CLINICAL STUDY PROTOCOL

An Open Label Phase 2 Trial to Evaluate Safety, Tolerability, and Efficacy of G-FLIP (Low Doses of Gemcitabine, Fluorouracil [5FU], Leucovorin, Irinotecan, and Oxaliplatin), Followed by G-FLIP-DM (G-FLIP + Low Doses of Docetaxel and Mitomycin C), When Used in Combination with Vitamin C, in Patients with Advanced Pancreatic Cancer

Protocol Number: G-FLIP-VitC-Ph2

NCT Number: NCT01905150

Study Drugs: G-FLIP, G-FLIP-DM, and Vitamin C (Ascorbic Acid)

Current Version: January 6, 2015

STUDY SYNOPSIS

<table>
<tr><td>Study Title</td><td>An Open Label Phase 2 Trial to Evaluate Safety, Tolerability, and Efficacy of G-FLIP (Low Doses of Gemcitabine, Fluorouracil [5FU], Leucovorin, Irinotecan, and Oxaliplatin), Followed by G-FLIP-DM (G-FLIP + Low Doses of Docetaxel and Mitomycin C), When Used in Combination with Vitamin C, in Patients with advanced Pancreatic Cancer</td></tr>
<tr><td>Study No.</td><td>G-FLIP-VitC-Ph2</td></tr>
<tr><td>Study Objectives</td><td>The objective of this study is to evaluate the safety, tolerability and efficacy of G-FLIP, when used in combination with ascorbic acid, in patients with advanced pancreatic cancer. The objective of this study is also to evaluate the safety, tolerability and efficacy of G-FLIP-DM, when used in combination with ascorbic acid, in patients with advanced pancreatic cancer who develop DP with G-FLIP treatment. The primary endpoint is 12-month survival rate. The secondary endpoints include Overall Survival (OS), Quality of Life (QOL), Response Rate (RR), Progression-Free-Survival (PFS), and safety.</td></tr>
<tr><td>Study Drugs</td><td>G-FLIP, G-FLIP-DM, and Vitamin C (Ascorbic Acid)</td></tr>
<tr><td>Study Design</td><td>Sample Size: There will be 30 “evaluable” study subjects in this study.

Treatments:

G-FLIP: All study subjects are treated with G-FLIP. Each treatment cycle of G-FLIP is 2 weeks, with G-FLIP given on Days 1 and 2 of each cycle. If study subjects exhibit Disease Progression (DP), treatment with G-FLIP will stop, and they will be treated with G-FLIP-DM.

G-FLIP-DM: Study subjects who exhibit DP with G-FLIP treatment will be treated with G-FLIP-DM. Each G-FLIP-DM treatment cycle is 2 weeks, with G-FLIP-DM given on Days 1 and 2 of each cycle.

Ascorbic Acid: Ascorbic acid will be administered twice weekly throughout the study, given on any 2 separate days of the week.

In 50% of the study subjects (i.e., 15 evaluable study subjects), treatment with ascorbic acid will begin on the same week when G-FLIP begins. In the other 50% of the study subjects (i.e., the other 15 evaluable study subjects), treatment with ascorbic acid will be delayed by 2 cycles. Results from these 2 groups of study subjects would allow comparison of potential acute safety of ascorbic acid, when used in combination with G-FLIP.

Open-Label: This is an open-label study, where investigators and study subjects are not blinded to the treatment.

Randomization: The assignment of study subjects will be randomized, as long as they meet eligibility criteria of the study.</td></tr>
<tr><td>Dosing of G-FLIP</td><td>G-FLIP is administered on Days 1 and 2 of every 2-week cycle. The dosing of G-FLIP is shown in Table A (below):

Table A: Administration of G-FLIP
<table>
<tr><th rowspan="2">Drug (Dose)</th><th colspan="2">Administration</th></tr>
<tr><th>Day 1</th><th>Day 2</th></tr>
<tr><td>Gemcitabine (500 mg/m^2)</td><td>Infused IV over 50 mins</td><td></td></tr>
<tr><td>Leucovorin (200 mg/m^2)</td><td>Infused IV over 30 mins</td><td></td></tr>
<tr><td>Irinotecan (80 mg/m^2)</td><td>Infused IV over 90 mins</td><td></td></tr>
<tr><td>5-FU (1,500 mg/m^2)</td><td colspan="2">Infused IV continuously over 20 hrs</td></tr>
<tr><td>Oxaliplatin (40 mg/m^2)</td><td></td><td>IV infusion over 2 hrs</td></tr>
<tr><td colspan="3">IV = intravenous or intravenously</td></tr>
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STUDY SYNOPSIS (cont'd)

