	X		X[I]			
β-hCG[C]	X					
CA19-9	X		X			
Troponin-I or T	X		X			
BNP	X		X			
ECHO or MUGA[K]	X		X[J]			X[B]
ECG	X		X[D]			X[B]
CT scan	X				X	
Tosedostat			X[G]			
Capecitabine			X[H]			
Research blood for proteomics		X	X[E]			
Research blood for PKs (phase 1 only)			X[F]			
Archival tissue[L]		X				
Fresh biopsy				X[M]		
AE assessment[N]		X	X			X

A: Every 3 months for 1 year
B: 1 month after end of study treatment, then every 6 months until the study closes
C: Women of childbearing potential only
D: ECG will be done weekly during Cycle 1. If ECGs are normal (or abnormal, but not related to study drug and/or clinically significant), ECGs will only be required on Day 1 of each cycle starting Cycle 2. However, if cycle 1 ECGs are abnormal and related to study drug, continue weekly ECGs.
E: Not drawn on C1D1
F: C2 only
G: Daily on Days 1-21 of each cycle
H: Daily on Days 1-14 of each cycle
I: Weekly during Cycle 1 of Phase I
J: The screening assessment will count as the C1D1 assessment
K. Echocardiogram preferred; prior approval from PI or designee required for MUGA
L: If available, archival tissue to be provided
M. Patients who have a PR will be required to undergo biopsy if deemed safe for the patient and tissue is feasible to obtain.
N: From baseline through 30 days after treatment ends.

11.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
Registration Form Eligibility Form On-Study Form	Prior to starting treatment
Treatment Form Correlatives Form	Every cycle
DLT Form	End of Cycle 1
Toxicity Form	Continuous
Treatment Summary Form	Completion of treatment
Follow Up Form	Every 3 months for 1 year after end of treatment
Tumor Measurement Form	Baseline, end of every even numbered cycles, and end of treatment
MedWatch Form	See Section 7.0 for reporting requirements

12.0 MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 6 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 6 weeks (not less than 4) weeks following initial documentation of objective response.

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.

12.2 Disease Parameters

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

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater 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 reproducibly 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.

12.3 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: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

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-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound 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 Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 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.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical

literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

12.4 Response Criteria

12.4.1 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 the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the 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 progressions).

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.

12.4.2 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.

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).

12.4.3 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 Lesions	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

12.4.4 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.

12.4.5 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

13.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least five patients have been enrolled) or one year after accrual has opened (if fewer than five patients have been enrolled at the six-month mark).

During the phase I dose escalation, the Principal Investigator will review all patient data at least monthly (or before each dose-escalation if occurring sooner than monthly), and provide a semi-annual report to the Quality Assurance and Safety Monitoring Committee (QASMC). During the phase II, the Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason

- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date and accrual by cohort
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities separated by cohorts with the number of dose-limiting toxicities indicated
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

14.0 STATISTICAL CONSIDERATIONS

14.1 Sample Size

In the phase I part of the study, a de-escalation 3+3 design is used to determine the recommended phase II dose of tosedostat when combined with capecitabine in patients with advanced or metastatic pancreatic adenocarcinoma. The miminal number of patients needed for the phase I part of the study is 6 patients assuming no DLT is observed in Dose Level 1. The maximal number of patients is 12 patients.

For the phase II part of the study, the primary endpoint of the study is to assess the progression-free survival (PFS) of the combination therapy. Based on historical data, the PFS of 2.0 months was observed wtih either 5-FU or capecitabine in the second-line setting, so a median PFS of 4 months for the combination reigmen would be considered clininally meaningful for further development. With a sample size of 36 patients including 3-6 patients from the phase I portion, the study has power 0.80 to identify an increase of the median PFS (2.0 to 4.0 months) at a 0.05 significance level, assuming 12 months of accrual and 6 months of follow-up. We will consider this phase II part as a pilot study for the PFS as endpoint; therefore a sample size of 36 is adequate. We expect to enroll 3-4 patients per month; therefore it is feasible to recruit 36 patients within 1 year.

