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Clinical Cancer Research

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

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Abstract

Purpose: We determined the maximum tolerated dose (MTD), safety, pharmacokinetics, pharmacodynamics, and preliminary activity of OSI-906, a potent, oral, dual inhibitor of insulin-like growth factor-1 receptor (IGF1R) and insulin receptor (IR), in patients with advanced solid tumors.

Experimental Design: This was a multicenter, open-label, dose escalation phase I study evaluating three intermittent dosing schedules of once-daily OSI-906 [schedule (S) 1, days 1–3 every 14 days; S2, days 1–5 every 14 days; S3, days 1–7 every 14 days]. A fed-fasting expansion cohort was included in the study.

Results: Seventy-nine patients were enrolled: 62 in S1, 4 in S2, and 13 in S3. S2 was discontinued. Dose-limiting toxicity comprised grade 3–4 hyperglycemia, vomiting, fatigue, and prolonged QTc interval. The MTD and recommended phase II dose of OSI-906 was 600 mg for both S1 and S3 schedules. Other common adverse events were grade 1–2 nausea, vomiting, fatigue, and diarrhea. The pharmacokinetics of OSI-906 was dose linear, and the terminal half-life ranged between 2 and 6 hours. High-fat meals had a moderate effect on the pharmacokinetics of OSI-906. At the MTD, inhibition of IGF1R and IR was observed in peripheral blood mononuclear cells. An increase in plasma IGF1 concentrations, an indirect measure of IGF1R signaling inhibition, was seen at doses $\geq$ 450 mg. Two patients with adrenocortical carcinoma achieved partial responses.

Conclusion: The MTD of 600 mg was well tolerated and associated with preliminary antitumor activity. These data support further evaluation of OSI-906 in solid tumors. *Clin Cancer Res; 21(4); 693–700. ©2014 AACR.*

See related commentary by Yee, p. 667

Introduction

Activation of the insulin growth factor (IGF) pathway by binding of IGF1, IGF2, and insulin to IGF1 receptor (IGF1R) plays a key role in the growth and development of normal tissues. In recent years, compounds targeting IGF1R have become an area of intense investigation as a result of the recognition that this receptor also plays a role in cancer development and progression (1–3). Inhibition of IGF1R by various approaches, including antisense RNA (4), anti-IGF1R antibodies (5–9), and small-molecule inhibitors (10) has been shown to reduce tumor growth in human tumor xenograft models. However, the results of clinical trials have been disappointing, and clinical efficacy has only been identified in patients with certain tumors.

Several studies have indicated that insulin receptor (IR), which also mediates IGF signaling, is overexpressed in breast, colon, lung, ovarian, and thyroid cancers, thus playing a significant role in the development and progression of these malignancies (11). Furthermore, there is evidence to suggest that compensatory receptor tyrosine kinase (RTK) signaling is a major mode of resistance to antitumor agents that selectively target a single RTK in tumor cells. Indeed, preclinical studies have shown that amplified IR signaling conveys intrinsic resistance to IGF1R inhibitors (12, 13). Dual inhibition of IGF1R and IR may result in improved efficacy in IGF1R/IR–driven tumors, also by preventing IGF1R/IR–mediated compensatory signaling.

OSI-906 is a potent, oral, small-molecule inhibitor of both IGF1R and IR (14). Preclinical data suggested that OSI-906 may be better tolerated at higher doses using an intermittent dosing schedule, without any impact on efficacy. We conducted a first-in-human study evaluating three intermittent dosing schedules of OSI-906 in patients with solid tumors. This study was conducted

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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 (IGF1R) and insulin (IR) receptors was generally well tolerated when administered once daily on days 1 to 3 (S1) and days 1 to 7 (S3) of a 14-day schedule, with evidence of antitumor activity. The pharmacokinetic profile of OSI-906 revealed dose-dependent drug exposure, with no significant accumulation observed after repeated dosing. At the maximum tolerated dose of 600 mg, 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, confirming proof-of-concept biologic activity. Intermittent dosing of OSI-906 is being investigated in combination with weekly paclitaxel in patients with ovarian cancer.

in parallel with a trial examining continuous dosing schedules of OSI-906 (15).

Materials and Methods

Patient population

Male and female patients aged ≥ 18 years who had histologically or cytologically proven malignancy that was metastatic and refractory to established therapy were candidates for this study. Inclusion criteria were life expectancy ≥ 12 weeks; Eastern Cooperative Oncology Group performance status of 0–2; fasting glucose ≤125 mg/dL (7 mmol/L) at baseline; electrolytes within normal limits; and adequate hematopoietic, hepatic, and renal function. Patients with any of the following exclusion criteria were not enrolled on the trial: documented history of diabetes; uncontrolled significant cardiac disease, including second- or third-degree heart block or ischemic heart disease; QTc interval > 450 msec at baseline; poorly controlled hypertension; and congestive heart failure of New York Heart Association (NYHA) ≥ Class II. Additional details on exclusion criteria and concomitant treatments are presented in the Supplementary Materials and Methods.