<table>
<tr><td>Dosing of G-FLIP-DM</td><td>G-FLIP-DM is administered to study subjects who exhibit DP with G-FLIP treatment. The dosing of G-FLIP-DM is shown in Table B (below):
Table B: Administration of G-FLIP-DM
<table>
<tr><th rowspan="2">Drug (Dose)</th><th colspan="2">Administration</th></tr>
<tr><th>Day 1</th><th>Day 2</th></tr>
<tr><td>Gemcitabine (400 mg/m^2)</td><td>Infused IV over 50 mins</td><td></td></tr>
<tr><td>Leucovorin (200 mg/m^2)</td><td>Infused IV over 30 mins</td><td></td></tr>
<tr><td>Irinotecan (80 mg/m^2)</td><td>Infused IV over 90 mins</td><td></td></tr>
<tr><td>5-FU (1,500 mg/m^2)</td><td colspan="2">Infused IV continuously over 20 hrs</td></tr>
<tr><td>Docetaxel (25 mg/m^2)</td><td></td><td>Infused IV over 1 hr</td></tr>
<tr><td>Oxaliplatin (30 mg/m^2)</td><td></td><td>Infusion IV over 2 hrs</td></tr>
<tr><td>Mitomycin C (5 mg/m^2)[a]</td><td></td><td>Infused IV over 15 mins</td></tr>
</table>
IV = intravenous or intravenously
[a] Given during the first 2 out of every 3 cycles.</td></tr>
<tr><td>Dosing of Ascorbic Acid</td><td>Ascorbic acid (100 g in 1 liter) is infused intravenously (IV) twice weekly, given on any 2 separate days of the week.

Ascorbic acid administration is given throughout the study, including during the follow-up period when treatment with G-FLIP or G-FLIP-DM has been terminated due to DP. If study subjects miss up to 4 infusions over 4 weeks, they are still eligible to remain in the study. The times and dates of Ascorbic acid administration, and if study subjects miss intended administration, must be recorded.</td></tr>
<tr><td>Dose Delay and Dose Modification</td><td>In the event of adverse drug reactions related to G-FLIP and G-FLIP-DM, dose delay and dose modification will be dependent on the type of toxicities. The dose modification scheme for G-FLIP is outlined in Appendix A, and that for G-FLIP-DM in Appendix B.

For ascorbic acid related reactions including infusion reactions, hypersensitivity reactions, chills, etc., the dose of ascorbic acid can be reduced to 75 g and can further be reduced to 50 g if necessary.</td></tr>
<tr><td>Concomitant Medications and Prophylactic Treatment</td><td>Other than G-FLIP, G-FLIP-DM and ascorbic acid, patients cannot receive any other standard or investigational treatment for their cancer, or any study drugs for any non-cancer indications, while on this study. All concomitant medications (including names, dosage and schedule) must be recorded.

Prophylactic treatment for drug-related symptoms can be given according to Package Inserts of the study drugs and clinical practice. Supportive treatment may include anti-emetic, anti-diarrhea, anti-pyretic, anti-allergic, anti-hypertensive, analgesics, antibiotics, allopurinol, and others such as blood products and bone marrow growth factors. Patients may use erythropoietin for anemia. The investigator may utilize erythropoietic factors, or blood or platelet transfusions at their discretion.</td></tr>
<tr><td>Duration of Treatment and Follow-Up</td><td>At least six months of treatment is recommended for study subjects who have a response from G-FLIP or G-FLIP-DM, unless or until:
- Patients exhibit disease progression in the opinion of the principal investigator
- Unacceptable toxicity from the treatment
- Patient withdrawal of consent (Note: The investigator should make every effort to contact the subject to perform a final evaluation and to determine the reason(s) for withdrawal from the study.)
- Investigator's discretion to withdraw patients from the study because continued participation in the study is not in the patient's best interest.
- Underlying illness: a condition, injury, or disease unrelated to the intended disease which the study is investigating, that renders continuing treatment unsafe or regular follow-up impossible
- General or specific changes in the patient's condition that renders the patient ineligible for further investigational treatment
- Non-compliance with investigational treatment, protocol-required evaluations or follow-up visits