14.2 Data Analysis

PFS and OS will be estimated by Kaplan-Meier product limit method. The progression-

free survival and overall survival probabilities at certain time points (e.g. 3 months, 6 months) will be presented as well. The overall response rate (ORR) and CA19-9 response will be characterized by summary statistics (frequency and proportion). The logistic regression model will be considered to explore the predictive molecular biomarkers, the prognostic biomarkers for treatment response, and to investigate the correlation between genetic alterations and response to treatment.

14.3 Interim Analysis

After 10 evaluable patients have enrolled to the phase II portion of the study, an interim analysis will be conducted to look at response to date to assess for continuation of the study.

14. REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer Statistics. CA Cancer J Clin. 2013. 63:11-30
2. Conroy T, Desseigne F., Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011. 364(19):1817-1825.
3. Morertel C. Chemotherapy of gastrointestinal cancers. N Engl J Med. 1978. 299(19):1049-1052.
4. Burris H, Moore M, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol. 1997. 15(6):2403-2413.
5. Von Hoff D, Ervin T, Arena F, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013. 369(18):1691-1703.
6. Pelzer U, Schwaner I, Stieler J, et al. Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: a phase III-study from the German CONKO-study group. Eur J Cancer. 2011. 47(11):1676-1681.
7. Oettle H, Riess H, Stieler J, et al. Second-Line Oxaliplatin, Folinic Acid, and Fluorouracil Versus Folinic Acid and Fluorouracil Alone for Gemcitabine-Refractory Pancreatic Cancer: Outcomes From the CONKO-003 Trial. J Clin Oncol. 2014; Epub ahead of print.
8. Hurwitz H, Uppal N, Wagner SA, et al. A Randomized Double-Blind Phase 2 Study of Ruxolitinib or Placebo with Capecitabine as Second-line Therapy in Patients with Metastatic Pancreatic Cancer. Oral presentation at ASCO 2014.
9. Von Hoff D, Li CP, Wang-Gillam A, et al. NAPOLI-1: Randomized Phase 3 Study of MM-398 (NAL-IRI), with or Without 5-Fluorouracil and Leucovorin, Versus 5-Fluorouracil and Leucovorin, in Metastatic Pancreatic Cancer Progressed On Or Following Gemcitabine-Based Therapy. Oral presentation at ESMO 16th World Congress on Gastrointestinal Cancer, 2014.
10. Hashida H, Takabayashi A, Kanai et al. Aminopeptidase N is involved in cell motility and angiogenesis: its clinical significance in human colon cancer. Gastroenterology. 2002. 122(2):376-386.
11. Dubois, RN. Leukotriene A4 signaling, inflammation, and cancer. J Natl Cancer Inst. 2003. 95(14):1028-1029.
12. Chen X, Li N, Wang S, et al. Leukotriene A4 hydrolase in rat and human esophageal adenocarcinoma and inhibitory effects of bestatin. J Natl Cancer Inst. 2003. 95(14):1053-1061.
13. Ikeda N, Nakajima Y, Tokuhara T, et al. Clinical significance of aminopeptidase N/CD13 expression in human pancreatic carcinoma. Clin Cancer Res. 2003. 9(4):1503-1508.
14. Saric T, Graef C, Goldberg A. Pathway for degradation of peptides generated by proteasomes: a key role for thimet oliopeptidase and other metallopeptidases. J Biol Chem. 2004. 279(45):46723-46732.
15. Krige D, Needham L, Bawden L, et al. CHR-2797: An antiproliferative aminopeptidaseinhibitor that leads to amino acid deprivation in human leukemic cells. Cancer Res. 2008. 68(16):6669-6679.
16. Wickstrom M, Larsson R, Nygren P, et al. Aminopeptidase N (CD13) as a target for cancer chemotherapy. Cancer Sci. 2011. 102(3):501-508.