Approval was obtained from the appropriate ethics committees and regulatory authorities for the participating centers. All patients gave written informed consent before trial entry, and the study was conducted according to the principles of the Declaration of Helsinki and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals ICH Harmonised Tripartite Guideline for Good Clinical Practice.

Study design

This was a multicenter, phase I, open-label, dose escalation study in patients with advanced solid tumors. The primary objectives were to determine the maximum tolerated dose (MTD) and to establish the recommended phase II dose of oral once-daily OSI-906 for each of the three intermittent dosing schedules. The secondary objectives were to evaluate safety, including dose-limiting toxicities (DLTs), and pharmacokinetic profiles and to seek preliminary evidence of antitumor activity. Separate cohorts of three to six eligible patients were assigned to one of three intermittent dosing schedules (S1–S3) with a 14-day treatment cycle (S1, days 1–3; S2, days 1–5; S3, days 1–7), starting at a dose of 10 mg in S1. A separate, randomized, fed-fasted expansion cohort was enrolled, once the MTD was established, to evaluate the effect of a high-fat meal on the pharmacokinetics of OSI-906. A minimum of 12 subjects were required in this expansion cohort based on the variability in the pharmacokinetics of OSI-906.

Dose escalation and determination of MTD

Dose escalation proceeded independently in each schedule and was dependent on toxicity (graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, v3) in the previous cohort. If there were no toxicities related to OSI-906 or if the maximum grade of toxicity related to OSI-906 was grade 1 in the first treatment period for any patient in the cohort, then dose escalation of up to 100% was implemented. If there was any ≥ grade 2 toxicity related to OSI-906 in the first treatment period for any patient in the cohort, then dose escalation was limited to a maximum of 50% in all future cohorts.

A DLT was defined as any toxicity considered to be related to the study drug and occurring in the initial 14-day treatment period; specifically, grade 4 neutrophil count for ≥ 7 days; ≥ grade 3 febrile neutropenia; ≥ grade 3 clinically or microbiologically documented infection with ≥ grade 3 neutropenia or grade 4 thrombocytopenia or grade 3 thrombocytopenia accompanied by bleeding or requiring transfusion; ≥ grade 3 fatigue; ≥ grade 3 gamma-glutamyl transpeptidase; ≥ grade 3 nausea, vomiting, or diarrhea if not premedicated or adequately treated; ≥ grade 3 hypertension if not adequately treated; ≥ grade 3 signs or symptoms of glucose intolerance or ≥ grade 2 hyperglycemia accompanied by symptoms of glucose intolerance; ≥ grade 3 electrolyte abnormalities due to glucose intolerance and not attributable to another cause; positive blood ketones accompanied by ≥ grade 2 hyperglycemia or acidosis, grade 4 hyperglycemia; inability to complete the designated schedule; or inability to begin a second treatment period by day 29 due to drug-related toxicity.

If a DLT occurred in any one patient, up to three additional patients were to be entered at the same dose level for a total of up to six evaluable patients per cohort. If one of six patients had a DLT in an expanded cohort, dose escalation was limited to a maximum of 30% in all future cohorts. If two or more patients experienced DLT, the MTD was exceeded (i.e., two or more patients with DLT of a maximum of six evaluable patients). Dose escalation ceased, and additional patients were to be treated at the next lower dose level or an intermediate dose level (if appropriate) to determine the MTD and establish a recommended phase II dose of OSI-906 for each schedule. Dosing in S2 and subsequently in S3 was initiated after review of safety and pharmacokinetic data from six dose levels in S1.

Safety

Safety was assessed by monitoring for DLTs; adverse events (AEs); 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

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Table 1. Demographics and baseline characteristics

Characteristic		Treatment schedule		
		S1 ($n = 62$)	S2 ($n = 4$)	S3 ($n = 13$)
Gender, *n* (%)	Female	30 (48)	1 (25)	7 (54)
	Male	32 (52)	3 (75)	6 (46)
Age, y	Median	55.0	61.7	53.0
	Range	18.0–76.0	48–71	28.0–69.0
ECOG PS, *n* (%)	0	16 (26)	0	4 (31)
	1	44 (71)	4 (100)	8 (62)
	2	2 (3)	0	1 (8)
Tumor type, *n* (%)	NSCLC	17 (27)	0	2 (15)
	Other	12 (19)	2 (50)	3 (23)
	Sarcoma	10 (16)	0	1 (8)
	Adrenocortical	9 (15)	1 (25)	5 (38)
	Carcinoma	8 (13)	0	2 (15)
	Colorectal	2 (3)	0	0
	Breast	2 (3)	0	0
	Ovarian	2 (3)	0	0
	Melanoma	0	0	0
	Renal	0	1 (25)	0
Prior lines of systemic therapy, *n* (%)	0–2	16 (26)	2 (50)	4 (31)
	3–5	26 (42)	2 (50)	9 (69)
	6–7	6 (10)	0	0
Prior radiation, *n* (%)	No	32 (52)	1 (25)	6 (46)
	Yes	30 (48)	3 (75)	7 (54)
Prior surgery, *n (%)*	No	20 (32)	2 (50)	4 (31)
	Yes	42 (68)	2 (50)	9 (69)
Prior endocrine, immunotherapy, and other agents, *n* (%)	No	59 (95)	2 (50)	13 (100)
	Yes	3 (5)	2 (50)	0

