2 STUDY SYNOPSIS

Name of Company:	**Name of Finished Product:**	**Name of Active Ingredient:**
OSI Pharmaceuticals, Inc.		

Title of Study:

A Randomized, Open Label, Phase II Study of OSI-7904L versus 5-FU/LV as First-Line Treatment in Patients with Unresectable, Locally Advanced or Metastatic Adenocarcinoma of the Biliary Tract

Studied Period:	**Phase of Development:** 2
Date first patient started therapy: 27 AUG 2004 Date last patient completed: 07 SEP 2005	

Publications Based on Study

None

Objectives:

The primary objective of this study was to determine the objective response rates in patients with untreated unresectable, locally advanced or metastatic cancer of the biliary tract who were treated with OSI-7904L or 5-FU/Leucovorin (LV).

The secondary objectives of this study were to assess the toxicity and tolerability of OSI-7904L; evaluate the overall survival; [redacted]; and further evaluate the pharmacokinetic profile of OSI-7904L (in Stage 2 of the study only).

Methodology:

This was a multicenter, randomized, open-label, noncomparative, phase 2 study of OSI-7904L versus 5-FU/LV as first-line treatment in patients with biliary tract cancers. Patients were stratified by tumor type (gallbladder cancer vs other biliary tumor types) and center, and randomized to OSI-7904L or 5-FU/LV.

In Stage 1, 10 evaluable patients were to be recruited to each arm. If no responses were observed, the study was to be terminated. If the OSI-7904L arm was terminated early, then the entire study was to be closed. If the 5-FU/LV arm was terminated, but at least 1 response was observed in the OSI-7904L arm, randomization was not to continue and all patients were to be treated with OSI-7904L during the second stage of the study. If the study was not terminated after Stage 1, an additional 19 evaluable patients were to be accrued in each arm for a total of 29 patients in each arm (Stage 2). If 4 or more responses were observed among the 29 patients, the treatment would be declared effective.

Number of Patients (planned/analyzed):

Stage 1 – 20 planned (10 in each treatment arm); 22 analyzed (11 in each treatment arm)

Stage 2 – The study was terminated at the end of Stage 1.

Diagnosis and Main Criteria for Inclusion:

Patients must have had histologically or cytologically documented unresectable, locally advanced or metastatic adenocarcinoma of the biliary tract (gallbladder, intrahepatic, perihilar, or distal extrahepatic tumors). Patients must have been ≥ 18 years of age; had an ECOG performance status ≤ 2; had a life expectancy ≥ 12 weeks; had no prior chemotherapy for locally advanced or metastatic disease; had radiotherapy that had not exceeded 25% of the bone marrow reserve and from which the patient had recovered from the acute and toxic affects; and had adequate hematopoietic, hepatic, and renal function.

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Study Drug, Dose and Mode of Administration:

OSI-7904L was formulated as a sterile, liposomal dispersion of OSI-7904L in a solution composed of 9% sucrose buffer in water for injection. The product was presented in a glass vial containing approximately 5 mg of OSI-7904L in 10 mL of solution.

The starting dose for OSI-7904L was 12 mg/m^2. OSI-7904L diluted in 5% dextrose in water for injection (D5W) was given by 30-minute infusion on Day 1 every 21 days.

Lot numbers: [redacted], [redacted]

Combination Chemotherapy, Dose and Mode of Administration, Batch Numbers:

Leucovorin 200 mg/m^2 was given as a 2-hour infusion, followed by bolus 5-FU 400 mg/m^2 and a 46-hour infusion of 5-FU 2400 mg/m^2. This regimen was repeated every 14 days.

Duration of Treatment:

If a patient responded to therapy (ie, complete or partial response), treatment may have continued for at least 2 additional cycles after confirmed response or if deemed appropriate, until disease progression or toxicity occurred.

Patients with stable disease may have continued therapy for as long as the investigator felt they were benefiting from treatment. OSI-7904L or 5-FU/LV should have been discontinued in cases of disease progression and/or intolerable toxicity.