17. Reid A, Protheroe A, Attard G, et al. A first-in-man phase I and pharmacokinetic study on CHR-2797 (Tosedostat), an inhibitor of M1 aminopeptidases, in patients with advanced solid tumors. Clin Cancer Res. 2009. 15(15):4978-4985.
18. Van Herpen C, Eskens F, de Jonge M, et al. A phase Ib dose-escalation study to evaluate safety and tolerability of the addition of the aminopeptidase inhibitor tosedostat (CHR-2797) to paclitaxel in patients with advanced solid tumours. Br J Cancer. 2010. 103(9):1362-1368.
19. Ikeda N, Nakajima Y, Tokuhara T, et al. Clinical significance of aminopeptidase N/CD13 expression in human pancreatic carcinoma. Clin Cancer Res. 2003. 9(4):1503-1508.
20. Lowenberg B, Morgan G, Ossenkoppele G, et al. Phase I/II clinical study of Tosedostat, an inhibitor of aminopeptidases, in patients with acute myeloid leukemia and myelodysplasia. J Clin Oncol. 2010. 28(28):4333-4338.
21. Biankin A, Waddell N, Kassahn K, et al. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. Nature. 2012. 491(7424):399-405.
24. Mortimore G, and Schworer, C. Induction of autophagy by amino-acid deprivation in perfused rat liver. Nature. 1977. 270:174-176.

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APPENDIX A: ECOG Performance Status Scale

Grade	Description
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'S MEDICATION DIARY

Today's Date: _____ Cycle: _____ Patient Name: _____ Study ID#: _____

INSTRUCTIONS TO THE PATIENT:

1. Take _____mg (___capsules) of tosedostat daily, for 21 days, in the morning after food at approximately the same time each day. Take it with a glass of water. Swallow the capsules whole and do not chew the capsules.
2. Take _____mg in the AM (___tablets) and _____mg in the PM (___tablets) of capecitabine twice daily, for 14 days, after food at approximately the same times each day. Take it with a glass of water. Swallow the tablets whole and do not chew the tablets.
3. Record the date, the number of capsules and tablets taken, and when you took them.
4. If you forget to take any doses within 6 hours of the usual time, then do not take that dose. Restart at the next time you would normally take a dose.
5. If you notice any side effects, please record them in the comments section. Record the time if you should vomit.
6. Please return the forms to your physician or your study coordinator when you go to your next appointment. Please bring your unused study medications and/or empty bottles with you to each clinic visit so that a pill count can be done.

Day	Date	Tosedostat		Capecitabine AM		Capecitabine PM		Comments
		Time	# of capsules	Time	# of tablets	Time	# of tablets	
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								
15				***DO NOT TAKE CAPECITABINE BEYOND DAY 14***				
16								
17								
18								
19								
20								
21								

APPENDIX C: List of QT Prolonging Medications

The following table presents a list of drugs that prolong, may prolong or are unlikely to prolong the QTc. Please note that this list is frequently updated. For the most current list of medications, users should be directed to the following website: *http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm.*

Generic Name	Brand Names	Risk Category
Albuterol (salbutamol)	Proventil®, Ventolin®, Ventolin-HFA®, Accuneb®, Combivent®, Vospire-ER®, ProAir HFA®, Duoneb®	Avoid in congenital long QT
Alfuzosin	Uroxatral®	Possible Risk of TdP
Amantadine	Symmetrel®, Symadine®	Conditional Risk of TdP
Amiodarone	Cordarone®, Pacerone®, Nexterone®	Risk of TdP
Amisulpride	Solian®, Supitac®, Soltus®, Amitrex®, Amazeo®	Conditional Risk of TdP
Amitriptyline	Elavil® (Discontinued 6/13), Tryptomer®, Tryptizol®, Laroxyl®, Saroten®, Sarotex® Lentizol®, Endep®	Conditional Risk of TdP
Amoxapine	Asendin®, Amokisan®, Asendis®, Defanyl®, Demolox®, Moxadil®	Conditional Risk of TdP
Amphetamine	Adderal-XR®, Dexedrine®, Dextroamp®	Avoid in congenital long QT
Anagrelide	Agrylin®, Xagrid®	Risk of TdP
Apomorphine	Apokyn®, Ixense®, Spontane®, Uprima®	Possible Risk of TdP
Arformoterol	Brovana®	Avoid in congenital long QT
Aripiprazole	Abilify®, Aripiprex®	Possible Risk of TdP
Arsenic trioxide	Trisenox®	Risk of TdP
Astemizole (Off US mkt)	Hismanal®	Risk of TdP
Atazanavir	Reyataz®	Possible Risk of TdP
Atomoxetine	Strattera®	Avoid in congenital long QT
Azithromycin	Zithromax®, Zmax®	Risk of TdP
Bedaquiline	Sirturo®	Possible Risk of TdP
Bepridil (Off US mkt)	Vascor®	Risk of TdP
Bortezomib	Velcade®, Bortecad®	Possible Risk of TdP
Bosutinib	Bosulif®	Possible Risk of TdP
Chloral hydrate	Aquachloral®, Novo-Chlorhydrate®, Somnos®, Noctec®,	Conditional Risk of TdP