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; s, schedule.

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 $\geq$ 60 msec compared with the day 1 predose value or an absolute increase of > 500 msec at any time.

Pharmacokinetics

In the dose escalation cohorts, blood samples were collected for pharmacokinetic assessment at 0 (predose), 1, 2, 3, 4, 6, 8, 10, or 12 and 24 hours postdose on day 1 (all schedules), day 3 (S1 only), day 5 (S2 only), and day 7 (S3 only). Urine samples were also collected on the same days.

The pharmacokinetics of OSI-906 under fasted and fed conditions were also examined using a standard crossover design in a separate expansion cohort of 12 patients who were randomized to take OSI-906 at a dose of 300 mg (two 150-mg tablets) once daily using S1 after an overnight fast in the first treatment period and after a standard high-fat meal in the second treatment period or vice versa. Blood samples for pharmacokinetic assessment were collected on day 1 of both treatment periods.

To assess the relative bioavailability of two of the formulations used in the study (tablets and capsules), seven patients in the S1 dose-bridging cohort were given 150-mg tablets (total dose, 600 mg) to compare with 100-mg capsules (total dose, 600 mg) in a noncrossover manner. Pharmacokinetic assessments for these patients were compared with those of patients who took capsules in both S1 (6 patients) and S3 (10 patients).

Plasma and urine concentrations of OSI-906 were determined using validated liquid chromatography/mass spectrometry methods. Pharmacokinetic parameters were estimated by a noncompartmental method.

Pharmacodynamics

In the dose escalation cohorts, blood samples were collected at 0 (predose), 4, and 24 hours postdose on day 1 (all schedules), day 3 (S1 only), day 5 (S2 only), and day 7 (S3 only), at predose on day 15 (all schedules) for pharmacodynamic biomarker

Table 2. Treatment-related AEs occurring in at least two patients over the study period

	Treatment schedule/OSI-906 dose (mg)								
	S1						S2	S3	
	10–80 ($n = 12$)	150 ($n = 4$)	300 ($n = 23$)	450 ($n = 4$)	600 ($n = 13$)	750 ($n = 6$)	450 ($n = 4$)	450 ($n = 3$)	600 ($n = 10$)
Any AE, *n* (%)	4 (25)	1 (25)	9 (39)	2 (50)	11 (85)	5 (83)	1 (25)	1 (33)	5 (50)
Nausea	0	1 (25)	2 (9)	1 (25)	5 (38)	3 (50)	0	1 (33)	3 (30)
Vomiting	0	0	0	0	3 (23)	4 (67)	0	1 (33)	3 (30)
Diarrhea	1 (8)	1 (25)	1 (4)	0	3 (23)	1 (17)	0	0	3 (30)
Fatigue	1 (8)	1 (25)	3 (23)	1 (25)	3 (23)	0	0	0	1 (10)
Hyperglycemia	0	0	3 (13)	0	2 (15)	1 (17)	0	0	1 (10)

NOTE: All the patients who received at least one dose of OSI-906.

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Table 3. Summary of pharmacokinetic parameters after single and multiple dosing of OSI-906 (S1)

