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

Robin L. Jones1, Edward S. Kim2, Pilar Nava-Parada3, Salma Alam1, Faye M. Johnson4, Andrew W. Stephens5, Ronit Simantov6, Srinivasu Poondru6, Rich Gedrich6, Scott M. Lippman7, Stan B. Kaye1, and Craig P. Carden1

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 ≥ 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...
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.

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 infection with 

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

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

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

<table>
<thead>
<tr>
<th>Dose, mg</th>
<th>Evaluable, n</th>
<th>T_{max}, h</th>
<th>C_{max}, µg/mL</th>
<th>AUC_{0-24 h}, µg h/mL</th>
<th>Vz/F, L</th>
<th>CL/F, L/h</th>
<th>t_{1/2, z}, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>3</td>
<td>2.0 (2.0–3.0)</td>
<td>0.20 (0.20–0.30)</td>
<td>2.0 (2.0–0.30)</td>
<td>2.0 (2.0–0.30)</td>
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</tr>
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<td>3</td>
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<td>2.0 (2.0–0.30)</td>
<td>2.0 (2.0–0.30)</td>
<td>2.0 (2.0–0.30)</td>
</tr>
<tr>
<td>40</td>
<td>3</td>
<td>2.0 (2.0–3.0)</td>
<td>0.20 (0.20–0.30)</td>
<td>2.0 (2.0–0.30)</td>
<td>2.0 (2.0–0.30)</td>
<td>2.0 (2.0–0.30)</td>
<td>2.0 (2.0–0.30)</td>
</tr>
<tr>
<td>80</td>
<td>1</td>
<td>2.0 (2.0–3.0)</td>
<td>0.20 (0.20–0.30)</td>
<td>2.0 (2.0–0.30)</td>
<td>2.0 (2.0–0.30)</td>
<td>2.0 (2.0–0.30)</td>
<td>2.0 (2.0–0.30)</td>
</tr>
<tr>
<td>100</td>
<td>1</td>
<td>2.0 (2.0–3.0)</td>
<td>0.20 (0.20–0.30)</td>
<td>2.0 (2.0–0.30)</td>
<td>2.0 (2.0–0.30)</td>
<td>2.0 (2.0–0.30)</td>
<td>2.0 (2.0–0.30)</td>
</tr>
</tbody>
</table>

#### Abbreviations:
- AUC_{0-24 h}: area under the concentration-time curve from the time of dosing to 24 hours post-dose.
- C_{max}: maximum plasma concentration.
- CL/F: apparent body clearance.
- T_{max}: time to reach maximum concentration.
- Vz/F: volume of distribution.

#### Notes:
- Data are presented as median (range).
- AEs were reported in 10% or more of patients across all treatment arms.
- The most frequent AEs were hyperglycemia, fatigue, diarrhea, nausea, and vomiting.
- One patient had grade 4 hyperglycemia.
- No DLT was observed at doses of OSI-906 ≤ 450 mg in any schedule.
- DLT was observed at a dose of 600 mg in S3.
- OSI-906 was well tolerated across all schedules.
- The safety data were similar across all schedules.
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- DLT was observed at a dose of 600 mg in S3.
- OSI-906 was well tolerated across all schedules.
- The safety data were similar across all schedules.
(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 ≥ 300 mg (Table 2). At doses ≥ 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 (Cmax) 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 concentrations of OSI-906 were obtained for all patients who received OSI-906 at doses ≥ 300 mg (Table 2). At doses ≥ 600 mg, treatment-related grade 3 hyperglycemia was reported in four patients. No patients discontinued the study due to hyperglycemia.

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 Cmax 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 (AUCtau) 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 Cmax (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 (tmax) 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)

<table>
<thead>
<tr>
<th>Treatment schedule, day/OSI-906 dose (mg)</th>
<th>S2, Day 1</th>
<th>S3, Day 1</th>
<th>S2, Day 5</th>
<th>S3, Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>450</td>
<td>450</td>
<td>450</td>
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<td>500</td>
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<td>600</td>
<td>600</td>
<td>600</td>
<td>600</td>
<td>600</td>
</tr>
<tr>
<td>Evaluate, n</td>
<td>4</td>
<td>3</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>tmax, h</td>
<td>6.0 (2.1–12.0)</td>
<td>8.0 (6.0–12.2)</td>
<td>4.0 (2.0–24.0)</td>
<td>3.4 (2.9–4.0)</td>
</tr>
<tr>
<td>Cmax, µg/mL</td>
<td>3.08 (1.17–5.60)</td>
<td>2.78 (2.49–5.62)</td>
<td>4.55 (0.572–10.9)</td>
<td>3.45 (1.25–10.8)</td>
</tr>
<tr>
<td>AUCmax, µg × h/mL</td>
<td>24.3 (13.3–52.7)</td>
<td>25.5 (22.1–26.4)</td>
<td>46.6 (5.58–182)</td>
<td>31.8 (10.9–108)</td>
</tr>
<tr>
<td>CL/F, L/h</td>
<td>17.7 (8.2–35.6)</td>
<td>17.4 (16.9–20.1)</td>
<td>11.8 (6.67–31.1)</td>
<td>18.0 (3.90–40.4)</td>
</tr>
<tr>
<td>t1/2, h</td>
<td>3.40 (2.24–5.78)</td>
<td>2.57 (2.40–2.79)</td>
<td>4.06 (2.20–2.88)</td>
<td>4.91 (3.97–6.35)</td>
</tr>
<tr>
<td>Vz/F, L</td>
<td>885 (490–149)</td>
<td>581 (60.2–74.3)</td>
<td>72.0 (452–101)</td>
<td>144 (30.6–253)</td>
</tr>
</tbody>
</table>

Abbreviations: AUCmax, area under the concentration-time curve during dosing interval; CL/F, apparent body clearance after extravascular dosing; Cmax, maximum plasma concentration; s, schedule; t1/2, terminal elimination half-life; tmax, median time to reach observed concentration; Vz/F, volume of distribution.

n = 7, n = 6.
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 of observed prolongation, none of which were 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
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 IGFIR 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.

References