	Somnote®	
Chloroquine	Aralen®	Risk of TdP
Chlorpromazine	Thorazine®, Largactil®, Megaphen®	Risk of TdP
Ciprofloxacin	Cipro®, Cipro-XR®, Neofloxin®	Conditional Risk of TdP
Cisapride (Off US mkt)	Propulsid®	Risk of TdP
Citalopram	Celexa®, Cipramil®	Risk of TdP
Clarithromycin	Biaxin®, Prevpac®	Risk of TdP
Clomipramine	Anafranil®	Conditional Risk of TdP
Clozapine	Clozaril®, Fazaclo®, Versacloz®	Possible Risk of TdP
Cocaine	Cocaine	Risk of TdP
Crizotinib	Xalkori®	Possible Risk of TdP
Dabrafenib	Tafinlar®	Possible Risk of TdP
Dasatinib	Sprycel®	Possible Risk of TdP
Desipramine	Pertofrane®, Norpramine®	Conditional Risk of TdP
Dexmedetomidine	Precedex®, Dexdor®, Dexdomitor®	Possible Risk of TdP
Dexmethylphenidate	Focalin®, Focalin-XR®	Avoid in congenital long QT
Dextroamphetamine (d-Amphetamine)	Dexedrine®, dexamphetamine, dexamfetamine, (S)-(+)-amphetamine, Dextrostat®	Avoid in congenital long QT
Dihydroartemisinin+piperaquine	Eurartesim®	Possible Risk of TdP
Diphenhydramine	Benadryl®, Nytol®, Unisom®, Sominex®, Dimedrol®, Daedalon®	Conditional Risk of TdP
Disopyramide	Norpace®	Risk of TdP
Dobutamine	Dobutrex®	Avoid in congenital long QT
Dofetilide	Tikosyn®	Risk of TdP
Dolasetron	Anzemet®	Possible Risk of TdP
Domperidone (Not on US mkt)	Motilium®, Motillium®, Motinorm Costi®, Nomit®	Risk of TdP
Dopamine	Intropine®	Avoid in congenital long QT
Doxepin	Sinequan®, Silenor®, Aponal®, Adapine®, Doxal®, Deptran®, Sinquan®	Conditional Risk of TdP
Dronedarone	Multaq®	Risk of TdP
Droperidol	Inapsine®, Droleptan®, Dridol®, Xomolix®	Risk of TdP
Ephedrine	Rynatuss®, Broncholate®	Avoid in congenital long QT
Epinephrine (Adrenaline)	Primatene®, Bronkaid®	Avoid in congenital long QT
Eribulin	Halaven®	Possible Risk of TdP