OSI-906 pharmacokinetic parameters following single oral administration (S1, day 1)										
Dose, mg	**10**	**20**	**40**	**80**	**150**	**300[a]**	**450**	**600**	**750**	
Evaluable, *n*	3	3	3	3	4	6	4	13	6	
t_{max}, h	2.1 (2.0–3.0)	4.0 (1.1–6.0)	3.0 (2.0–6.0)	2.0 (1.0–3.0)	3.1 (2.1–3.2)	3.0 (1.0–25.7)	7.5 (2.0–8.0)	3.9 (2.0–5.9)	4.1 (3.0–6.1)	
C_{max}, μg/mL	0.106 (0.0700–0.128)	0.176 (0.140–0.178)	0.460 (0.220–0.577)	0.531 (0.416–1.76)	1.08 (0.800–2.70)	2.68 (0.638–6.76)	3.20 (1.19–4.86)	5.39 (3.40–9.01)	8.02 (5.81–17.3)	
AUC_{tau}, μg × h/mL	0.408 (0.173–0.671)	0.724 (0.621–0.984)	2.19 (1.28–3.96)	2.68 (2.19–7.75)	8.92 (4.63–16.7)	19.8 (3.61–51.1)	25.2 (10.6–70.3)	56.3 (22.2–98.5)	84.1 (47.7–235)	
AUC_{inf}, μg × h/mL	0.408 (0.173–0.672)	0.725 (0.621–0.990)	2.21 (1.31–3.97)	2.69 (2.20–7.79)	9.10 (4.64–16.8)	17.1 (3.77–54.2)	19.1 (10.6–32.2)	56.4 (22.4–106)	76.2 (52.6–117)	
CL/F, L/h	24.5 (14.9–57.8)	27.6 (20.2–32.2)	18.1 (10.1–30.6)	29.7 (10.3–36.4)	16.6 (8.91–32.3)	17.5 (5.54–79.6)	23.5[d] (14.0–42.3)	10.6 (5.64–26.8)	10.8 (6.41–14.3)	
$t_{1/2\lambda z}$, h	2.10 (1.94–2.23)	2.20 (2.01–2.75)	3.24 (2.15–4.67)	3.14 (2.72–4.31)	3.07 (2.72–4.31)	2.81 (1.99–5.32)	3.62 (2.24–8.75)	3.59 (2.35–25.6)	6.08 (1.94–10.1)	
Vz/F, L	68.6 (45.1–186)	87.7 (80.2–93.5)	84.7 (31.3–206)	136 (46.6–142)	91.9 (36.7–127)	65.5 (29.2–418)	135 (66.0–136)	67.1 (32.4–122)	47.6 (39.4–129)	
OSI-906 pharmacokinetic parameters following multiple oral administrations (S1, day 3)										
Evaluable, *n*	**3**	**3**	**3**	**3**	**4**	**6**	**4**	**12**	**4**	
t_{max}, h	4.0 (2.0–6.0)	2.0 (2.0–3.0)	2.0 (2.0–2.1)	2.0 (2.0–2.0)	2.0 (2.0–3.0)	2.5 (2.0–3.9)	6.0 (2.0–8.0)	3.0 (1.1–12.0)	2.0 (1.2–4.2)	
C_{max}, μg/mL	0.0950 (0.177–0.174)	0.203 (0.0938–0.262)	0.413 (0.156–0.473)	0.472 (0.444–1.51)	1.77 (1.09–6.67)	3.37 (0.985–8.05)	4.03 (1.94–6.67)	5.71 (4.03–9.51)	6.55 (3.87–8.68)	
AUC_{tau}, μg × h/mL	0.413 (0.147–0.796)	0.958 (0.401–1.21)	2.16 (0.820–2.42)	2.09 (1.99–8.22)	13.0 (6.57–16.5)	24.7 (7.53–99.2)	33.7 (15.4–112)	53.4[c] (30.7–104)	55.3 (33.1–80.8)	
AUC_{inf}, μg × h/mL	0.413 (0.148–0.802)	0.958 (0.402–1.22)	2.16 (0.837–2.45)	2.10 (2.01–8.36)	13.5 (6.61–16.6)	24.8[b] (7.84–124)	16.0 (15.5–16.4)	53.7[d] (30.9–110)	59.1 (33.1–82.2)	
CL/F, L/h	24.2 (12.5–66.7)	20.9 (16.3–49.8)	18.6 (16.3–47.8)	38.0 (9.57–39.8)	11.2 (9.04–22.7)	12.6[b] (2.42–38.3)	28.3 (27.5–29.1)	11.2[d] (5.46–19.4)	10.7 (9.12–22.7)	
$t_{1/2\lambda z}$, h	2.80 (2.20–3.73)	2.17 (2.06–3.45)	2.83 (1.43–3.83)	3.85 (2.82–3.97)	3.75 (2.85–5.36)	3.45 (2.99–9.77)	4.15 (2.63–11.3)	4.64[c] (2.56–13.5)	3.86 (2.22–6.54)	
Vz/F, L	76.8 (67.0–274)	81.3 (62.2–156)	90.2 (38.2–195)	155 (54.8–221)	78.7 (37.2–99.6)	57.0[b] (23.6–264)	120 (110–130)	66.0[d] (39.2–133)	79.4 (32.9–92.1)	

NOTE: Day 1 AUC_{inf}, CL/F, Vz/F: number of patients at 300 (5), 450 (3), 600 (11), and 750 (14).

Abbreviations: AUC_{inf}, area under the concentration–time curve from the time of dosing up to infinity with extrapolation of terminal phase; AUC_{tau}, area under the concentration time curve during dosing interval; CL/F, apparent body clearance after extravascular dosing; C_{max}, maximum plasma concentration; s, schedule; $t_{1/2\lambda z}$, terminal elimination half-life; t_{max}, median time to reach observed concentration; Vz/F, volume of distribution.

