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A Phase I Study of Continuous Oral Dosing of OSI-906, a Dual Inhibitor of Insulin-Like Growth Factor-1 and Insulin Receptors, in Patients with Advanced Solid Tumors

Igor Puzanov[1], Colin R. Lindsay[2], Laura Goff[1], Jeff Sosman[1], Jill Gilbert[1], Jordan Berlin[1], Srinivasu Poondru[3], Ronit Simantov[3], Rich Gedrich[4], Andrew Stephens[5], Emily Chan[1], and T.R. Jeffry Evans[2,6]

Abstract

Purpose: OSI-906 is a potent inhibitor of insulin-like growth factor-1 receptor (IGF1R) and insulin receptor (IR). The purpose of this study was to determine the MTD, safety, pharmacokinetics, pharmacodynamics, and preliminary activity of OSI-906 in patients with advanced solid tumors.

Patients and Methods: This was a nonrandomized, open-label, phase I, dose-escalation study in patients with advanced solid tumors. The study also included a diabetic expansion cohort and a biomarker expansion cohort of patients with colorectal cancer. Patients were treated with OSI-906 by once- or twice-daily continuous dosing schedules.

Results: Of 95 patients enrolled in the study, 86 received at least one dose of OSI-906. Dose-limiting toxicities included QTc prolongation, grade 2 abdominal pain and nausea, hyperglycemia, and elevation of aspartate aminotransferase and alanine aminotransferase (all grade 3). The MTDs were established to be 400 mg once daily and 150 mg twice daily. The recommended phase II dose was determined as 150 mg twice daily. OSI-906 was rapidly absorbed with a half-life of 5 hours, and steady-state plasma concentrations were achieved by day 8. Pharmacodynamic effects on IGF1R and IR phosphorylation were levels observed and correlated with plasma concentrations of OSI-906. Thirty-one patients had stable disease as their best response. One patient with melanoma had a radiographic partial response and underwent resection, during which only melanocytic debris but no viable tumor tissue was identified.

Conclusions: At the established MTD, OSI-906 was well tolerated and antitumor activity was observed. These results support further evaluation of OSI-906 in solid tumors. *Clin Cancer Res; 21(4); 701–11. ©2014 AACR.*

See related commentary by Yee, p. 667

Introduction

Insulin-like growth factor-1 receptor (IGF1R) is widely expressed in normal human tissues and is required for embryonic development and postnatal growth. The binding of its cognate ligands, insulin-like growth factor-1 (IGF1) and -2 (IGF2), activates the intrinsic tyrosine kinase activity of IGF1R, resulting in its autophosphorylation and recruitment of the downstream signaling protein insulin receptor substrate (IRS) to the cell membrane, which subsequently activates both phosphoinositide 3-kinase-Akt and the MAPK pathways (1). IRS protein also mediates the activity of insulin receptor (IR), which shares 60% homology (1) with IGF1R. Two isoforms of IR, IR-A and IR-B, which result from posttranscriptional alternative splicing, have been shown to form hybrid receptors with IGF1R, adding further complexity to the IGF signaling pathway (1).

Several studies have shown that both the IGF1R and IR play a role in cancer development and progression (2). Upregulation of IGF1 receptor and its ligands has been observed in several tumor types (3–10). Inhibition of IGF1R by various approaches, including antisense (11), anti-IGF1R antibodies (12–14), dominant-negative IGF1R (15), and small-molecule inhibitors (16), has been shown to reduce tumor growth in human tumor xenograft models. However, activity in subsequent clinical trials has been less promising than initially expected. The inhibition of IGF1R and IR may be useful for inhibition of cancer cell survival because, in some cancers, IGFs also signal through IR/IGF1R heterodimers (1). In addition to its role in contributing to malignant transformation, activation of the IGF pathway plays a pivotal role in mediating resistance to established treatment in various solid tumors, such as colorectal cancer (2), suggesting that inhibitors targeting this pathway may be useful as single agents as well as in combination with other drugs.

OSI-906 is a potent, oral small-molecule inhibitor of both IGF1R and IR, which has shown promising activity profiles in several cancer cell lines as well as xenograft models (17,

[1]Vanderbilt Ingram Cancer Center, Nashville, Tennessee. [2]Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom. [3]Astellas Pharma Global Development, Inc., Northbrook, Illinois. [4]OSI Pharmaceuticals, Boulder, Colorado. [5]Piramal Imaging GmbH, Berlin, Germany. [6]University of Glasgow, Glasgow, United Kingdom.

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Current address for R. Gedrich: Kolltan Pharmaceuticals, Inc., New Haven, CT.

Corresponding Author: Igor Puzanov, Vanderbilt Ingram Cancer Center, 1301 Medical Center Drive, Nashville, TN 37232. Phone: 615-936-6398; Fax: 615-343-7602; E-mail: igor.puzanov@vanderbilt.edu

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Translational Relevance

In this first-in-human study, OSI-906, a novel dual inhibitor of the insulin-like growth factor 1 receptor (IGF1R) and insulin receptor (IR), was well tolerated when administered by once-daily or twice-daily continuous dosing schedule to patients with advanced solid tumors, with an MTD of 150 mg twice daily. The inclusion of a cohort of diabetic patients, which is a unique feature of this study, supported the acceptable tolerability profile of OSI-906 in this patient population. At the MTD, decreased phosphorylation of IGF1R and IR was observed in peripheral blood mononuclear cells and was paralleled by increases in plasma IGF1, a surrogate marker of IGF1R inhibition, providing proof-of-target modulation by OSI-906. Continuous dosing with OSI-906 resulted in antitumor activity, with a significant proportion of patients with colorectal cancer experiencing stable disease as their best clinical response. Several phase II studies combining OSI-906 with other agents are currently ongoing.

18). Preclinical toxicology studies reported induction of hyperglycemia as one of the main treatment-related toxicities associated with OSI-906.

We report here a phase I study evaluating the safety, efficacy, pharmacokinetics, and pharmacodynamics of once- and twice-daily continuous oral dosing schedules of OSI-906 in patients with advanced solid tumors. In this study, we also explored two parallel expansion cohorts at the recommended phase II dose. One cohort was designed to investigate biomarkers and comprised patients with advanced colon cancer ($n = 20$). The second cohort consisted of patients with advanced solid tumors and active type 2 diabetes to explore the safety of OSI-906 in this patient population. This study was conducted in parallel with a trial evaluating two intermittent dosing schedules of OSI-906 (19).

Materials and Methods

Patients

Male and female patients aged 18 years or older were eligible for trial entry if they had a verified advanced solid malignancy, refractory to conventional therapy or for which there was no effective therapy, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and a predicted life expectancy of >12 weeks. Eligibility criteria also included adequate hematologic, hepatic, and renal function; serum potassium, calcium, and magnesium within the institution's normal range; and fasting glucose $\leq$125 mg/dL (7 mmol/L) at baseline (except for patients in the diabetic expansion cohort). Patients were eligible for trial entry if they had not received chemotherapy or radiotherapy (unless palliative and non–myelosuppressive) within 3 weeks of entering the study (4 weeks for carboplatin or investigational agents; 6 weeks for nitrosoureas and mitomycin C). Patients should have discontinued hormonal therapy or tyrosine kinase inhibitors before study entry and recovered from treatment-related toxicities of any prior therapy apart from alopecia, fatigue, or grade 1 neurotoxicity.

Patients were excluded if they had a documented history of diabetes (except for patients in the diabetic expansion cohort), if they had uncontrolled or significant cardiovascular disease, known brain metastasis, prolonged QT syndrome or Fridericia-corrected QTc > 450 ms, poorly controlled hypertension, $\geq$ class II New York Heart Association congestive heart failure, history of any kind of stroke, any type of active seizure disorder, or any active or uncontrolled infections, serious illnesses, or medical or psychiatric conditions that could interfere with the patient's participation in the study. Prohibited medications within 14 days of study dosing and during the study treatment included those known to cause QT interval prolongation and glucocorticoids.