Summary and Conclusions:

Patient Characteristics:

Twenty-two patients were enrolled and received at least 1 dose of study treatment: 11 patients in each of the 2 treatment groups. The proportion of males to females was different in the 2 treatment groups: 7 of the 11 patients in the OSI-7904L group were female compared with 4 of the 11 patients in the 5-FU/LV group. Also, the median age for patients in the OSI-7904L group was higher than in the 5-FU/LV group: 62 years (range 40 to 74) compared with 56 years (range 46 to 73). [redacted].

Summary of Safety:

Both treatment arms of the study were generally well tolerated. Eleven patients were treated with OSI-7904L at an initial dose of 12 mg/m^2 every 3 weeks. A total of 36 cycles of OSI-7904L (equating to approximately 108 weeks on treatment) were administered with a median of 2 per patient (range 1 – 8). Of these 11, only 2 had their dose reduced and/or delayed and in both patients these adjustments were for toxicity [redacted]. These data indicate this schedule of OSI-7904L is fairly well tolerated in this group of patients.

Three patients on the OSI-7904L treatment arm died on study due to disease progression. Three patients experienced serious adverse events related to OSI-7904L: [redacted] rash and [redacted] hyperbilirubinemia, pruritus, abdominal pain, stomatitis, neutropenia, and pyrexia.

The most commonly reported OSI-7904L-related adverse events were stomatitis, vomiting, fatigue, rash, pruritus, and nausea. All of these events were mild to moderate in severity [redacted]

Eleven patients received LV 200 mg/m^2 as a 2-hour infusion, followed by bolus 5-FU 400 mg/m^2 and a 46-hour infusion of 5-FU 2400 mg/m^2 as their initial dose. This regimen was repeated every 14 days. The total number of cycles administered was 88 (equating to approximately 176 weeks on treatment), significantly higher than in the OSI-7904L arm. The median number of 5-FU/LV cycles administered was 6 (range 6 to 12 cycles). The longer treatment duration of patients in this group does not appear to be due to an increase in tolerability, but more likely due to an increase in efficacy. None of these 11 patients had dose reductions or interruptions for toxicity, indicating this treatment was well tolerated.

The most commonly reported 5-FU/LV-related adverse events in this treatment group were nausea, fatigue, and

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anorexia. All were of mild to moderate severity. No related serious adverse events were reported in the 5-FU/LV arm.

There were no notable changes in hematology or clinical chemistry laboratory values in either treatment arm that suggested drug toxicity, [redacted]

Summary of Efficacy:

None of the 11 patients in the OSI-7904L group responded. Four patients had their disease stabilized on study. As dictated by the protocol, the study was thus terminated due to this lack of response in the OSI-7904L group. Of the 11 patients in the 5-FU/LV group, [redacted], 10 had stable disease, and none progressed on study.

The median time to progression was 7.40 weeks for OSI-7904L (95% CI: 15.10 – 12.10) and 18.00 weeks for 5-FU/LV (95% CI: 12.90 – 25.10). Median overall survival for the OSI-7904L treatment arm was 23.70 weeks (95% CI: 8.10 – 35.30), while that for the 5-FU/LV treatment arm was not reached at the time of data cut-off, although the lower 95% CI boundary was 29.40 weeks. There were a high number of censored patients in the 5-FU/LV arm. Although there was no formal comparison of the data, this modified de Gramont regimen appears to have controlled the disease much better than OSI-7904L in this patient population.

Conclusions:

Both treatment arms of the study were generally well tolerated. The most commonly reported OSI-7904L-related adverse events were mild to moderate stomatitis, vomiting, fatigue, rash, pruritus, and nausea. The most commonly reported 5-FU/LV-related adverse events were mild to moderate nausea, fatigue, anorexia, vomiting, and stomatitis.

As mandated by the protocol, the absence of response during the first stage in the OSI-7904L treatment arm resulted in the termination of the study. The number of patients with disease stabilization was 4 out of 11 in the OSI-7904L treatment arm and 10 of 11 in the 5-FU/LV treatment arm.

Date of the Report: 08 MAR 2006