[a]Excluded patients in the fast-fed cohort; [b]$n = 2$; [c]$n = 11$; [d]$n = 10$.

assessments in plasma and peripheral blood mononuclear cells (PBMCs). Procedures for isolation of PMBC cells and quantification of IGF1 plasma levels and IGF1R and IR phosphorylation are described in the Supplementary Materials and Methods. No archival tumor tissue was collected.

Efficacy

Efficacy was determined by clinical tumor measurements and imaging techniques. Response was assessed using Response Evaluation Criteria for Solid Tumors, v 1.0 (14). Disease control rate (DCR) was calculated as the number of responders and patients with stable disease divided by the total number of patients evaluable for efficacy in each cohort.

Results

Patient disposition

The trial was conducted at two sites. The date of first enrollment was July 5, 2007 and the date of last evaluation was September 20, 2010. A total of 79 patients were enrolled in the study (Supplementary Fig. S1). The clinical characteristics of these patients are shown in Table 1. All patients were included in the safety analysis, and all patients enrolled in S1 and S2, and the majority in S3 (85%) were evaluable for DLT. All patients enrolled under S2 and S3, and the majority in S1 (92%), were also evaluable for pharmacokinetic analysis, and at least 62% were evaluable for efficacy.

The S2 schedule was discontinued after initial analysis of pharmacokinetics; pharmacodynamics and toxicity concluded that it was insufficiently different to the S3 schedule.

Dose escalation and MTD

No DLT was observed at doses of OSI-906 $\leq$ 450 mg in any treatment schedule. A total of seven patients had a DLT, including five patients in S1 and two patients in S3.

One of the first six patients in S1 who were treated at an initial dose of 600 mg had grade 3 hyperglycemia. In S1, at an initial dose of 750 mg, one patient had grade 3 hyperglycemia, and one patient had grade 2 vomiting and was unable to complete the designated schedule. At the same dose in S1, one patient had grade 3 QTc prolongation. One patient in the tablet cohort treated at 600 mg in S1 had hyperglycemia. In S3, one of the first six patients treated at an initial dose of 600 mg experienced grade 4 fatigue, whereas another patient had grade 3 hyperglycemia at the same dose.

On the basis of the observed DLT, the MTD and recommended phase II dose for OSI-906 was determined to be 600 mg given once daily for both S1 and S3 dosing schedules.

Safety

Over the entire study period, most patients experienced AEs (97% in S1, 100% in S2, 77% in S3). For all treatment schedules, $\leq$ 50% of patients had AEs that were considered to be treatment-related. Table 2 summarizes treatment-related AEs occurring over the entire study period across the three dosing schedules. The most frequent treatment-related AEs during the study, irrespective of grade, were nausea, vomiting, fatigue, diarrhea, and hyperglycemia. Most of the treatment-related AEs were grade 1 or 2 in severity. Nine patients (eight in S1 and one in S3) had grade 3 treatment-related AEs at doses of OSI-906 $\geq$ 300 mg. The most common grade 3 treatment-related AEs were hyperglycemia

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(two patients at 600 mg and one patient at 750 mg in S1; one patient at 600 mg in S3), vomiting (two patients at 600 mg in S1), and nausea (2 patients at 600 mg in S1). One patient in S3 had grade 4 fatigue that was considered to be related to the study drug. Three patients permanently discontinued study drug due to treatment-related AEs: vomiting in one patient (S1, 750 mg) and prolonged QTc interval in two patients (one in S1, 750 mg; one in S3, 600 mg).

Across all treatment schedules, 21 patients had serious AEs (SAEs), eight of which were considered to be treatment-related. In S1, treatment-related SAEs included grade 3 nausea and vomiting in one patient (600 mg), grade 3 QTc prolongation in one patient (750 mg), grade 3 hyperglycemia in three patients (two at 600 mg and one at 750 mg), and grade 3 hypoglycemia in one patient (750 mg). In S3, treatment-related SAEs included grade 4 fatigue in one patient (600 mg) and grade 3 hyperglycemia in one patient (600 mg).

Nine patients developed hyperglycemia, which was considered to be treatment-related in seven patients, all of whom received OSI-906 at doses $\geq$ 300 mg (Table 2). At doses $\geq$ 600 mg, treatment-related grade 3 hyperglycemia was reported in four patients. No patients discontinued the study due to hyperglycemia.

Two patients died during the trial, and an additional three patients died within 30 days of the last dose of OSI-906. None of the deaths were considered to be treatment-related.

Cardiac safety. On the basis of QTc interval measurements completed at a central electrocardiogram laboratory, 10 of the 79 patients included in the study had clinically significant QTc interval increase. Two patients had QTc electrocardiogram prolongations that were considered to be related to OSI-906: one in S1 at 750 mg (grade 2) and one in S3 at 600 mg (grade 3). Both patients withdrew from the study due to AEs.