Patients in the biomarker expansion cohort had histologically documented colorectal cancer that was locally advanced or metastatic and refractory to established forms of therapy and that were required to have archival tissue available and a lesion accessible for biopsy. Up to 20 patients were to be recruited to this exploratory study cohort. Patients recruited in the diabetic expansion cohort had active type 2 diabetes mellitus not requiring insulin or insulinotropic therapy and a fasting glucose of $\leq$150 mg/dL (8.3 mmol/L) at baseline. Patients being treated with noninsulinotropic oral antihyperglycemic therapy must have been on stable doses for $\geq$4 weeks before study entry. Patients with type 1 diabetes mellitus or type 2 diabetes mellitus requiring insulinotropic oral therapies or insulin were excluded. Additional inclusion and exclusion criteria are provided in Supplementary Materials. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice with the ethical principles of the current Declaration of Helsinki and approved by the research ethics committee at each of the participating institutions. All patients provided written, informed consent before performing any study-related procedures.

Study design, objectives, and treatments

This was a nonrandomized, open-label, phase I dose-escalation study in patients with advanced solid tumors. The primary objective was to determine the MTD and establish the recommended phase II dose of oral OSI-906 for both once-daily and twice-daily dosing schedules. Secondary objectives were to evaluate safety, including dose-limiting toxicities (DLT), pharmacokinetic, and pharmacodynamic profiles, and to seek preliminary evidence of antitumor activity. The study also comprised two separate expansion cohorts for exploratory studies, including patients with locally advanced or metastatic colorectal cancer (biomarker expansion cohort, unselected on *KRAS* mutation status; $n = 20$) and patients with advanced solid tumors and active type 2 diabetes (diabetic expansion cohort; $n = 9$). The safety, pharmacokinetics, and preliminary antitumor activity of OSI-906 were also evaluated in the expansion cohorts as secondary objectives. The correlation between the mutational status of *KRAS* and treatment response in the biomarker expansion cohort was evaluated as an exploratory objective.

Patients in the dose-escalation cohort received OSI-906 gelatin capsules once daily or twice daily 1 hour after food by continuous dosing schedule for 21 days; thereafter, patients could continue treatment in the absence of disease progression or unacceptable toxicity. The starting dose of 10 mg once daily was based on 1/10 of the highest nonseverely toxic dose in a 28-day repeat-dose toxicity study in rats. The study started with an initial once-daily regimen, and a twice-daily regimen was initiated after clinically significant–related toxicity $\geq$ grade 2 was observed in any patient

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at the once-daily dose regimen. Once the MTD had been determined, the expansion cohorts (patients with colorectal cancer and diabetes) were open, and patients received OSI-906 tablets at a dose of 150 mg twice daily.

Dose escalation and determination of the MTD

Dose escalation was dependent on toxicity (graded using the National Cancer Institute—Common Terminology Criteria for Adverse Events, version 3). Dose escalation was in 100% increments until the first documented ≥ grade 2 toxicity, excluding nausea, vomiting, or diarrhea, if not premedicated or adequately treated, following which doses were escalated up to a maximum of 50%. At least 3 patients were enrolled in each dose cohort. If a DLT occurred, the cohort was expanded up to a maximum of 6 patients.

DLT was defined as grade 4 neutropenia for ≥7 consecutive days; febrile neutropenia (defined as absolute neutrophil count <1,000/mm^3 with temperature ≥38.5°C); thrombocytopenia (≤25,000 cells/mm^3 or ≤50,000 cells/mm^3 with bleeding or requiring platelet transfusion); and any ≥grade 3 nonhematologic toxicity except ≥ grade 3 fatigue (unless ≥2-grade increase from baseline), ≥ grade 3 gamma-GT, ≥ grade 3 nausea, vomiting, or diarrhea if not premedicated or adequately treated, or ≥ grade 3 hypertension, if not adequately treated. Isolated nonfasting grade 3 hyperglycemia was not considered a DLT. However, ≥ grade 3 signs or symptoms of glucose intolerance (including frequent urination, excessive thirst, extreme hunger, unusual weight loss, increased fatigue, irritability, and blurred vision) that interfered with activities of daily living and was accompanied by ≥grade 2 hyperglycemia (glucose > 160 mg/dL or 8.9 mmol/L); fasting glucose > 250 mg/dL or 13.9 mmol/L; ≥ grade 3 electrolyte (Na, K, Ca, Mg, Cl, phosphate, and bicarbonate) abnormalities due to glucose intolerance and not attributable to another cause; positive blood ketones (≥ULN); or grade 4 hyperglycemia (glucose > 500 mg/dL or 27.8 mmol/L) were all considered to be a DLT. Interruption of oral dosing for more than 5 days due to toxicity within the first 21 days of continuous dosing or an inability to begin a second treatment period by day 36 due to drug-related toxicity of any grade was also considered to be a DLT. Therefore, early onset of chronic low-grade toxicities that lead to significant dose interruption could also be included in dose-escalation decisions, even in the absence of acute, higher-grade toxicities that conventionally constitute DLTs. The MTD was defined as the dose level below which >1 of 3, or ≥2 of up to 6 patients experienced a DLT.

Study treatment continued until progressive disease, death, pregnancy, withdrawal of consent, or unacceptable toxicity. All patients were followed for a minimum of 30 days after the last dose of study therapy, or until recovery from any treatment-related toxicity.

Safety and efficacy assessment

Safety was assessed by monitoring for DLTs, adverse events (AE), serious adverse events (SAE), changes in clinical laboratory data (hematology, chemistry, blood glucose, and urinalysis), vital signs, electrocardiograms including assessment of QT interval (Fridericia formula) and physical examination. Electrocardiogram assessments were conducted at baseline and during the study at predose and postdose at various time points. QTc interval prolongations were identified at the study sites, and electrocardiograms were provided to a central laboratory for retrospective review. A clinically significant increase in QTc interval was defined as an increase of ≥60 ms compared with the day 1 predose value or an absolute increase of >500 ms at any time.

Clinical assessments, vital signs, urinalysis, HbA1c, full blood count, biochemical profile, and assessment of ECOG performance status were performed on day 1 of each treatment cycle. In addition, clinical assessments, vital signs, blood urea, electrolytes, creatinine and glucose, and urine glucose (dipstick) were performed daily on days 2 to 5 of cycle 1. Blood glucose and ketones were measured using a home glucometer twice daily (prebreakfast and preevening meal) for days 1 to 21 of the first treatment cycle, and full blood count and biochemical profile were performed weekly for the first 42 weeks of treatment. Electrocardiograms were performed on day 1 (predose and 2, 4, and 12 hours after the initial dose), and days 2 to 5, 8, and 15 (predose and between 2 and 4 hours postdose) of the initial 21-day treatment period, and on day 1 (predose) of every 21-day treatment period thereafter.

Tumor size was evaluated by computed tomography, magnetic resonance imaging, or by physical examination in patients before starting study therapy. Assessments were repeated at the end of every two treatment cycles using the same assessment modality as at baseline. Responses to treatment were assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (20). Disease control rate (DCR) was calculated as the number of responders and patients with stable disease as their best radiologic response divided by the total number of patients evaluable for efficacy in each cohort.

Pharmacokinetic analyses

Blood samples were collected immediately before dosing and at 1, 2, 3, 4, 6, 8, 10 to 12, and 24 hours (patients on once-daily dosing only) after dosing on days 1 and 22, and before dosing on days 8 and 15. Urine was collected for 0 to 6, 6 to 12, and 12 to 24 hours on days 1 and 22 (patients on once-daily dosing only). Plasma and urine concentrations of OSI-906 were measured by validated high-performance liquid chromatography coupled with tandem mass spectrometry method. Pharmacokinetic parameters for each patient were calculated using a noncompartmental model. Testing of deviation from dose proportionality of plasma pharmacokinetic parameters was performed using power models.