After treatment, study subjects should be followed so that information on survival and post study treatment are available for at least 1 year after the study subjects participate in the trial.</td></tr>
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STUDY SYNOPSIS (cont'd)

Efficacy Assessments	The efficacy of the study drugs will be assessed according to the following parameters: Response Criteria of Complete Response (CR), Partial Response (PR), Stable Disease (SD), and Progressive Disease (Disease Progression or DP) will be derived from CT or MRI according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (Eisenhauer et al. 2009). A summary of RECIST 1.1 is shown in Appendix C. Response Rate (RR) is the number of study subjects, expressed as a percentage of the total number of study subjects participated in the trial, who exhibit PR or CR that has been confirmed from 2 consecutive scans (CT or MRI). Progression-Free-Survival (PFS) is the length of time when SD (or better) of a study subject is first documented until the time when DP, or death from any cause, occurs. Overall Survival ($OS_{treatment}$) is the time from which the study subjects are first treated with G-FLIP to the time when death from any cause occurs. $OS_{diagnosis}$, which is the time from which the study subjects are first diagnosed with advanced pancreatic cancer to the time when death from any cause occurs, will also be recorded. 12-Month Survival Rate is the number of study subjects, expressed as a percentage of the total number of study subjects in the trial, who survive for 12 months starting from the time when the study subjects are accrued to the trial. The 12-Month Survival Rate for study subjects who survive for 12 months starting from the time when the study subjects are first diagnosed with advanced pancreatic cancer will also be recorded.
Safety Assessments	The efficacy of the study drugs will be assessed from the first dose to 1 month after last dose of the study drugs. The assessments will be based on the following parameters, performed at baselines and at various times during the study: - physical exams - evaluation of symptoms - vital signs - ECOG performance status and survival - clinical pathology (clinical chemistry, renal function [assessed utilizing the Cockcroft-Gault formula], hematology, and coagulation) - urinalysis - QOL, assessed as described by Aaronson NK, et al. 1993.
Inclusion Criteria	Inclusion: Patients must meet all inclusion criteria before enrollment: A. Patients must have histologically or cytologically confirmed metastatic (Stage IV), locally advanced unresectable (stage III), or locally recurrent pancreatic adenocarcinoma, and have never been treated with any chemotherapy or have received prior chemotherapy for their cancer. B. Eastern Cooperative Oncology Group (ECOG) performance status being 0-2. C. Expected survival >3 months. D. Patients 18 years of age and older of both genders. E. Women of child-bearing potential (i.e., women who are pre-menopausal or not surgically sterile) must use accepted contraceptive methods (abstinence, intrauterine device [IUD], oral contraceptive or double barrier device) during the study, and must have a negative serum or urine pregnancy test within 2 weeks prior to treatment initiation. F. Fertile men must practice effective contraceptive methods during the study, unless documentation of infertility exists. G. At least 2 weeks must have elapsed from any prior surgery or hormonal therapy.

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STUDY SYNOPSIS (cont'd)