Pharmacokinetics

Pharmacokinetic parameters for OSI-906 were obtained for all dose cohorts and are summarized in Tables 3 and 4. Observed maximum plasma concentration (C_{max}) on day 1 was attained between 2 and 4 hours, with values increasing in a dose-dependent manner (Table 3). The median terminal half-life of OSI-906 was within the range of 2.10 and 6.08 (Table 3). Plasma exposure [area under the concentration–time curve from the time of dosing up to infinity with extrapolation of terminal phase (AUC_{inf})] increased with increasing doses of OSI-906 (Table 3). The same pattern of pharmacokinetics characteristics was also observed on day 3 after repeated dosing (Table 3).

Plasma concentrations on day 1 were similar after administration of OSI-906 450 mg to patients in both S2 and S3 regimens, with higher values observed at 600 mg in S3 (Table 4). In both regimens, the median C_{max} values were comparable with those observed at corresponding doses in S1. As reported for S1, AUC values increased with increasing doses of OSI-906 (Table 4).

The ratio between AUC during the time interval between consecutive dosing (AUC_{tau}) on the first and last days of the treatment cycle for the three dosing schedules indicated that there was no substantial accumulation of OSI-906 after once daily administration up to 7 days (Supplementary Tables S1 and 2). Across all dosing schedules, the median amount of unchanged OSI-906 excreted in urine was < 0.3% of the administered dose. The relative bioavailability of OSI-906 from tablets appears to be slightly lower than that from capsules (data not shown).

The effect of food on the pharmacokinetics of OSI-906. Plasma pharmacokinetic parameters of OSI-906 in the fed-fasted cohort are illustrated in Fig. 1. The geometric mean ratio (fed-to-fasted) indicated higher C_{max} (16%) and AUC (38%) under fed condition compared with fasted condition. The median terminal half-life was similar for both treatments (4.39 vs. 4.02 hours). Comparison of the median time to reach observed maximum concentration (t_{max}) in the fed and fasted state indicated that food significantly delayed absorption (median difference 2.8 hours, $P = 0.0005$; Wilcoxon signed-rank test).

Pharmacodynamics

Detectable phosphorylated IGF1R and phosphorylated IR levels were observed in seven of the 11 patients receiving 600 mg of OSI-906 in S1. In these patients, decreased IGF-1R and IR phosphorylation was observed on days 1 and 3 of dosing and returned to predose levels by day 14 (Fig. 2A).

At 600 mg in S1, IGF1 concentrations increased during the 3-day dosing period in the first 14-day treatment cycle, achieving maximal concentrations 24 hours after the third dose. IGF1 concentrations returned to near predose levels at the end of the 14-day dosing cycle (Fig. 2B). A relationship between increased IGF1 and plasma concentrations of OSI-906 was observed (Fig. 2C).

Table 4. Summary of pharmacokinetic parameter following single (day 1) and multiple dosing (days 5 and 7) of OSI-906 (S2 and S3)

	Treatment schedule, day/OSI-906 dose (mg)					
	S2, Day 1	S3, Day 1		S2, Day 5	S3, Day 7	
	450	450	600	450	450	600
Evaluable, *n*	4	3	10	4	3	7
t_{max}, h	6.0 (2.1–12.0)	8.0 (6.0–12.2)	4.0 (2.0–24.0)	3.4 (2.9–4.0)	3.0 (2.0–4.1)	3.0 (2.0–6.1)
C_{max}, μg/mL	3.08 (1.17–5.60)	2.78 (2.49–3.62)	4.55 (0.572–10.9)	3.45 (1.25–10.0)	4.75 (2.83–5.74)	4.11 (2.11–9.78)
AUC_{tau}, μg × h/mL	24.3 (13.3–52.7)	25.5 (22.1–26.4)	46.6 (5.58–182)	31.8 (10.9–108)	26.2 (17.7–35.9)	28.8 (21.0–113)
AUC_{inf}, μg × h/mL	25.5 (13.4–54.6)	25.9 (22.4–26.6)	50.7[a] (19.3–89.9)	33.3 (11.2–115)	26.3 (17.9–36.0)	30.8[b] (21.1–119)
CL/F, L/h	17.7 (8.24–33.6)	17.4 (16.9–20.1)	11.8[a] (6.67–31.1)	18.0 (3.90–40.4)	17.1 (12.5–25.2)	19.6[b] (5.04–28.4)
$t_{1/2\lambda z}$, h	3.40 (2.24–5.78)	2.57 (2.40–2.79)	4.06 (2.20–22.8)	4.91 (3.97–6.55)	2.54 (2.46–3.47)	3.44 (2.65–14.3)
Vz/F, L	88.5 (49.0–149)	68.1 (60.2–74.5)	72.0[a] (43.1–101)	144 (30.6–255)	62.8 (44.4–126)	96.8[b] (34.9–252)

Abbreviations: AUC_{inf}, area under the concentration-time curve from the time of dosing up to infinity with extrapolation of terminal phase; AUC_{tau}, area under the concentration time curve during dosing interval; CL/F, apparent body clearance after extravascular dosing; C_{max}, maximum plasma concentration; s, schedule; $t_{1/2\lambda z}$, terminal elimination half-life; t_{max}, median time to reach observed concentration; Vz/F, volume of distribution.
[a]$n = 7$; [b]$n = 6$.