Pharmacodynamic analyses

Blood samples were collected for analysis of IGF1R and IR phosphorylation in peripheral blood mononuclear cells (PBMC) and of IGF1 levels in plasma. For patients on the once-daily and twice-daily administration schedules, blood samples were collected immediately before dosing (0 hours), 4, and 24 hours after dosing on day 1 and day 22, and before dosing on days 8 and 15. For PBMC isolation, samples were collected into CPT vacutainer tubes (Becton Dickinson) containing sodium heparin as an anticoagulant. PBMCs were isolated by centrifugation at 1,500 × *g* for 20 minutes at room temperature in a centrifuge with a swinging bucket rotor. The cell layer was resuspended in a final volume of 10 mL in PBS containing 0.1% BSA and 2 mmol/L EDTA and then centrifuged at 300 × *g* for 10 minutes at room temperature. The supernatant was removed, and the cell pellets were stored

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at −80°C until analysis. Cells were lysed with RIPA buffer (Millipore) plus protease and phosphatase inhibitors (diluted 1:100; Sigma-Aldrich) and 1 mmol/L Vanadate. IGF1R and IR phosphorylation were measured using the Proteome Profiler Human Phospho-RTK Array Kit (R&D Systems). The phosphorylated IGF1R and IR signals were quantified by digital assessment of pixel density using Science Lab Image Gauge 4.0 software (FUJIFILM). Pixel densities for phosphorylated IGF1R and IR and a representative IgG-negative control were normalized to local background in adjacent areas of the blot. IgG-negative control signals (assay background) were assigned a value of 1, and phosphorylated IGF1R and IR signals were then reported signal intensities relative to the assay background. Patients with detectable predose phospho-IGF1R (p-IGF1R) and phospho-IR (p-IR) signals in PBMCs (signal intensity >2) were included in subsequent analyses. For plasma preparation, samples were collected into a vacutainer tube containing EDTA and centrifuged (1,500–2,000 × *g* for 10 minutes under refrigeration) within 30 minutes of collection. Aliquots were stored at −80°C. Total plasma IGF1 concentrations were determined with the Total IGF-1 ELISA Kit (DSL/Beckman Coulter) according to the manufacturer's protocol. Intra- and interassay coefficients of variation (CV) were determined to be <9% and <7%, respectively. Intraday (plate-to-plate) and interday assay CVs were determined to be <6% and <17%, respectively. Substantial intersubject variability has been reported in plasma IGF1 concentrations in healthy individuals and patients with cancer. To facilitate interpatient comparisons in this study, IGF1 concentrations were normalized to day 1 predose levels and expressed as a percentage of the predose value (% predose). Intrasubject variability was assessed in serial blood samples collected from healthy volunteers. The CV was determined to be <15% and was used as a guide to indicate substantial changes in plasma IGF1 concentrations relative to predose values as indicated [predose set as 100% + two intrasubject CVs (30%)]. Relationships between plasma IGF1 and plasma concentrations of OSI-906 were also assessed. Curve fitting was performed by nonlinear regression analysis (GraphPad Prism 5; GraphPad Software, Inc.).

KRAS mutational analysis

DNA was isolated from available archival tumor tissue samples ($n = 24$) derived from patients with locally advanced or metastatic colorectal cancer from the colon cancer biomarker expansion cohort ($n = 20$) and from selected patients in the dose-escalation and diabetic expansion cohorts ($n = 4$).

Tumor tissue blocks or slides were sent to Response Genetics for quality assessment, tissue sectioning, and isolation of DNA. M13-tailed PCR primers for *KRAS* amplification were designed to focus on the mutation hotspots of exons 2 and 3. The resulting PCR fragments were then analyzed by Surveyor Nuclease digestion (Transgenomic), followed by high-performance liquid chromatography on the Transgenomic High Sensitivity WAVE Nucleic Acid Fragment Analysis System (Transgenomic). Surveyor Nuclease/WAVE chromatograms for each sample were compared with wild-type controls to identify tumors with *KRAS* mutations. Cycle sequencing analysis of PCR fragments for tumors expressing *KRAS* mutations was performed with the Applied Biosystems 3730XL instrument (Life Technologies Corporation) using universal M13-tailed amplification primers for bidirectional sequencing.

PCR fragments were analyzed by Surveyor Nuclease digestion. Ten microliters of each of the PCR products was used in a reaction containing 1 μL of 0.15 mmol/L MgCl2, 1 μL of Enhancer Cofactor, 1 μL Surveyor Enhancer W2, and 2 μL Surveyor Nuclease W. The reaction was incubated at 42.0°C for 30 minutes, and the reaction was stopped by adding 1 μL of Stop Solution. All reagents were provided within the Surveyor Nuclease Kit from Transgenomic. Surveyor Nuclease will recognize all heterozygous mismatches, such as single-nucleotide polymorphisms, small insertions, small deletions, or indels (insertion and deletion at the same location within an amplicon). The enzyme cuts both DNA strands 3′ of the site of the alteration. This generates digestion fragments which, in turn, will indicate the presence of a heterozygous variation. Following Surveyor Nuclease digestion, digestion fragments were detected using high-performance liquid chromatography on the Transgenomic High Sensitivity WAVE Nucleic Acid Fragment Analysis System (Transgenomic). Samples were passed through a DNASep cartridge (Transgenomic) at 45.0°C and eluted with a linear acetonitrile gradient in a 0.1 mol/L triethylammonium acetate buffer (pH 7.0) at a constant flow rate of 0.9 mL/min. Eluted digestion fragments were detected by a UV detector (Transgenomic). To improve the sensitivity of the analysis, Transgenomic WAVE Optimized HS Staining Solution I (Transgenomic), a DNA-intercalating dye, was mixed with the eluate following UV detection, and fluorescent intensity was measured by a fluorescence detector (Transgenomic) with excitation at 490 nm and emission at 520 nm, according to the instructions of the manufacturer.

Results

Patient characteristics

Ninety-five patients were enrolled in the study from the Vanderbilt Ingram Cancer Center (Nashville, TN) and the Beatson West of Scotland Cancer Centre (Glasgow, UK) between 2007 and 2011. Patient characteristics for both dosing

Table 1. Demographics and baseline characteristics for once-daily and twice-daily regimens

	Once-daily regimen ($N = 38$)	Twice-daily regimen ($N = 57$)
Mean (SD) age, years	57.5	60.0
Gender, *n* (%)		
Male	23 (61)	37 (65)
Female	15 (39)	20 (35)
ECOG performance status, *n* (%)		
0	15 (39)	17 (30)
1	18 (47)	28 (49)
2	5 (13)	12 (21)
Tumor type, *n* (%)		
Colorectal	12 (32)	35 (61)
Pancreatic	5 (13)	2 (4)
Gastric	4 (11)	1 (2)
NSCLC	0	4 (7)
Renal	2 (5)	1 (2)
Esophageal	2 (5)	1 (2)
Sarcoma	1 (3)	3 (5)
Melanoma	1 (3)	2 (4)
Breast	1 (3)	0
Adrenal carcinoma	1 (3)	0
Ovarian	1 (3)	0
Others	8 (21)	8 (14)

NOTE: Baseline characteristics of all patients who enrolled in the study including those in the expansion cohorts ($n = 31$; twice-daily regimen).
Abbreviation: NSCLC, non–small lung cell carcinoma.

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regimens are summarized in Table 1. The most common tumor types were colorectal, pancreatic, and non–small cell lung cancer. For the once-daily treatment regimen, the majority of patients had previously received one, two, or three courses of chemotherapy (18% each), and 68% had undergone disease-related surgeries. Most of the patients in the twice-daily regimen had received three (30%) or four (23%) courses of chemotherapy, and 84% had undergone disease-related surgical procedures.

Treatment and disposition

Eighty-six patients, 57 in the dose-escalation cohorts and 29 in the expansion cohorts (20 in the colorectal cancer cohort and nine in the diabetic cohort), received at least one dose of OSI-906 (Supplementary Fig. S1). Of the 9 patients who did not receive the study drug, 7 were not treated for ethical or medical reasons or noncompliance; no reason was reported for the remaining 2 patients. Of all the patients enrolled in the dose-escalation cohorts, 87% treated with OSI-906 once daily and 89% treated with OSI-906 twice daily discontinued treatment (Supplementary Fig. S1). Of the 31 patients enrolled in the expansion cohorts, 89% in the diabetic cohort and 91% in the biomarker cohort discontinued treatment. The majority of patients discontinued treatment due to disease progression. Overall, 13 patients (11 in the dose-escalation cohorts and 2 in the expansion cohorts) discontinued treatment due to treatment-related AEs and SAEs (Supplementary Fig. S1). The majority of patients in each regimen were evaluable for DLTs, safety, efficacy, and pharmacokinetics (Supplementary Fig. S1).

Patients received OSI-906 once daily in one of eight dose cohorts: 10, 20, 40, 75, 150, 300, 400, and 450 mg, or twice daily in one of five dose cohorts: 20, 40, 75, 150, and 200 mg.