Erythromycin	E.E.S.®, Robimycin®, EMycin®, Erymax®, Ery-Tab®, Eryc Ranbaxy®, Erypar®, Eryped®, Erythrocin Stearate Filmtab®, Erythrocot®, E-Base®, Erythroped®, Ilosone®, MY-E®, Pediamycin®, Zineryt®, Abboticin®, Abboticin-ES®, Erycin®, PCE Dispertab®, Stiemycine®, Acnasol®, Tiloryth®	Risk of TdP
Escitalopram	Cipralex®, Lexapro®, Nexito®, Anxiset-E® (India), Exodus® (Brazil), Esto® (Israel), Seroplex®, Elicea®, Lexamil®, Lexam®, Entact® (Greece), Losita® (Bangladesh), Reposil® (Chile), Animaxen® (Colombia), Esitalo® (Australia), Lexamil® (South Africa)	Risk of TdP
Famotidine	Pepcid®, Fluxid®, Quamatel®	Possible Risk of TdP
Felbamate	Felbatol®	Possible Risk of TdP
Fenfluramine (Off US mkt)	Pondimin®, Ponderax®, Adafax®	Avoid in congenital long QT
Fingolimod	Gilenya®	Possible Risk of TdP
Flecainide	Tambocor®, Almarytm®, Apocard®, Ecrinal®, Flécaine®	Risk of TdP
Fluconazole	Diflucan®, Trican®	Conditional Risk of TdP
Fluoxetine	Prozac®, Sarafem®, Fontex®	Conditional Risk of TdP
Formoterol	Foradil®, Foradile®, Oxeze®, Oxis®, Atock®, Atimos®, Atimos Modulite®, Perforomist®, Dulera®, Symbiocort®, Vannair®, Quikhale FB®	Avoid in congenital long QT
Foscarnet	Foscavir®	Possible Risk of TdP
Fosphenytoin	Cerebyx®, Prodilantin®	Possible Risk of TdP

Furosemide (Frusemide)	Lasix®, Fusid®, Frumex®	Conditional Risk of TdP
Galantamine	Reminyl®, Nivalin®, Razadyne-ER®,	Conditional Risk of TdP
Gatifloxacin (Off US mkt)	Tequin®	Possible Risk of TdP
Gemifloxacin	Factive®	Possible Risk of TdP
Granisetron	Kytril®, Sancuso®, Granisol®	Possible Risk of TdP
Grepafloxacin (Off market worldwide)	Raxar®	Risk of TdP
Halofantrine	Halfan®	Risk of TdP
Haloperidol	Haldol® (US & UK), Aloperidin®, Bioperidolo®, Brotopon®, Dozic®, Duraperidol® (Germany), Einalon S®, Eukystol®, Halosten®, Keselan®, Linton®, Peluces®, Serenace®, Serenase®, Sigaperidol®	Risk of TdP
Hydrochlorothiazide	Apo-Hydro®, Aquazide H®, BP Zide®, Dichlotride®, Hydrodiuril®, HydroSaluric®, Hydrochlorot®, Microzide®, Esidrex®, Oretic®	Conditional Risk of TdP
Ibutilide	Corvert®	Risk of TdP
Iloperidone	Fanapt®, Fanapta®, Zomaril®	Possible Risk of TdP
Imipramine (melipramine)	Tofranil®	Conditional Risk of TdP
Indapamide	Lozol®, Natrilix®, Insig®	Conditional Risk of TdP
Isoproterenol	Medihaler-Iso®, Isuprel®	Avoid in congenital long QT
Isradipine	Dynacirc®	Possible Risk of TdP
Itraconazole	Sporanox®, Onmel®	Conditional Risk of TdP
Ivabradine (Not on US mkt)	Procoralan®, Coralan®, Corlentor®, Coraxan®, Ivabid®, Bradia®	Conditional Risk of TdP
Ketoconazole	Nizoral®, Sebizole®, Ketomed®, Keton®	Conditional Risk of TdP
Lapatinib	Tykerb®, Tyverb®	Possible Risk of TdP
Levalbuterol (levsalbutamol)	Xopenex®, Levolin®, Axazest®	Avoid in congenital long QT
Levofloxacin	Levaquin®, Tavanic®	Risk of TdP
Levomethadyl (Off US mkt)	Orlaam®	Risk of TdP