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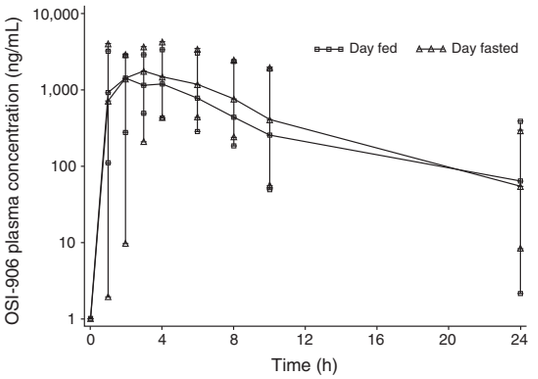

Figure 1.
Effect of food on median (minimum–maximum) plasma OSI-906 concentrations (ng/mL) versus time (S1 fed-fasted cohort, day 1). S, schedule.

Efficacy

Of the 66 patients evaluable for response, two patients in S1 with adrenocortical carcinoma achieved a partial response at doses of 450 mg and 300 mg. These patients remained on the study for 703 and 199 days, respectively. Twenty-seven patients had stable disease as their best response, with seven patients experiencing stable disease for 24 weeks or longer. The DCR rate was 43.6% in S1, 66.7% in S2, and 37.5% in S3.

Discussion

This first-in-human phase I trial has shown that intermittent dosing of OSI-906, a selective dual inhibitor of the IGF1R and IR, is well tolerated, with no unexpected toxicities. The MTD of OSI-906 for S1 was 600 mg given once daily on days 1 to 3 every 14 days. The MTD for S3 was also 600 mg once daily on days 1 to 7, every 14 days.

The clinical toxicities of OSI-906 reported in this study are consistent with those observed with antibodies targeting IGF1R and include hyperglycemia and gastrointestinal toxicities, such as nausea, vomiting, and diarrhea (6–9). Overall, 37% of patients developed hyperglycemia, which was mostly grade 2 in severity. Because of potential cardiovascular effects of agents targeting IGF1R, QTc intervals were assessed in all patients by electrocardiogram. Clinically significant QTc interval prolongations were observed in 13% of patients. However, these QTc prolongations, none of which were >100 msec, were considered to be treatment related in only two patients. The assessment regarding relatedness of QTc prolongation to OSI-906 was made by individual investigators at the time without aggregate data, thus representing the opinion of an individual in a nonrandomized trial. Consequently, causality cannot be definitively attributed in a nonrandomized trial.

When compared with continuous dosing of OSI-906 at the recommended phase II dose (150 mg twice daily), intermittent dosing with OSI-906 600 mg resulted in a lower incidence of hyperglycemia (15% and 10% for S1 and S3, respectively, vs. 21%) and a slightly higher occurrence of nausea (38% and 30% for S1 and S3, respectively, vs. 28%) (15). Liver function test abnormalities, which were considered to be related to OSI-906, were not reported in the intermittent dosing schedule (15).

OSI-906 was rapidly absorbed after oral administration and pharmacokinetics were dose-proportional. Pharmacokinetic data did not indicate substantial accumulation of OSI-906 following once-daily dosing for up to 7 days, most likely owing to its relatively short plasma elimination half-life, which ranged between 2 and 6 hours. The effect of food on the pharmacokinetics of OSI-906 was modest, suggesting that the agent can be administered with or without food.

The assessment of the pharmacodynamics of OSI-906 and its relationship to OSI-906 systemic exposure was a secondary

