Linsitinib (OSI-906) Datasheet

Biological Activity

OSI-906 is currently under a Phase III clinical trial in adrenocortical carcinoma (ACC).

OSI-906 is a selective inhibitor of IGF-IR and IR with IC50 of 35 nM and 75 nM, respectively.

IC50

35 nM

75 nM

InsR

OSI-906 inhibits tumor growth in an IGF-IR-driven xenograft mouse model, with 100% TGI and 55% regression at a dose of 75 mg/kg and 60% TGI and no regression at a dose of 25 mg/kg. OSI-906 administration induces different elimination half-lives of itself in dog, rat, and mice; the elimination half-lives are 1.18 hours, 2.64 hours, and 2.14 hours, respectively.

OSI-906 inhibits the growth of tumors in NCI-H292 xenograft mouse model with 100% TGI and 55% regression at a dose of 75 mg/kg and 60% TGI and no regression at a dose of 25 mg/kg. OSI-906 administration induces different elimination half-lives of itself in dog, rat, and mice; the elimination half-lives are 1.18 hours, 2.64 hours, and 2.14 hours, respectively.

OSI-906 inhibits proliferation of several tumor cell lines including non-small-cell lung cancer and colorectal cancer (CRC) tumor cell line with EC50 of 0.021 to 0.810 μM.

In vitro

OSI-906 inhibits IGF-IR autophosphorylation and activation of the downstream signaling proteins Akt, ERK/1/2, and S6 kinase with IC50 of 0.028 to 0.13 μM. OSI-906 enables an intermediate conformation of the target protein through interactions with the C-helix. OSI-906 displays favorable metabolic stability in liver microsomes. OSI-906 fully inhibits both IR and IGF-IR phosphorylation at a concentration of 1 μM.

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In vivo

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Clinical Trials

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Features

Protocol (Only for Reference)

Kinase Assay

Protein kinase assays are either performed in-house by ELISA-based assay methods (IGF-IR, IR, EGFR and KOR) or at Upstate Inc. by a radiometric method with ATP at 100 μM concentration. In-house ELISA assays use poly(Glu:Tyr) as the substrate bound to the surface of 96-well assay plates and phosphorylation is detected using an antiphospho-tyrosine antibody conjugated to horseradish peroxidase. The bound antibody is quantified using ABTS as the peroxidase substrate by measuring absorbance at 405 nm. All assays use purified recombinant kinase catalytic domains. Recombinant enzymes of human IGF-IR or EGFR are expressed as an NH2-terminal glutathione S-transferase fusion protein in insect cells and are purified in house. IC50 values are determined from the sigmoidal dose–response plot of percent inhibition versus log10 compound concentration. A minimum of three measurements, performed in duplicate, are carried out with in-house assays unless otherwise indicated. OSI-906 at a concentration of 1 μM is profiled versus a panel of kinases using the ProfilerPro™ Kinase Selectivity Assay Kit.

Cell Line Assay

Cell Lines

MCF7, NCI-H292, Colo-205, HT29, H358, H1703, BxPC3, A673, SW620, DU4475, HepG2 and Hepa-1, RKO 3T3/huIGF-IR and H292 cells

Concentrations

0.02-0.8 μM

Incubation Time

3 days

Methods

For assays of cell proliferation, cells are seeded into 96-well plates in appropriate media containing FCS 10% and incubated for 3 days in the presence of OSI-906 at various concentrations. Inhibition of cell growth is determined by luminescent quantification of intracellular ATP content using CellTitre Glo. Data is presented as a fraction of maximal proliferation, calculated by dividing the cellular density in the presence of varying concentrations of OSI-906 by the cellular density of control cells treated with vehicle (DMSO) only.

Animal Study

Animal Models

IGF-IR-driven full-length human IGF-IR and IGF-I driven xenograft mouse model

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<th>Parameter</th>
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<tr>
<td>Formulation</td>
<td>25 mM tartaric acid</td>
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<tr>
<td>Doses</td>
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<tr>
<td>Administration</td>
<td>Orally administrated at once-daily oral dose for 14 days</td>
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References


PLEASE KEEP THE PRODUCT UNDER -20°C FOR LONG-TERM STORAGE.

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