IPI-493, a potent, orally bioavailable Hsp90 inhibitor of the ansamycin class

John Lee, Louis Griefer, Ed Holton, Kelly Slocum, John Coco, Jennie Ge, Emmanuel Normant, Jen Hoyt, Alice Lin, Jiff Cushing, Jens Sydor, Jim Wright

Infinite Pharmaceuticals Inc., 780 Memorial Drive, Cambridge, Massachusetts USA; Broad Institute of MIT and Harvard, Cambridge, MA; Bind Biosciences, Cambridge, MA

Abstract

IPI-493, a potent, orally bioavailable Hsp90 inhibitor of the ansamycin class

Background:

The cytoskeletal heat shock protein 90 (Hsp90) has emerged as an important target in cancer due to its essential role in several key oncoproteins regulating critical functions, including cell cycle regulation, apoptosis, proliferation, and cell survival. To date, the most powerful and validated Hsp90 inhibitors are geldanamycin derivatives, a class of compounds which results in the degradation of key client proteins (e.g., Akt, EGFR, HER2, Bcl-2, and Bcl-xL) and other disease-progressive proteins. Additionally, due to several properties of Hsp90 inhibitors have recently advanced into clinical trials including ansamycin compounds (e.g. 17-AAG, IPI-1451) and other non-traditional inhibitors (e.g. Pimasertib, IPI-1451, IPI-493). The latter is the subject of this presentation.

We have developed an oral formulation for 17-AG (IPI-493), the major metabolite of IPI-504 (retaspimycin hydrochloride) and 17-AAG. This compound binds tightly to purified Hsp90 and the binding is not considerably dependent on the redox state of the NADH/NADH system. Additionally, the pharmacokinetic properties of IPI-493 are significantly better than IPI-504. The high affinity of IPI-493 for purified Hsp90 is not considerably influenced by reduction in the 17-demethoxygeldanamycin (17-AG). This is in marked contrast to other ansamycin derivatives (e.g. 7-AAG) where the pharmacokinetics is approximately 10 times more potent than the structure-derived 17-AAG. When tested against a panel of normal and cancer cell lines, IPI-493 selectively inhibits the growth of cancer cells 

Results:

Multiple formulations of IPI-493 were designed and tested for oral bioavailability. Formulations were identified that led to significantly improved systemic exposure in dogs and after administration. Similar formulations also led to high IPI-493 exposure in mice following oral dosing. The formulations also provide dose responsive exposure across a therapeutic dose range.

Conclusion:

IPI-493 has demonstrated efficacy in the NSCLC xenograft model H1650 as demonstrated by in vivo efficacy data. IPI-493 entered Phase I clinical development in 2008.

Background & Rationale

Heat shock protein 90 (Hsp90) is a highly conserved protein that is critical to the proper folding and degradation of key client proteins. Hsp90 is overexpressed in many different cancers and is responsible for the maintenance of several oncoproteins, including EGFR, PI3K, Akt, and ERK. As a result, Hsp90 is a potential target for anticancer therapy. However, the primary active metabolite of IPI-493, 17-AG, has significant systemic exposure in dogs and mice following oral administration of 17-AAG. The pharmacokinetic properties of IPI-493 are significantly better than IPI-504. Additionally, the pharmacokinetics is approximately 10 times more potent than the structure-derived 17-AAG. When tested against a panel of normal and cancer cell lines, IPI-493 selectively inhibits the growth of cancer cells.

Results: Formulation

IPI-493 is the primary active metabolite of IPI-493 and 17-AAG. IPI-493 formulation, dog 2

Results: in vitro activity

Binding of IPI-493 under reducing and non-reducing conditions

Results: in vivo efficacy & activity

Efficacy of IPI-493 in a mouse xenograft model of NSCLC cell line H1650

Conclusion

IPI-493 is currently in Phase I clinical development.

Data response efficacy of IPI-493 in a mouse xenograft model of NSCLC cell line H1650 [GEP (stabilization)]

Client protein (mutant EGFR) suppression and caspase-3 induction in NSCLC

H1650 mouse xenograft tumors

Dosing: OSI, PO, 10mg/kg

Tumor Volume (mm3)

0 5 10 15 20

0 2468

75 100 125 150 175 200

87%

IPI-493 dose escalation in CD-1 mice

IPI-493 concentation (ng/ml)

0 5 10 15 20 25 30 35 40

IPI-493 As measured by IHC of caspase-3 levels in NSCLC H1650 mouse xenograft tumors

Prefered synthetic derivatives designed from structure-based drug design (e.g. purine derivatives, isoxazoles, pyrazoles). IPI-504 and 17-AAG have demonstrated efficacy in the NSCLC xenograft model H1650. IPI-504 is a potent oral RING finger protease inhibitor of the gemdantamycin class. IPI-504 is orally bioavailable and has demonstrated clinical activity in patients with metastatic GIST (The RING trial). Geldanamycin derivatives incorporate the advantages of natural products (high efficacy and selectivity) but certain derivatives have demonstrated other unsatisfactory toxicity (methylamidomycin, DMSO) or low oral bioavailability (6-8). We have developed a potent, orally bioavailable Hsp90 inhibitor of the ansamycin class, IPI-493.