For the once-daily cohorts, the median number of dosing days ranged from 17 (10 mg) to 190 days (20 mg). For the twice-daily cohorts, the median number of dosing days ranged between 11 days (at a dose of 200 mg) and 85 days (40 mg). The number of dosing days ranged between 13 and 127 days in the diabetic expansion cohort and 3 and 252 days in the biomarker cohort.

Dose escalation and MTD

DLTs were observed in 6 patients in total (3 patients each for the once-daily and twice-daily dosing schedules). One patient at the 400 mg once daily had grade 3 QTc prolongation. The QTc interval at screening (day −3) was 429 ms, and grade 3 toxicity (>500 ms) occurred 12 hours after dosing on day 2 with resolution by day 3 with transient grade 2 QTc prolongation 2 to 4 hours after dosing on day 3, after which the study drug was permanently discontinued. At 450 mg once daily, one patient experienced grade 2 abdominal pain and nausea, which was considered to be due to study drug and which led to dose interruption (>5 days in cycle 1); another patient developed grade 3 hyperglycemia. One patient at 150 mg twice daily developed grade 3 elevation of aspartate aminotransferase (AST). One patient at 200 mg twice daily, who had known liver metastases, developed grade 3 elevation of bilirubin with grade 4 elevation of both alanine aminotransferase (ALT) and AST that were considered to be related to study drug. At the same dose, grade 3 hyperglycemia was observed in one patient. On the basis of the observed DLT, the MTDs for the once- and twice-daily treatment schedules were determined to be 400 mg and 150 mg, respectively. The recommended phase II dose for OSI-906 was determined as 150 mg twice daily.

Safety

All patients experienced at least one AE during the study, with 76% of patients on the once-daily regimen and 85% of patients on the twice-daily regimen experiencing AEs that were considered by the investigators to be related to study drug. The majority of patients in the once-daily (58%) and twice-daily (70%) treatment regimens experienced drug-related AEs that were a maximum severity of grade 1 or 2. A total of 18% and 7% of patients in the once- and twice-daily regimens, respectively, experienced grade 3 AEs. Other than the grade 4 ALT and AST DLTs discussed previously, no other drug-related grade 4 toxicities were reported.

The most frequently reported drug-related AEs were vomiting, nausea, and fatigue for the once-daily regimen (Table 2) and nausea, fatigue, and hyperglycemia for the twice-daily cohort (Table 3). Six percent of patients in the once-daily regimen and 8% of those in the twice-daily regimen experienced a treatment-related SAE. For the once-daily regimen, drug-related SAEs included increased blood creatinine, renal failure, and acute renal failure. For the twice-daily regimen, drug-related SAEs included increased ALT and AST, anorexia, vomiting, increased blood creatinine, and acute renal failure.

Table 2. Drug-related AEs occurring at any time during treatment with once daily OSI-906

	Initial OSI-906 dose (mg)							
AEs	**10 ($n = 6$)**	**20 ($n = 3$)**	**40 ($n = 4$)**	**75 ($n = 3$)**	**150 ($n = 3$)**	**300 ($n = 4$)**	**400 ($n = 6$)**	**450 ($n = 4$)**
Any AE, *n* (%)	4 (67)	2 (67)	2 (50)	3 (100)	3 (100)	2 (50)	5 (83)	4 (100)
Gastrointestinal	3 (50)	1 (33)	0	3 (100)	2 (67)	2 (50)	1 (17)	3 (75)
Vomiting	3 (50)	0	0	2 (67)	1 (33)	1 (25)	0	2 (50)
Nausea	2 (33)	0	0	2 (67)	2 (67)	0	0	2 (50)
Diarrhea	0	0	0	0	0	2 (50)	1 (17)	0
Abdominal pain	0	0	0	0	0	0	0	2 (50)
General	0	2 (67)	2 (50)	0	0	0	3 (50)	1 (25)
Fatigue	0	2 (67)	2 (50)	0	0	0	3 (50)	1 (25)
Skin and subcutaneous tissue	0	1 (33)	1 (25)	2 (67)	1 (33)	2 (50)	0	0
Metabolism and nutrition	0	0	0	0	0	2 (50)	1 (17)	3 (75)
Hyperglycemia	0	0	0	0	0	0	1 (17)	3 (75)
Anorexia	0	0	0	0	0	1 (25)	0	1 (25)
Nervous system	0	0	0	2 (67)	1 (33)	1 (25)	0	2 (50)
Renal and urinary	0	0	0	0	0	0	2 (33)	0

NOTE: Drug-related AEs of all patients who received at least one dose of OSI-906 (safety analysis set). Events during follow-up are excluded. AEs are sorted by decreasing incidence overall for the once-daily regimen, first by system organ class, then by preferred term, and then alphabetically for preferred terms with the same incidence overall.

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Table 3. Drug-related AEs occurring at any time during treatment with twice-daily OSI-906

	Initial OSI-906 dose (mg)				
AEs	**20 ($n = 5$)**	**40 ($n = 3$)**	**75 ($n = 3$)**	**150 ($n = 39$)**	**200 ($n = 3$)**
Any AE, *n* (%)	2 (40)	1 (33)	2 (67)	37 (95)	3 (100)
Metabolism and nutrition	2 (40)	1 (33)	0	14 (36)	2 (67)
Hyperglycemia	2 (40)	0	0	8 (21)	1 (33)
Anorexia	0	1 (33)	0	3 (8)	1 (33)
Hyponatremia	0	0	0	3 (8)	0
Hypoalbuminemia	0	0	0	2 (5)	0
Hypokalemia	0	0	0	2 (5)	0
Gastrointestinal	1 (20)	0	1 (33)	13 (33)	3 (100)
Nausea	0	0	1 (33)	11 (28)	2 (67)
Vomiting	0	0	1 (33)	4 (10)	2 (67)
Constipation	0	0	0	2 (5)	1 (33)
Investigations	0	0	0	15 (38)	2 (67)
ALT increased	0	0	0	2 (5)	1 (33)
AST increased	0	0	0	2 (5)	1 (33)
Blood creatinine increased	0	0	0	3 (8)	0
Hemoglobin decreased	0	0	0	3 (8)	0
Weight decreased	0	0	0	3 (8)	0
Gamma-glutamyltransferase increased	0	0	0	2 (5)	0
General	0	0	2 (67)	13 (33)	1 (33)
Fatigue	0	0	2 (67)	11 (28)	0
Nervous system	0	0	0	11 (28)	3 (100)
Lethargy	0	0	0	7 (18)	3 (100)
Dizziness	0	0	0	3 (8)	0
Skin and subcutaneous tissue	0	0	0	9 (23)	0
Hyperhidrosis	0	0	0	3 (8)	0
Pruritus	0	0	0	3 (8)	0
Musculoskeletal and connective tissue	0	0	0	5 (13)	0
Muscle spasms	0	0	0	2 (5)	0
Musculoskeletal pain	0	0	0	2 (5)	0
Myalgia	0	0	0	2 (5)	0
Renal and urinary	0	0	0	3 (8)	0
Respiratory, thoracic, and mediastinal	0	0	0	3 (8)	0
Cough	0	0	0	2 (5)	0
Cardiac disorders	0	0	0	2 (5)	0

NOTE: Drug-related AEs of all patients who received at least one dose of OSI-906 (safety analysis set) including those in the expansion cohorts ($n = 29$; 20 in colorectal cancer and 9 in diabetic patients cohort). Events during follow-up are excluded. AEs are sorted by decreasing incidence overall for the once-daily regimen, first by system organ class, then by preferred term, and then alphabetically for preferred terms with the same incidence overall.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

For the expansion cohorts, 78% of patients in the diabetic cohort and 90% of patients in the biomarker cohort had an AE in the first 21 days of treatment that was considered to be drug related. One patient in the diabetic cohort and one patient in the colorectal cohort discontinued drug due to AEs on days 15 and 26, respectively. The most frequent drug-related AEs were hyperglycemia and fatigue in the diabetic cohort and nausea and fatigue in the biomarker cohort (Supplementary Table S1). There were no reported deaths during treatment with OSI-906. Ten patients died within 30 days of their last dose of OSI-906. All deaths were due to disease progression and were not considered to be treatment related.