Lisdexamfetamine	Vyvanse®	Avoid in congenital long QT
Lithium	Eskalith®, Lithobid®	Possible Risk of TdP
Mesoridazine (Off US mkt)	Serentil®	Risk of TdP
Metaproterenol	Metaprel®, Alupent®	Avoid in congenital long QT
Methadone	Dolophine®, Symoron®, Amidone®, Methadose®, Physeptone®, Heptadon®	Risk of TdP
Methamphetamine (methamfetamine)	Desoxyn®, Pervitin®, Anadrex®, Methedrine®, Syndrox®	Avoid in congenital long QT
Methylphenidate	Ritalin®, Concerta®, Focalin®, Daytrana®, Methylin®	Avoid in congenital long QT
Metronidazole	Flagyl® and many others	Conditional Risk of TdP
Midodrine	ProAmatine®, Amatine®, Gutron®	Avoid in congenital long QT
Mifepristone	Korlym®, Mifeprex®	Possible Risk of TdP
Mirabegron	Myrbetriq®	Possible Risk of TdP
Mirtazapine	Remeron	Possible Risk of TdP
Moexipril/HCTZ	Uniretic®, Univasc®	Possible Risk of TdP
Moxifloxacin	Avelox®, Avalox®, Avelon®	Risk of TdP
Nelfinavir	Viracept®	Conditional Risk of TdP
Nicardipine	Cardene®	Possible Risk of TdP
Nilotinib	Tasigna®	Possible Risk of TdP
Norepinephrine (noradrenaline)	Levophed®	Avoid in congenital long QT
Norfloxacin	Noroxin®, Ambigram®	Possible Risk of TdP
Nortriptyline	Pamelor®, Sensoval®, Aventyl®, Norpress®, Allegron®, Noritren®, Nortrilen®	Conditional Risk of TdP
Ofloxacin	Floxin®	Possible Risk of TdP
Olanzapine	Zyprexa®, Zydis®, Relprevv®	Possible Risk of TdP
Ondansetron	Zofran®, Anset®, Ondemet®, Zuplenz®, Emetron®, Ondavell®, Emeset®, Ondisolv®, Setronax®	Risk of TdP
Oxytocin	Pitocin®, Syntocinon®	Possible Risk of TdP
Paliperidone	Invega®, Xepilon®	Possible Risk of TdP
Pantoprazole	Protonix® and others	Conditional Risk of TdP
Paroxetine	Paxil®, Aropax®, Pexeva®, Seroxat®, Sereupin®	Conditional Risk of TdP
Pasireotide	Signifor®	Possible Risk of TdP
Pazopanib	Votrient®	Possible Risk of TdP

Pentamidine	Pentam®	Risk of TdP
Perflutren lipid microspheres	Definity®	Possible Risk of TdP
Phentermine	Adipex P®, Adiphene® (India), Anoxine-AM®, Ionamin®, Duromine®, Metermine®, Miraprontv, Obephen®, Obermine®, Obestin-30®, Phentremine®, Phentrol®, Phenterex®, Phentromin®, Pro-Fast SA®, Redusa®, Panbesy®, Obenix®, Oby-Trim®, Teramine®, Zantryl®, Sinpet®, Supremin®, Suprenza®, Umine®, Weltmine®	Avoid in congenital long QT
Phenylephrine	Neosynephrine®	Avoid in congenital long QT
Phenylpropanolamine	Acutrim®, Dexatrim®	Avoid in congenital long QT
Pimozide	Orap®	Risk of TdP
Pipamperone (Not on US Mkt)	Dipiperon (E.U), Propitan (Japan)	Possible Risk of TdP
Posaconazole	Noxafil®, Posamol®	Conditional Risk of TdP
Probucol (Off US mkt)	Lorelco®	Risk of TdP
Procainamide (Oral off US mkt)	Pronestyl®, Procan®	Risk of TdP
Promethazine	Phenergan®	Possible Risk of TdP
Protriptyline	Vivactil®	Conditional Risk of TdP
Pseudoephedrine	PediaCare®, Sudafed®	Avoid in congenital long QT
Quetiapine	Seroquel®	Possible Risk of TdP
Quinidine	Quinaglute®, Duraquin®, Quinact®, Quinidex®, Cin-Quin®, Quinora®	Risk of TdP
Quinine sulfate	Qualaquin®	Conditional Risk of TdP
Ranolazine	Ranexa®, Ranozex®	Possible Risk of TdP
Rilpivirine	Edurant®, Complera®, Eviplera®	Possible Risk of TdP
Risperidone	Risperdal®	Possible Risk of TdP
Ritodrine (Off US mkt)	Yutopar®	Avoid in congenital long QT
Ritonavir	Norvir®	Conditional Risk of TdP
Roxithromycin (Not on US Mkt)	Rulide®, Xthrocin®, Roxl-150®, Roxo®, Surlid®, Rulide®, Biaxsig®, Roxar®, Roximycinv®, Roxomycin®, Rulid®, Tirabicin®, Coroxin®	Possible Risk of TdP
Salmeterol	Serevent®	Avoid in congenital long QT
Saquinavir	Invirase®(combo)	Possible Risk of TdP

