**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. Jones, Edward S. Kim, Pilar Nava-Parada, Salma Alam, Faye M. Johnson, Andrew W. Stephens, Ronit Simantov, Srinivasu Poondru, Rich Gedrich, Scott M. Lippman, Stan B. Kaye, and Craig P. Carden

**Methods**

**Patients (additional details)**

Patients were not eligible for entry if they had a documented history of diabetes mellitus, significant cardiac disease (unless well controlled), cerebrovascular accident, active seizure disorder, or previously diagnosed brain metastases.

Drugs with the potential of causing QT interval prolongation and glucocorticoids (with the exception of hormone replacement therapy or inhalers) were discontinued within 14 days prior to day 1 dosing. Concurrent anticancer therapy was not permitted except for certain types of endocrine therapy in males with prostate cancer.

**Pharmacodynamics (additional details)**

For peripheral blood mononuclear cell (PBMC) isolation, 8-mL samples were collected into CPT vacutainer tubes (Becton, Dickinson and Company; Franklin Lakes, NJ) containing sodium heparin as an anticoagulant. PBMCs were isolated by centrifugation at 1500 × 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 phosphate-buffered saline containing 0.1% BSA 2 mM EDTA and then centrifuged at 300 × g for 10 minutes at room temperature. The supernatant was removed, and the cell pellets were stored at –80oC until analysis. Cells were lysed with RIPA Buffer (Upstate/Millipore, Billerica, MA) plus protease and phosphatase inhibitors (diluted 1:100; Sigma) and 1 mM vanadate. Insulin-like growth factor-1 receptor (IGF-1R) and insulin receptor (IR) phosphorylation were measured using the Proteome Profiler Human Phospho-RTK Array Kit (catalog no. ARY001; R&D Systems, Minneapolis, MN). The phosphorylated IGF-1R and IR signals were quantified by digital assessment of pixel density using Image Gauge 4.0 software (Fujifilm Science Lab, Tokyo, Japan). Pixel densities for phosphorylated IGF-1R and IR and a representative immunoglobulin G (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 IGF-1R and IR signals intensities were then reported relative to the assay background. Patients with detectable predose phosphorylated IGF-1R (p-IGF-1R) and phosphorylated-IR (p-IR) signals in PBMCs (signal intensity ≥ 2) were included in subsequent analyses. Preclinical studies had determined that only a subset of individuals (~50%) had detectable levels of p-IGF-1R and p-IR in PBMCs and that this phosphorylation could be modulated by treatment of PBMCs *ex vivo* with OSI-906.

For plasma preparation, 5-mL samples were collected into a Vacutainer tube containing EDTA and centrifuged (1500–2000 g for 10 minutes under refrigeration) within 30 minutes of collection. Aliquots were stored at –80oC. Total plasma IGF-1 concentrations were determined with the Total IGF-1 ELISA Kit (catalog no. 10-5600; DSL/Beckman Coulter, Webster TX) according to the manufacturer’s protocol. Intra- and interassay coefficients of variation (CVs) 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 insulin-like growth factor 1 (IGF-1) concentrations in healthy individuals and cancer patients. To facilitate interpatient comparisons in this study, IGF-1 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 utilized as a guide to indicate substantial changes in plasma IGF-1 concentrations relative to predose values as indicated (predose set as 100% + two intrasubject CVs [30%]). Relationships between plasma IGF-1 and plasma concentrations of OSI-906 were also assessed. Curve fitting was performed by nonlinear regression analysis (GraphPad Prism 5, GraphPad Software, Inc., La Jolla, CA).

**Results (additional results)**

**Table 1.** Ratio of area under the curve during the time interval between consecutivedosing (AUCtau) on day 3 to AUCtau on day 1 (schedule 1 [S1])

|  |  |
| --- | --- |
|  | **OSI-906 dose (mg)** |
|  | **10** | **20** | **40** | **80** | **150** | **300\*** | **450** | **600** | **750** |
| **Evaluable, *n*** | 3 | 3 | 3 | 3 | 4 | 6 | 4 | 11 | 4 |
| **Geometric mean** **(90% CI)**  | 1.01(0.760–1.33) | 1.02(0.523–1.98) | 0.728(0.390–1.36) | 0.909(0.720–1.18) | 1.31(1.02–1.70) | 1.55(1.14–2.09) | 1.34(0.951–1.89) | 1.21(0.966–1.52) | 0.721(0.336–1.55) |

\*Exclude patients in the fed-fasted cohort. All patients who had sufficient pharmacokinetic sampling associated with day 1 or other appropriate OSI-906 doses.

CI, confidence interval.

**Table 2.** Ratio of area under the curve during the time interval between consecutivedosing (AUCtau) on day 5 (S2) or day 7 (S3) to AUCtau on day 1

|  |  |
| --- | --- |
|  | **Treatment schedule/OSI-906 dose (mg)** |
|  | **S2** | **S3** |
|  | **450** | **450** | **600** |
| **Evaluable, *n***  | 4 | 3 | 7 |
| **Geometric mean** **(90% CI)** | 1.20(0.609–2.38) | 1.04(0.505–2.13) | 1.24(0.723–2.11) |

All patients who had sufficient pharmacokinetic sampling associated with day 1 or other appropriate OSI-906 doses.

CI, confidence interval.