Hyperglycemia

Hyperglycemia was considered to be treatment related in similar proportions of patients in the once-daily (12%) and twice-daily (11%) schedules. In the once-daily regimen, hyperglycemia occurred only at the two highest doses, whereas no dose-related pattern for its occurrence could be established in the twice-daily regimen. One patient treated with OSI-906 200 mg twice daily discontinued the study due to hyperglycemia.

In the diabetic expansion cohorts, grade 1 hyperglycemia was reported in 5 patients, with 3 patients experiencing transient grade 2 and 3 hyperglycemia during the course of the treatment. No alteration in diabetes medications versus baseline was required during the study.

Cardiac safety

Overall, 8 patients had grade 1 to 3 QTc prolongation, 4 with the once-daily regimen and 4 with the twice-daily regimen. In addition to the patient with dose-limiting grade 3 QTc prolongation (400 mg once daily), grade 2 QTc prolongation was observed during cycle 1 in 4 patients (days 1, 4, 5, and 8) at 450 mg once daily (2 patients) and 150 mg twice daily (2 patients). One additional patient developed grade 3 QTc prolongation as a new finding after 865 days (75 mg twice daily). In the opinion of the treating investigators, 3 patients in the once-daily dosing and 1 patient in the twice-daily dosing group had QT prolongations that were related to the study drug.

Pharmacokinetic analyses

In the dose-escalation cohorts, OSI-906 was rapidly absorbed after once-daily and twice-daily dosing on days 1 and 22 (Tables 4, 5, and 6). Plasma elimination parameters calculated on days 1 and 22 (Tables 4, 5, and 6) indicated that OSI-906 was eliminated quickly, and that volume of distribution (Vz/F) and clearance (CL/F) were not dose dependent. Similar results were observed for

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Table 4. Plasma OSI-906 pharmacokinetic parameters after single dosing (once-daily regimen, day 1)

Dose (mg)	10	20	40	75	150	300	400	450
Evaluable, *n*	6	3	4	3	3	4	6	4
t_{max} (h)	2.5 (1.0–10.0)	2.0 (1.0–4.0)	2.5 (2.0–4.0)	3.0 (0.8–4.0)	3.0 (2.0–6.1)	3.1 (2.0–8.0)	3.0 (1.9–24)	3.6 (3.0–6.0)
C_{max} (ng/mL)	76.6 (44.8–1,120)	171 (74.1–192)	420 (354–1,620)	1,040 (538–1,260)	1,440 (1,380–1,670)	2,725 (1,490–6,710)	2,905 (594–4,160)	5,415 (3,020–10,200)
AUC_{tau} (ng × h/mL)	223[a] (205–630)	630 (523–777)	1,874 (1,687–7,992)	4,621 (4,193–4,990)	9,811 (4,922–12,063)	26,527 (95,556–48,525)	22,258 (3,440–51,005)	50,574 (26,440–82,550)
AUC_{inf} (ng × h/mL)	223[a] (201–635)	599 (541–7,590)	1,887 (1,694–8,059)	4,649 (4,265–50,780)	10,083 (4,879–12,327)	27,944 (5,504–48,675)	16,485 (3,677–27,742)	60,403 (26,880–91,663)
CL/F (L/h)	44,789[a] (15,757–9,639)	33,397 (26,363–36,962)	21,306 (4,963–23,609)	16,131 (14,678–7,583)	14,876 (12,169–30,745)	10,736 (6,163–54,509)	24,448 (14,418–108,784)	7,450 (4,909–16,741)
$t_{1/2lambdaz}$ (h)	2.20[a] (1.11–3.22)	2.22 (2.20–2.41)	3.10 (2.56–3.72)	3.64 (2.97–4.28)	3.85 (1.35–4.23)	2.53 (1.15–5.16)	3.52 (2.35–5.09)	6.91 (3.62–8.65)
Vz/F (L)	104,055[a] (71,740–150,546)	106,897 (83,750–128,718)	85,173 (23,923–122,544)	91,204 (69,123–92,359)	67,587 (60,094–90,737)	79,933 (22,498–90,122)	92,471 (79,733–798,673)	87,411 (48,955–92,930)

NOTE: Data for all patients who had sufficient pharmacokinetic sampling associated with the OSI-906 doses (pharmacokinetic analysis set).
Abbreviations: t_{max}, time to reach observed concentration; AUC_{tau}, area under the concentration-time curve during the time interval between consecutive dosing; AUC_{inf}, area under the concentration-time curve from the time of dosing up to infinity with extrapolation of terminal phase; $t_{1/2lambaz}$, terminal elimination half-life; NC, not calculated.
[a]$n = 5$.

Table 5. Plasma OSI-906 pharmacokinetic parameters after multiple dosing (once-daily regimen, day 22)

Dose (mg)	10	20	40	75	150	300	400	450
Evaluable, *n*	2	3	3	3	3	3	3	2
t_{max} (h)	2.5 (2.0–3.0)	2.0 (2.0–2.0)	3.0 (2.0–4.1)	3.0 (2.1–5.8)	3.9 (3.0–6.0)	4.0 (3.1–5.9)	5.9 (2.2–8.0)	4.1 (4.0–4.1)
C_{max} (ng/mL)	57.5 (40.4–74.6)	171 (163–212)	639 (473–642)	1,000 (684–1,250)	1,570 (1,120–1,860)	8,450 (4,440–13,600)	4,180 (1,420 to −4,450)	3,565 (2,820–4,310)
AUC_{0-tau} (ng × h/mL)	253 (210–295)	658 (655–865)	3,312 (2,365–3,878)	6,063 (5,969–6,220)	13,306 (6,890–15,774)	85,212 (19,348–180,665)	31,091 (8,690–83,533)	54,684 (36,481–72,886)
AUC_{inf} (ng × h/mL)	243 (206–279)	663 (658–871)	3,359 (2,383–4,028)	6,259 (5,987–6,505)	13,839 (6,900–15,097)	52,474 (19,352–85,597)	20,219 (9,021–31,418)	NC[a]
CL/F (L/h)	40,701 (33,842–47,559)	30,398 (23,132–30,525)	12,079 (10,314–16,910)	12,369 (12,058–12,566)	11,273 (9,631–21,711)	9,513 (3,521–15,505)	12,866 (4,789–46,029)	NC[a]
$t_{1/2lambdaz}$ (h)	2.13 (1.68–2.58)	3.28 (2.99–3.58)	3.88 (3.07–5.15)	4.05 (3.20–5.12)	3.96 (2.52–4.41)	2.69 (1.69–15.5)	3.93 (3.32–4.53)	10.1 (9.71–10.4)
Vz/F (L)	120,545 (115,309–125,780)	131,814 (109,596–156,858)	74,991 (67,594–76,595)	72,250 (58,059–89,033)	71,802 (55,067–79,150)	25,705 (13,656–37,754)	181,317 (61,554–301,080)	NC[a]

NOTE: Data for all patients who had sufficient pharmacokinetic sampling associated with the OSI-906 doses (pharmacokinetic analysis set).
Abbreviations: t_{max}, time to reach observed concentration; AUC_{tau}, area under the concentration-time curve during the time interval between consecutive dosing; AUC_{inf}, area under the concentration-time curve from the time of dosing up to infinity with extrapolation of terminal phase; $t_{1/2lambaz}$, terminal elimination half-life; NC, not calculated.
[a]$n = 0$.