Sertindole (Not on US mkt)	Serdolect®, Serlect®	Possible Risk of TdP
Sertraline	Zoloft®, Lustral®, Daxid®, Altruline®, Besitran®, Deprax®, Elrval®, Emergen®, Gladem®, Implicane®, Sedoran®, Sealdin®, SerivoLowfin®, Stimuloton®, Tresleen®, Sertralin Bluefish®	Conditional Risk of TdP
Sevoflurane	Ulane®, Sojourn®	Risk of TdP
Sibutramine (Off US mkt)	Meridia®	Avoid in congenital long QT
Solifenacin	VESIcare®	Conditional Risk of TdP
Sorafenib	Nexavar®	Possible Risk of TdP
Sotalol	Betapace®, Sotalex®, Sotacor®	Risk of TdP
Sparfloxacin (Off US mkt)	Zagam®	Risk of TdP
Sulpiride (Not on US Mkt.)	Dogmatil®, Dolmatil®, Eglonyl®, Espiride®, Modal®, Sulpor®	Risk of TdP
Sunitinib	Sutent®	Possible Risk of TdP
Tacrolimus	Prograf®, Prograf®, Advagraf®, Protopic®	Possible Risk of TdP
Tamoxifen	Nolvadex®(discontinued 6/13), Istubal®, Valodex®	Possible Risk of TdP
Telaprevir	Incivek®, Incivo®	Conditional Risk of TdP
Telavancin	Vibativ®	Possible Risk of TdP
Telithromycin	Ketek®	Possible Risk of TdP
Terbutaline	Brethine®, Bricanyl®, Brethaire®, Terbulin®	Avoid in congenital long QT
Terfenadine (Off US mkt)	Seldane®	Risk of TdP
Tetrabenazine (Orphan drug in US)	Nitoman®, Xenazine®	Possible Risk of TdP
Thioridazine	Mellaril®, Novoridazine®, Thioril®	Risk of TdP
Tizanidine	Zanaflex®, Sirdalud®	Possible Risk of TdP
Tolterodine	Detrol®, Detrusitol®	Possible Risk of TdP
Toremifene	Fareston®	Possible Risk of TdP
Trazodone	Desyrel® (discontinued 6/13), Oleptro®, Beneficat®, Deprax®, Desirel®, Molipaxin®, Thombran®, Trazorel®, Trialodine®, Trittico®, Mesyrel®	Conditional Risk of TdP
Trimethoprim-Sulfa	Septra®, Bactrim®, Sulfatrim®, Biseptol®,	Conditional Risk of TdP

	Co-trimoxazole®, Cotrim®, Septrin®, Trisul®	
Trimipramine	Surmontil®, Rhotrimine®, Stangyl®	Conditional Risk of TdP
Vandetanib	Caprelsa®	Risk of TdP
Vardenafil	Levitra®	Possible Risk of TdP
Vemurafenib	Zelboraf®	Possible Risk of TdP
Venlafaxine	Effexor®, Efexor®	Possible Risk of TdP
Voriconazole	VFend®	Conditional Risk of TdP
Vorinostat	Zolinza®	Possible Risk of TdP
Ziprasidone	Geodon®, Zeldox®	Possible Risk of TdP