Inclusion Criteria (cont'd)	H. Laboratory values ≤2 weeks must be: - Adequate hematologic (granulocyte count ≥1500/mm^3; white blood cell [WBC] ≥3500 cells/mm^3 or ≥3.5 bil/L; platelet count ≥150,000 cells/mm^3 or ≥150 bil/L; absolute neutrophil count [ANC] ≥1500 cells/mm^3 or ≥1.5 bil/L; and hemoglobin ≥9 g/dL or ≥90 g/L). - Adequate hepatic function (aspartate aminotransferase [AST/SGOT] ≤3x upper normal limit [UNL], alanine aminotransferase [ALT/SGPT] ≤3x UNL (≤5x UNL if liver metastases present), bilirubin ≤1.5x UNL). - Adequate renal function (serum creatinine ≤2.0 mg/dL). - Adequate coagulation ("International Normalized Ratio" or INR must be ≤1.5) unless on therapeutic anticoagulants. I. No evidence of active infection and no serious infections within the past month. J. Mentally competent, able to understand and willing to sign the informed consent form.
Exclusion Criteria	Exclusion: Patients with any of the following characteristics are excluded: A. Patients under the age of 18. B. Locally advanced resectable disease from pancreatic cancer. C. Previous radiotherapy for cerebral metastases, central nervous system (CNS) or epidural tumor. D. Patients receiving any other standard or investigational treatment for their cancer, or any other investigational agent for any non-cancer indication within the past 4 weeks. E. Patients with any active uncontrolled bleeding, or a bleeding diathesis (e.g., active peptic ulcer disease). F. Pregnant women, or women of child-bearing potential not using reliable means of contraception. G. Lactating females. H. Fertile men unwilling to practice contraceptive methods during the study period. I. Life expectancy less than 3 months. J. Any condition or abnormality which may, in the opinion of the investigator, compromise the safety of patients. K. Unwilling or unable to follow protocol requirements. L. Active heart disease including but not limited to symptomatic congestive heart failure, symptomatic coronary artery disease, symptomatic angina pectoris, symptomatic myocardial infarction, or symptomatic congestive heart failure. M. Patients with a history of myocardial infarction that is <3 months prior to registration. N. Patients with any amount of clinically significant pericardial effusion. O. Evidence of active serious infection. P. Patients with known HIV infection. Q. Requirement for immediate palliative treatment of any kind including surgery and radiation. R. Patients that have received a chemotherapy regimen requiring stem cell support in the previous 6 months. S. Patients with Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency; a history of oxalate renal calculi and/or hyperoxaluria; a history of systemic iron overload; and creatinine clearance <60 cc/minute. T. Any condition or abnormality which may, in the opinion of the investigator, compromise the safety of the patient.

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STUDY SYNOPSIS (cont'd)

Study Procedures

The study procedures outlined in Table C (below):

Table C: Study Procedures

Assessments	Pre-Study Screen[6]	Each 2-Week Cycle: Day 1	Day 2	Day 3	Day 4	Days 5-14
Informed consent	√					
Medical history	√					
Pregnancy test for women of child-bearing potential	√					
G-FLIP or G-FLIP-DM[1]		√	√			
Ascorbic Acid		Given twice weekly[2]				
Neupogen					√	
Evaluation of symptoms and vital signs	√[5]	√				
ECOG performance status, QOL, and survival (12-month survival rate and OS)	√	√				
Clinical chemistry[4], hematology and coagulation	√	√[3]				√
Urinalysis	√	√				
Efficacy assessments: - CT or MRI (for RR and PFS) - CA 19-9	 √ √	 Post Cycle 4, then every 6th cycle[7] Every other cycle[7]				
Survival and post-trial cancer treatment	Monitor bi-monthly via phone contact after patients are removed from study					

DP = Disease Progression; ECOG = Eastern Cooperative Oncology Group; G-FLIP = low doses of gemcitabine, fluorouracil (5FU), leucovorin, irinotecan, and oxaliplatin; G-FLIP-DM = G-FLIP + low doses of docetaxel and mitomycin C; hr = hour; IV = intravenous or intravenously; min = minute; OS = Overall Survival; PFS = Progression-Free-Survival; QOL = Quality of Life; RR = Response Rate.

[1] All study subjects are treated with G-FLIP. If study subjects exhibit DP, treatment with G-FLIP will stop and they will be treated with G-FLIP-DM.

[2] Ascorbic acid (100 g in 1 liter) is infused IV twice weekly, given on 2 separate days of the week.

[3] These tests are performed on Day 1 of each treatment cycle, with CBC results available for review before administration of the anti-tumor agents and other results available for review on Day 2.

[4] Renal function will be assessed utilizing creatinine and/or Cockcroft-Gault formula.

[5] Other than evaluation of symptoms and vital signs, height and weight, physical exam, medications, and date of diagnosis of advanced pancreatic cancer are also determined during pre-study medical screening.

[6] Pre-study screening tests, which are also enrollment evaluations, must be performed according the following time frames:

Within 4 weeks: tumor assessment (imaging scans [CT or MRI] and CA 19-9)

Within 2 weeks: medical history, physical exam, vital signs, height, weight, ECOG, evaluation of symptoms and medications, QOL, date of diagnosis of advanced pancreatic cancer, clinical chemistry, hematology, coagulation, and urinalysis.

Within 2 weeks: pregnancy test for women of child-bearing potential.

[7] Additional scans and CA 19-9 tests can be performed during the study at the discretion of the investigator.