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Table 6. Plasma OSI-906 pharmacokinetic parameters after single and multiple dosing (twice-daily regimen)

OSI-906 PK parameters following single oral administration (twice-daily regimen, day 1)					
Dose (mg)	**20**	**40**	**75**	**150**	**200**
Evaluable, *n*	**5**	**3**	**3**	**10**	**3**
t_{max} (h)	3.0 (2.0–4.0)	2.0 (1.0–4.0)	3.0 (2.0–4.0)	2.1 (1.0–3.2)	3.0 (1.2–3.2)
C_{max} (ng/mL)	242 (121–284)	401 (395–659)	762 (629–1,040)	1,705 (869–3,090)	2,050 (970–2,990)
AUC_{tau} (ng × h/mL)	830 (366–1,508)	1,761 (1,093–1,804)	3,601 (2,437–5,814)	8,453 (2,557–11,795)	12,508 (4,668–17,809)
AUC_{inf} (ng × h/mL)	861 (388–1,624)	1,812 (1,098–1,815)	4,240 (2,487–6,742)	9,475 (2,649–12,411)	9,680[a] (4,932–14,428)
CL/F (L/h)	23,237 (12,319–51,536)	22,077 (22,040–36,434)	17,687 (11,124–30,265)	15,839 (12,086–56,634)	27,207[a] (13,862–40,552)
$t_{1/2lambdaz}$ (h)	2.24 (1.64–3.06)	1.65 (1.45–1.83)	3.52 (1.80–4.10)	2.93 (2.09–4.58)	3.09 (2.55–6.58)
Vz/F (L)	59,414 (39,865–227,717)	58,429 (52,490–76,261)	78,528 (65,576–89,724)	77,780 (37,730–173,756)	105,360[a] (61,701–149,020)
OSI-906 PK parameters following multiple oral administrations (twice-daily regimen, day 22)					
Evaluable, *n*	**3**	**3**	**3**	**9**	**1**
t_{max} (h)	2.0 (1.0–8.0)	3.0 (3.0–4.0)	6.0 (2.0–12.0)	2.0 (1.0–3.1)	1.1 (1.1–1.1)
C_{max} (ng/mL)	173 (110–451)	489 (470–1,290)	1,420 (944–2,370)	3,110 (1,190–4,290)	2,970 (2,970–2,970)
AUC_{0-tau} (ng × h/mL)	846 (616–1,542)	1,996 (1,577–5,331)	11,540 (3,408–18,256)	25,280 (6,967–32,567)	16,070 (16,070–16,070)
AUC_{inf} (ng × h/mL)	1,117[a] (645–1,589)	3,566[a] (1,590–5,542)	3,560[b] (3,560–3,560)	24,747[c] (7,588–24,926)	17,769 (17,669–17,669)
CL/F (L/h)	23,642 (12,974–32,456)	20,045 (7,503–25,362)	6,499 (4,108–22,007)	7,332[d] (5,425–21,531)	12,446 (12,466–12,466)
$t_{1/2lambdaz}$ (h)	2.49[a] (2.33–2.65)	1.73[a] (1.35–2.10)	2.66[b] (2.66–2.66)	5.03[e] (2.93–8.85)	3.23 (3.23–3.23)
Vz/F (L)	83,741[a] (43,576–123,907)	36,052[a] (22,767–49,336)	84,306[b] (84,306–84,306)	46,793[c] (44,950–91,032)	58,058 (58,058–58,058)

NOTE: Data for all patients who had sufficient pharmacokinetic sampling associated with the OSI-906 doses (pharmacokinetic analysis set).

Abbreviation: t_{max}, time to reach observed concentration; AUC_{tau}, area under the concentration-time curve during the time interval between consecutive dosing; AUC_{inf}, area under the concentration-time curve from the time of dosing up to infinity with extrapolation of terminal phase; $t_{1/2lambaz}$, terminal elimination half-life; PK, pharmacokinetic.

[a]$n = 2$; [b]$n = 1$; [c]$n = 3$; [d]$n = 4$; [e]$n = 8$.

the expansion cohorts on days 1 and 22 (Supplementary Table S2).

For both once-daily and twice-daily regimens of OSI-906, dose proportionality was observed for maximum observed concentration (C_{max}) at days 1 and 22 (Supplementary Table S3). The slope for the area under the curve (AUC) showed a statistically significant deviation from 1 on day 22 ($P = 0.003$ and $P = 0.014$ for once-daily and twice-daily dosing, respectively) and approached significance on day 1 ($P = 0.074$ for once-daily dosing), indicating that AUC increased in a more than dose-proportional manner.

The median trough plasma concentrations after twice-daily 75, 150, and 200 mg dosing on days 8, 15, and 22 were similar, indicating that steady-state concentrations were achieved by day 8. Approximately 2-fold accumulation of OSI-906 was observed at steady state after twice-daily dosing at 150 mg.

Pharmacodynamic analyses

In the 150 mg twice-daily dose cohorts, IGF1R and IR phosphorylation levels were substantially reduced 4 hours after the first OSI-906 dose and returned to nearly predose levels by 12 hours after dosing on day 1 (Fig. 1A). On days 8, 15, and 22, IGF1R and IR phosphorylation levels were decreased relative to predose levels on day 1 at all the time points assessed (Fig. 1A). This effect correlated with predose plasma concentrations of OSI-906 (Fig. 1B). At 150 mg, total plasma IGF1 concentrations increased relative to predose value during the 21-day dosing period, achieving maximal concentrations 15 days after the first dose (Fig. 1C).

Efficacy

Overall, 30 patients (46%) had stable disease as their best response, with a DCR of 50% for the once-daily schedule and 46.3% in the twice-daily schedule. Overall, of the 36 patients with colorectal cancer in the study, 17 (47%) had stable disease as their best response. Of all the patients with stable disease, 20 (67%) remained on the study for longer than 14 weeks, with 2 patients remaining on study for longer than 39 weeks.

None of the patients treated with OSI-906 once daily achieved a complete response or a partial response (PR) as best clinical response. In twice-daily dosing, one patient with melanoma (lymph node, skin, and thoracic wall metastases) treated at 75 mg twice daily experienced a PR after therapy was begun and a pathologic complete response following surgery, which was performed 28 months after the patient entered the study to remove the right arm melanoma as well as the right axillary lymph nodes. The patient remains free of disease 15 months after stopping treatment with OSI-906 and 52 months since entering the study. The patient had previously received IFNα2bA adjuvant and chemotherapy with dacarbazine, paclitaxel, and carboplatin.

KRAS mutation analysis

Twenty-four tumor samples from patients with colorectal cancer were analyzed for *KRAS* mutations (20 from the expansion cohort, 3 from the diabetic cohort, one from the dose-escalation cohort). All these patients received 150 mg of OSI-906 twice daily. *KRAS* mutations were detected in 12 of 24 (50%) samples analyzed. One patient had a rare A59G mutation (21, 22). Twenty of 24 patients were evaluable for best clinical response. Disease stabilization was observed in 3 of 11 patients with wild-type *KRAS* tumors (33%). Five of 9 patients with mutant *KRAS* tumors (56%) had disease stabilization as their best clinical response. Patients with mutant *KRAS* tumors were on study longer than those with wild-type *KRAS* (median, 57 days vs. 42 days; Supplementary Fig. S2).

Discussion

The present study has shown that OSI-906, a selective dual inhibitor of the IGF1R and IR, has an acceptable tolerability and safety profile and is associated with preliminary clinical activity in patients with advanced solid tumors.

The majority of patients experienced treatment-related toxicity of grade 1 or 2 in severity, with the most frequently reported AEs being

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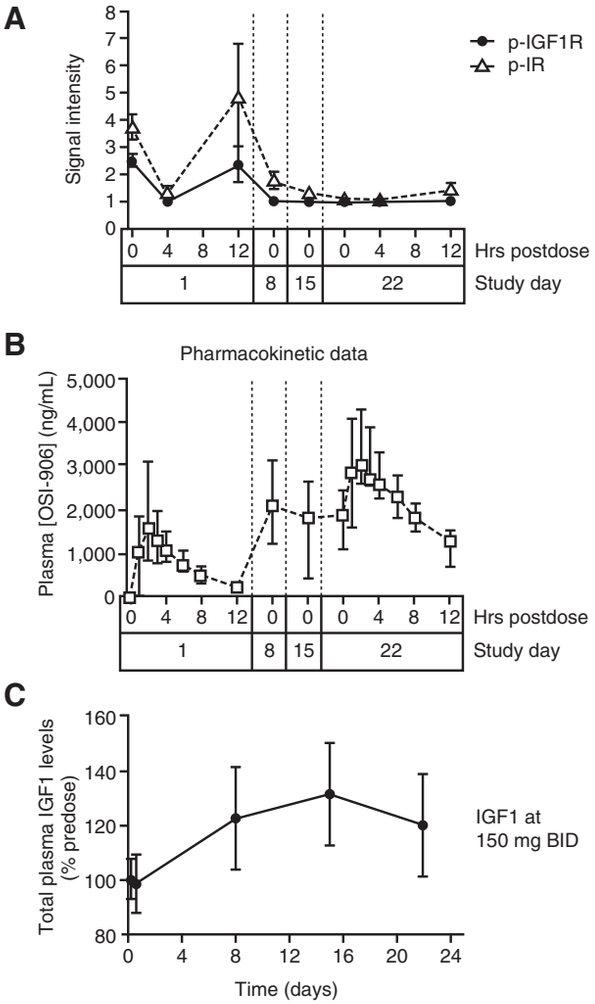