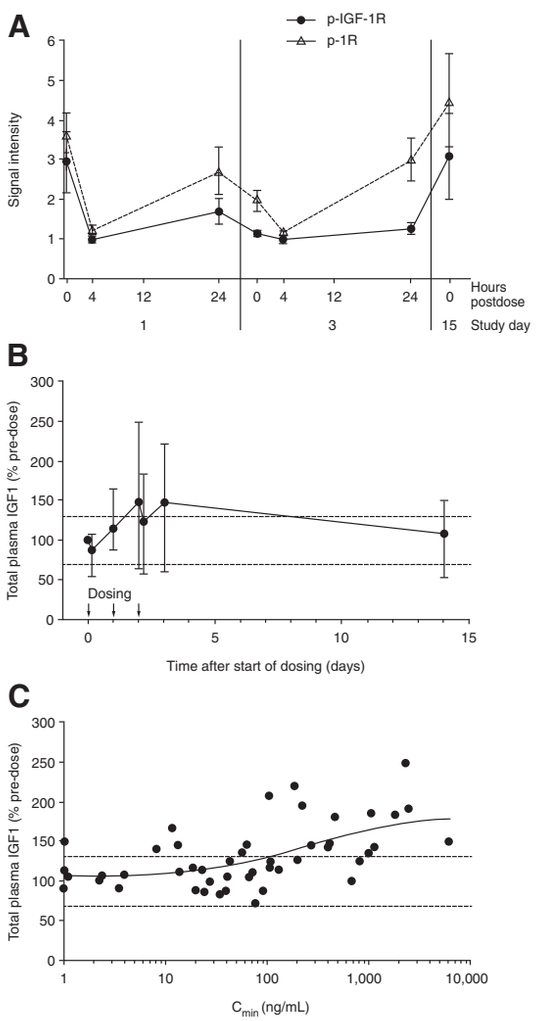

Figure 2.
Effects of OSI-906 on IGF1R and IR activity and levels and relationships to plasma OSI-906 exposure. A, effects on IGF1R and IR phosphorylation in PBMCs. Data are shown for patients in the dose escalation 600 mg S1 cohort with PBMC sample sets evaluable for pharmacodynamic assessment and with detectable p-IGF1R and p-IR signals ($n = 7$). Data are shown as means ± SEM. B, effects on total plasma IGF1 concentrations over time in 600-mg S1 cohort. Medians and ranges are shown for time points in the first treatment cycle ($n = 12$). For all plasma IGF1 graphs, horizontal lines indicate predose values (100%) ± 30% (two intrasubject assay CVs). C, changes in plasma IGF1 versus minimum plasma OSI-906 concentrations (C_{min}). Plasma IGF1 concentration observed 24 hours after the last dose were plotted against C_{min} before dosing on the last day of dosing for all patients on S1, S2, and S3 ($n = 54$). The curve was the result of nonlinear regression analysis. C_{min}, minimum plasma concentration; CV, coefficient of variation; p, phosphorylation.

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objective of the study. The inhibition of IGF1R and IR phosphorylation in PBMCs achieved at 600 mg in the S1 dosing regimen correlated with increased plasma levels of OSI-906 and was paralleled by increases in plasma IGF1, a surrogate marker of IGF1 inhibition (16). These results indicate that concentrations of OSI-906 sufficient to inhibit IGF1R signaling were achieved in patients on the intermittent dosing schedules. Of note, the effects on IGF1R and IR phosphorylation in PBMCs and plasma IGF1 appeared to be temporary, occurring during the OSI-906 dosing period and returning to near predose levels at the end of the first 14-day treatment cycle after the dosing holiday. This suggests that intermittent dosing may be useful in mitigating AEs that result from continuous target inhibition in patients. Intermittent dosing may also provide additional scheduling options for combinations with other agents. Although the evaluation of the efficacy of OSI-906 was not the primary objective of this study, there was preliminary evidence of antitumor activity. Notably, we observed partial responses in two patients with adrenocortical carcinoma, a rare tumor with few therapeutic options in which the IGF pathway has been shown to potentially drive tumorigenesis. However, response was not observed in 13 other patients with adrenocortical carcinoma, suggesting limited single-agent activity (response rate, 15%). Nevertheless, these data could still support the use of IGF1R inhibitors in combination with other agents in adrenocortical carcinoma, as it is likely that other molecular pathways are involved in these tumors.

Overall, the results of our study support the potential of targeting IGF1R and IR with OSI-906 in solid tumors and warrant its further evaluation, particularly in combination with other drugs. Preclinical data have indicated that IGF pathway inhibition can restore paclitaxel sensitivity to resistant ovarian cancer cells *in vitro* (17). This intermittent schedule is, therefore, being investigated in combination with weekly paclitaxel in patients with ovarian cancer (18). More recently, preclinical studies have highlighted the potential for combining OSI-906 with agents targeting the *MEK* pathway, specifically in non–small cell lung cancer, where resistance to EGFR inhibition is linked to *KRAS* mutations (19). Clinical evaluation of novel combinations, such as these, now appears to be warranted.

Disclosure of Potential Conflicts of Interest

P. Nava-Parada and S. Poondru are employees of Astellas Pharma USA. R. Simantov is an employee of OSI Pharmaceuticals. R. Gedrich is an employee of and has ownership interest (including patents) in OSI Pharmaceuticals. S.B. Kaye is a consultant/advisory board member for Astellas Pharma. No potential conflicts of interest were disclosed by other authors.

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