APPENDIX D: CTI SAE form

SERIOUS ADVERSE EVENT (SAE) REPORT FORM

PROTOCOL #: T55001

Subject#: SITE / SATELLITE/ SUBJ	**Investigator:**	**Country:**	**REPORT** ☐ Initial ☐ Followup #___ ☐☐ DD ☐☐☐ MMM ☐☐☐☐ YYYY

Sex: ☐ Male ☐ Female **Date of Birth:** ☐☐ DD ☐☐☐ MMM ☐☐☐☐ YYYY **Height:** ____ ☐in ☐cm **Weight:** ____ ☐ lb ☐kg

Patient's Primary Disease:_____ **Stage**: _____ **Date of diagnosis**: _____

RELEVANT MEDICAL HISTORY, PREEXISTING CONDITIONS, CONCURRENT ILLNESSES Attach additional information as needed.

	Serious Adverse Event Term Diagnosis (suspected or confirmed); symptoms if unknown	Grade CTCAE (ver. 4)	Onset Date (meets serious criteria) DDMMMYYYY	Reason Event is Serious *Use code numbers listed below*	Relationship of SAE to each Study Drug *Use code numbers listed below*		Action taken for each Study Drug as a result of this SAE *Use code numbers listed below*		SAE abated after drug stopped? Yes/No /NA	SAE reappeared when drug restarted? Yes/No /NA	End Date (no longer meets serious criteria) DDMMMYYYY	Outcome of event *Use code numbers listed below*
					TST	**CAP**	**PAC**	**CAP**				
1												
2												
3												

Reason event is Serious:
1: Death (cause of death)
2: Life threatening (immediate risk of death)
3: Hospitalization (initial or prolonged)
4: Persistent/ significant disability / Incapacity
5: Congenital anomaly / Birth Defect
6: Other Serious (Important medical events)

Relationship to Study Drug:
1: **Possibly**
2: **Unlikely**

Action taken with Study Drug as a result of this SAE:
1: Dose increased (specify dose and dates)
2: None (No action taken)
3: Dose reduced (specify dose and dates)
4: Drug interrupted (Skipped/Delayed/Interrupted)
5: Drug withdrawn (Permanently discontinued)
6: N/A (Study drug not applicable to this patient)
7: Unknown

Outcome of event:
1: Recovered
2: Recovered with sequelae (specify sequelae in narrative)
3: Recovering
4: Not recovered
5: Fatal (is the cause of death)
6: Unknown (describe in narrative)

IF HOSPITALIZED: Admission Date: ☐☐ DD ☐☐☐ MMM ☐☐☐☐ YYYY Discharge Date: ☐☐ DD ☐☐☐ MMM ☐☐☐☐ YYYY

IF PATIENT DIED: Cause(s) of Death: (primary)_____ (secondary) _____

Autopsy performed? ☐ Yes (attach certificate) ☐ No ☐ Pending ☐ Certificate not available Date of Death: ☐☐ DD ☐☐☐ MMM ☐☐☐☐ YYYY

Investigator:	**Subject#:**	*PROTOCOL #:*

	STUDY DRUG INFORMATION				**Start of Therapy**		**Current Therapy**			
Study Drug Name	**Lot No.**	**Exp. Date**	**Dose Route & Freq.**	**MFR Name**	**Initial Dose (mg)**	**Initial Start Date** (DD-MMM-YYYY)	**Current Cycle #**	**Current Dose (mg)**	**Current Cycle Start Date** (DD-MMM-YYYY)	**Last Dose Date (before SAE onset)** (DD-MMM-YYYY)
Tosedostat				CTI BioPharma						
Capecitabine (CAP)										

CONCOMITANT MEDICAL PRODUCTS AND THERAPY DATES Attach additional information as needed.

RELEVANT TESTS/LABORATORY DATA (Include dates) Attach additional information as needed.

DESCRIBE EVENT OR PROBLEM Describe from onset through resolution. Include treatments for the event, and rationale for causality

INVESTIGATOR'S SIGNATURE

Reporter Name: ☐ Physician ☐Pharmacist ☐ Nurse ☐Other_____ Phone:

Investigator's Name _____ (Print) _____ Investigator's Signature _____ Date