Figure 1.
Pharmacodynamic effects of OSI-906 in PBMCs and plasma. A, data are shown for patients in the dose-escalation 150 mg twice-daily (BID) cohort with PBMC sample sets evaluable for pharmacodynamic assessment and with detectable p-IGF1R ($n = 5$) and p-IR signals ($n = 6$). Samples obtained before dosing are labeled 0 hours. Signal intensity for IGF1R and IR phosphorylation in PBMCs is graphed relative to assay background (set at intensity of 1). p-IGF1R and p-IR data are shown as mean values ± SEs of the mean. B, pharmacokinetic data ($n = 6$) are shown as median values ± range. C, effects on total plasma IGF1 concentrations over time following treatment with OSI-906 150 mg twice daily ($n = 25$). Abbreviations: p-IGF-1R, phospho-insulin-like growth factor-1 receptor; p-IR, phospho-insulin receptor.

nausea and vomiting, fatigue, and hyperglycemia. Hyperglycemia has been among the most common treatment-related toxicities reported for monoclonal antibodies against IGF1R as well as tyrosine kinase inhibitors (1). Overall, 17 patients (19%) experienced hyperglycemia, the majority of whom (14) were receiving OSI-906 twice daily. To our knowledge, this is the first study of a tyrosine kinase inhibitor targeting IGF1R and IR to include a cohort of diabetic patients with advanced solid tumors. As expected, hyperglycemia was more prevalent in the diabetic expansion cohort versus the dose-escalation cohorts and biomarker expansion cohort. However, no alteration in diabetes medications was required during the study. Further, no patients had clinically significant elevated glycosylated hemoglobin or lactate levels during the study and, overall, no differences in safety were observed when comparing diabetic with nondiabetic patients with advanced solid tumors, supporting the acceptable tolerability profile of OSI-906 in patients with diabetes.

Overall, no clear safety differences were observed between the once-daily and twice-daily regimens. However, there was a higher incidence of patients discontinuing the study due to AEs in the once-daily regimen (15%) than in the twice-daily regimen (8%). The clinical relevance of this observation is yet to be established, and further investigations are needed. When comparing intermittent and continuous dosing regimens at the respective recommended phase II doses, continuous administration appeared to be associated with lower occurrence of gastrointestinal toxicities, including nausea and vomiting (19). More patients experienced hyperglycemia following continuous administration of OSI-906 at the recommended phase II dose, most likely owing to the inclusion of a diabetic expansion cohort in which, as expected, this toxicity was more common (19). Liver function test abnormalities, which were considered to be related to OSI-906, were only reported with continuous administration at the recommended phase II dose (19).

The pharmacokinetics and pharmacodynamics of OSI-906 were also characterized as secondary objectives. Following once-daily and twice-daily dosing, OSI-906 was rapidly absorbed with a half-life ranging between 1.65 and 10.1 hours. Exposure increases were not dose proportional.

At the recommended phase II dose of 150 mg twice daily, IGF1R and IR phosphorylation was substantially reduced 4 hours after administration of OSI-906. These effects correlated with plasma concentrations of OSI-906 and increased plasma IGF1 concentrations, an indirect measure of IGF signaling inhibition. The plasma concentrations of OSI-906 were above the predicted minimum plasma concentrations for antitumor activity based on preclinical studies (18). Thus, the plasma concentration of OSI-906 achieved at the recommended dose of 150 mg twice daily was sufficient to inhibit IGF1R and IR phosphorylation in PBMCs, providing proof of concept of biologic activity at the recommended dose for phase II studies. Overall pharmacokinetic and pharmacodynamic profiles of OSI-906 support twice-daily dosing for continuous inhibition of the IGF1R/IR pathway.

In this study, 30 patients (46%) had stable disease as their best clinical response. Notably, a complete response was observed in 1 patient with melanoma following surgery after 28 months of treatment with OSI-906. Further genetic analysis using next-generation sequencing, which is under way in this patient, may reveal the basis for the sensitivity to OSI-906 and aid the identification of patients most likely to respond to this targeted anticancer drug, as recently shown in bladder cancer with the mTOR inhibitor everolimus (23). Disease stabilization was observed in a significant number of patients with colorectal cancer (47%) in which the IGF pathway has been shown to play an important role in driving tumorigenesis (8, 24) as well as mediating resistance to established anticancer therapy, such as agents targeting the EGF pathway (2, 25). Strategies to overcome resistance in colorectal cancer by combining antibodies against IGF1R (IMC-A12) and EGF receptor (cetuximab) have shown limited efficacy in a phase II clinical trial (26). Notably, the dual IGF1R/IR tyrosine kinase inhibitor PQIP has been shown to enhance the antiproliferative effects of standard chemotherapy

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agents in colorectal cancer cell lines *in vitro* (27). The disease stabilization observed in patients with colorectal cancer in the present study may support the potential usefulness of OSI-906 when administered in combination with active chemotherapy in colorectal cancer.

KRAS, a key downstream effector of IGF1R and EGF receptor, is mutated in approximately 40% to 50% of colorectal cancers (28). The most common mutations identified in *KRAS* lead to constitutive expression of high levels of activated *KRAS* (28). Several retrospective assessments of *KRAS* status in phase III, randomized trials of therapies targeting EGF receptor have confirmed that the activity of these agents is restricted to patients with *KRAS* wild-type tumors (29, 30). In contrast, the efficacy of figitumumab, a monoclonal antibody against IGF1R, has been shown to be independent of *KRAS* mutational status in cancer cell lines and xenograft models (31). It is noteworthy that the results of the mutation analysis performed in a subset of patients with colorectal cancer in the present study suggest that *KRAS*-activating mutations do not correlate with a poor response to OSI-906 treatment. However, given the small number of tumors included in the present exploratory analysis, caution in the interpretation of the data should be used. Further and larger studies will be needed to fully characterize the role of *KRAS* mutational status in treatment response to OSI-906 in patients with colorectal cancer. This will further allow the identification of the patient population most likely to benefit from treatment with OSI-906.

In conclusion, based on the tolerability of the regimen, the evidence for antitumor activity, and its pharmacodynamic profile, the present study supports the strategy of targeting IGF1R and IR with continuous dosing of OSI-906 in patients with solid cancers. Several phase I/II studies combining OSI-906 with paclitaxel (32) and erlotinib (33, 34) are currently ongoing.

Disclosure of Potential Conflicts of Interest

L. Goff reports receiving a commercial research grant from OSI/Astellas. S. Poondru is an employee of Astellas Pharma Global Development. R. Simantov is an employee of Astellas Pharma Global Development and OSI Pharmaceuticals. R. Gedrich has ownership interest (including patents) in OSI Pharmaceuticals. E. Chan is a consultant/advisory board member for Amgen and Eli Lilly. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: I. Puzanov, S. Poondru, A. Stephens, T.R.J. Evans
Development of methodology: I. Puzanov, R. Gedrich, A. Stephens
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): I. Puzanov, C.R. Lindsay, L. Goff, J. Sosman, J. Berlin, S. Poondru, R. Gedrich, A. Stephens, E. Chan, T.R.J. Evans
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): I. Puzanov, C.R. Lindsay, L. Goff, S. Poondru, R. Simantov, R. Gedrich, E. Chan, T.R.J. Evans
Writing, review, and/or revision of the manuscript: I. Puzanov, C.R. Lindsay, L. Goff, J. Sosman, J. Gilbert, J. Berlin, S. Poondru, R. Simantov, R. Gedrich, A. Stephens, E. Chan, T.R.J. Evans
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): I. Puzanov, R. Gedrich
Study supervision: I. Puzanov, J. Sosman, A. Stephens, E. Chan, T.R.J. Evans
Others (phase I director, supervised weekly toxicity meetings and review of data issues to assure accurate and efficient reporting of data while trial was ongoing): J. Berlin

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References

1. Gao J, Chang YS, Jallal B, Viner J. Targeting the insulin-like growth factor axis for the development of novel therapeutics in oncology. Cancer Res 2012;72:3–12.
2. Pollak M. The insulin and insulin-like growth factor receptor family in neoplasia: an update. Nat Rev Cancer 2012;12:159–69.
3. el Atig F, Garrouste F, Remacle-Bonnet M, Sastre B, Pommier G. Alterations in serum levels of insulin-like growth factors and insulin-like growth-factor-binding proteins in patients with colorectal cancer. Int J Cancer 1994;57:491–7.
4. Hankinson SE, Willett WC, Colditz GA, Hunter DJ, Michaud DS, Deroo B, et al. Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. Lancet 1998;351:1393–6.
5. Ma J, Pollak MN, Giovannucci E, Chan JM, Tao Y, Hennekens CH, et al. Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-I and IGF-binding protein-3. J Natl Cancer Inst 1999;91:620–5.
6. Palmqvist R, Hallmans G, Rinaldi S, Biessy C, Stenling R, Riboli E, et al. Plasma insulin-like growth factor 1, insulin-like growth factor binding protein 3, and risk of colorectal cancer: a prospective study in northern Sweden. Gut 2002;50:642–6.
7. Peyrat JP, Bonneterre J, Hecquet B, Vennin P, Louchez MM, Fournier C, et al. Plasma insulin-like growth factor-1 (IGF-1) concentrations in human breast cancer. Eur J Cancer 1993;29A:492–7.
8. Pollak MN, Schernhammer ES, Hankinson SE. Insulin-like growth factors and neoplasia. Nat Rev Cancer 2004;4:505–18.
9. Stattin P, Rinaldi S, Biessy C, Stenman UH, Hallmans G, Kaaks R. High levels of circulating insulin-like growth factor-I increase prostate cancer risk: a prospective study in a population-based nonscreened cohort. J Clin Oncol 2004;22:3104–12.
10. Vadgama JV, Wu Y, Datta G, Khan H, Chillar R. Plasma insulin-like growth factor-I and serum IGF-binding protein 3 can be associated with the progression of breast cancer, and predict the risk of recurrence and the probability of survival in African-American and Hispanic women. Oncology 1999;57:330–40.
11. Resnicoff M, Tjuvajev J, Rotman HL, Abraham D, Curtis M, Aiken R, et al. Regression of C6 rat brain tumors by cells expressing an antisense insulin-like growth factor I receptor RNA. J Exp Ther Oncol 1996;1:385–9.
12. Cohen BD, Baker DA, Soderstrom C, Tkalcevic G, Rossi AM, Miller PE, et al. Combination therapy enhances the inhibition of tumor growth with the fully human anti-type 1 insulin-like growth factor receptor monoclonal antibody CP-751,871. Clin Cancer Res 2005;11:2063–73.
13. Garber K. IGF-1: old growth factor shines as new drug target. J Natl Cancer Inst 2005;97:790–2.
14. Wang Y, Hailey J, Williams D, Wang Y, Lipari P, Malkowski M, et al. Inhibition of insulin-like growth factor-I receptor (IGF-IR) signaling and tumor cell growth by a fully human neutralizing anti-IGF-IR antibody. Mol Cancer Ther 2005;4:1214–21.
15. Sachdev D, Hartell JS, Lee AV, Zhang X, Yee D. A dominant negative type I insulin-like growth factor receptor inhibits metastasis of human cancer cells. J Biol Chem 2004;279:5017–24.

16. García-Echeverría C, Pearson MA, Marti A, Meyer T, Mestan J, Zimmermann J, et al. In vivo antitumor activity of NVP-AEW541-A novel, potent, and selective inhibitor of the IGF-IR kinase. Cancer Cell 2004;5:231–9.
17. Ji QS, Mulvihill MJ, Rosenfeld-Franklin M, Cooke A, Feng L, Mak G, et al. A novel, potent, and selective insulin-like growth factor-I receptor kinase inhibitor blocks insulin-like growth factor-I receptor signaling in vitro and inhibits insulin-like growth factor-I receptor dependent tumor growth in vivo. Mol Cancer Ther 2007;6:2158–67.
18. Mulvihill MJ, Cooke A, Rosenfeld-Franklin M, Buck E, Foreman K, Landfair D, et al. Discovery of OSI-906: a selective and orally efficacious dual inhibitor of the IGF-1 receptor and insulin receptor. Future Med Chem 2009;1:1153–71.
19. Jones RL, Kim ES, Nava-Parada P, Alam S, Johnson FM, Stephens A, et al. Phase I study of intermittent oral dosing of the insulin-like growth factor-1 and insulin receptors inhibitor OSI-906 in patients with advanced solid tumors. Clin Cancer Res 2015;21:693–700.
20. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–16.
21. Stefanius K, Ylitalo L, Tuomisto A, Kuivila R, Kantola T, Sirniö P, et al. Frequent mutations of KRAS in addition to BRAF in colorectal serrated adenocarcinoma. Histopathology 2011;58:679–92.
22. Wójcik P, Kulig J, Okoń K, Zazula M, Moździoch I, Niepsuj A, et al. KRAS mutation profile in colorectal carcinoma and novel mutation–internal tandem duplication in KRAS. Pol J Pathol 2008;59:93–6.
23. Iyer G, Hanrahan AJ, Milowsky MI, Al-Ahmadie H, Scott SN, Janakiraman M, et al. Genome sequencing identifies a basis for everolimus sensitivity. Science 2012;338:221.
24. Shiratsuchi I, Akagi Y, Kawahara A, Kinugasa T, Romeo K, Yoshida T, et al. Expression of IGF-1 and IGF-1R and their relation to clinicopathological factors in colorectal cancer. Anticancer Res 2011;31:2541–5.
25. Benvenuti S, Sartore-Bianchi A, Di Nicolantonio F, Zanon C, Moroni M, Veronese S, et al. Oncogenic activation of the RAS/RAF signaling pathway impairs the response of metastatic colorectal cancers to anti-epidermal growth factor receptor antibody therapies. Cancer Res 2007;67:2643–8.
26. Reidy DL, Vakiani E, Fakih MG, Saif MW, Hecht JR, Goodman-Davis N, et al. Randomized, phase II study of the insulin-like growth factor-1 receptor inhibitor IMC-A12, with or without cetuximab, in patients with cetuximab- or panitumumab-refractory metastatic colorectal cancer. J Clin Oncol 2010;28:4240–6.
27. Flanigan SA, Pitts TM, Eckhardt SG, Tentler JJ, Tan AC, Thorburn A, et al. The insulin-like growth factor I receptor/insulin receptor tyrosine kinase inhibitor PQIP exhibits enhanced antitumor effects in combination with chemotherapy against colorectal cancer models. Clin Cancer Res 2010;16:5436–46.
28. Baldus SE, Schaefer KL, Engers R, Hartleb D, Stoecklein NH, Gabbert HE. Prevalence and heterogeneity of KRAS, BRAF, and PIK3CA mutations in primary colorectal adenocarcinomas and their corresponding metastases. Clin Cancer Res 2010;16:790–9.
29. Jonker DJ, O'Callaghan CJ, Karapetis CS, Zalcberg JR, Tu D, Au HJ, et al. Cetuximab for the treatment of colorectal cancer. N Engl J Med 2007;357:2040–8.
30. Tol J, Nagtegaal ID, Punt CJ. BRAF mutation in metastatic colorectal cancer. N Engl J Med 2009;361:98–9.
31. Ii M, Li H, Adachi Y, Yamamoto H, Ohashi H, Taniguchi H, et al. The efficacy of IGF-I receptor monoclonal antibody against human gastrointestinal carcinomas is independent of k-ras mutation status. Clin Cancer Res 2011;17:5048–59.
32. ClinicalTrials.gov_Study NCT00889382. Available from: http://www.clinicaltrials.gov/ct2/show/NCT00889382?term=OSI-906&rank=14. Accessed September 25, 2014.
33. ClinicalTrials.gov_Study. NCT01221077. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01221077?term=OSI-906&rank=3. Accessed September 25, 2014.
34. ClinicalTrials.gov_Study NCT01186861. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01186861?term=OSI-906&rank=9. Accessed September 25, 2014.

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