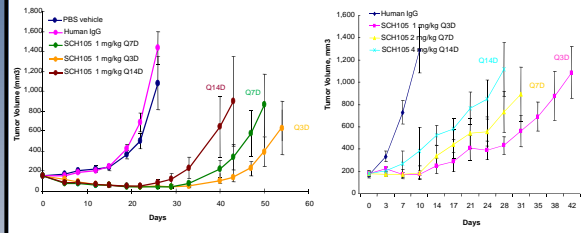


Abstract

Hepatocyte growth factor (HGF) is the soluble ligand for the c-Met receptor tyrosine kinase. The study of human and animal tumor models has provided compelling evidence that signaling through the HGF/c-Met pathway mediates a plethora of cellular activities that are involved in cancer cell dysregulation, tumorigenesis, and metastasis including proliferation, survival, angiogenesis, migration, and invasion. Tumor cell HGF/c-Met autocrine and paracrine loops have been reported in a number of human cancers including breast, lung, bladder, gastric, head and neck, glioma, multiple myeloma, leukemias, and certain sarcomas. SCH 900105, also known as AV-299, is a humanized IgG1 antibody with high affinity to HGF and neutralizes its biological functions with sub-nM potency. In vivo efficacy of SCH 900105 was explored in both autocrine and paracrine xenograft models. In these studies, SCH 900105 treatment resulted in significant tumor regression at doses as low as 0.1 mg/kg in one model. SCH 900105 treatment also demonstrated efficacy in paracrine models of the HGF-dependent xenograft lines in SCID mice engineered to produce human HGF. In these models, SCH 900105 treatment resulted in dose-dependent increases in completed SCH 900105/HGF in serum. Treatment also led to significant decreases in tumor phospho-c-Met levels, phospho-Akt, increased cleaved caspase-3, as well as decrease in Ki67 staining. To explore the effects of dosing schedule on tumor growth inhibition, xenograft studies were also performed with various dosing frequencies. All schedules resulted in initial tumor regression; however, SCH 900105 was most efficacious in causing tumor regression and delaying ultimate tumor escape when administered twice weekly compared to weekly or bi-weekly treatment. Several combination studies were also performed with other target therapeutics, chemotherapies and anti-angiogenic agents in subcutaneous and orthotopic models.

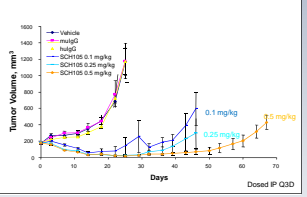
Optimal Dosing Schedule in U87 Model

Whether the dose is equivalent per injection or per cycle (2 wks), every three days was the most efficacious dosing schedule even with a 9 days half life in mice



Autocrine GBM Model

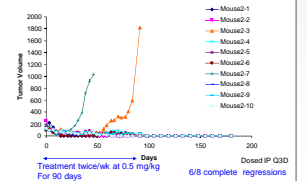
SCH 900105 resulted in tumor regression as low as 0.1 mg/kg in U87 Glioblastoma model



Antibody	dosage (mg/kg)	Tumor Growth Delay (days)	Partial Response	Complete Response	CR/PR
AV-299	0.1	29	4	0	4
AV-299	0.25	38	3	3	6
AV-299	0.5	38	3	3	6

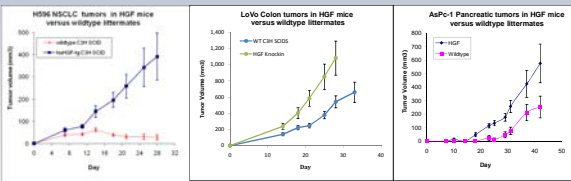
*PR and CR determined at day 39
 PR: <75% of initial vol; CR: no measurable tumor

SCH 900105 resulted in complete regressions in U87 Glioblastoma model for 180 days following a 90-day treatment period



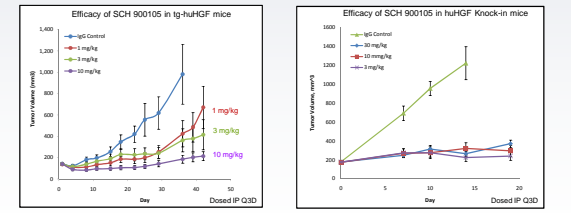
Paracrine Models in Mice Engineered with Human HGF

Human HGF offers a growth advantage in HGF-dependent tumors when grown in HGF engineered models



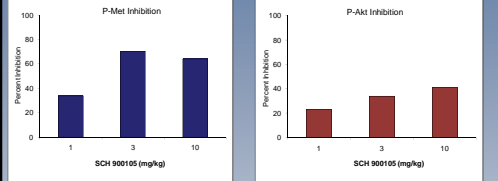
*Tg-huHGF mice were in-cocrossed from Van Andel Research Institute

SCH 900105 results in significant tumor growth inhibition in two different HGF models with H596 NSCLC tumors

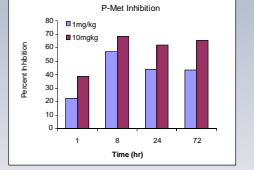


Pharmacodynamics of SCH 900105 in H596 NSCLC model

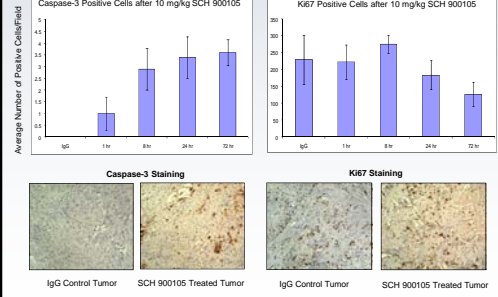
SCH 900105 treatment resulted in dose dependent inhibition of p-met and p-Akt as measured by MSD at the end of study



A single dose of SCH 900105 in H596 bearing mice resulted inhibition of p-met by 8 hrs that was maintained in the 10 mg/kg group out to 72 hrs

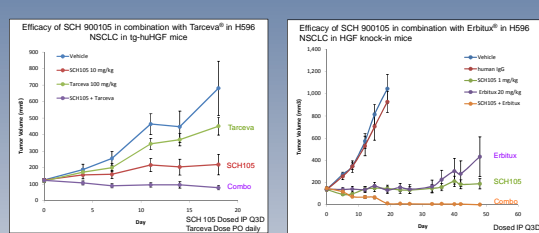


In the 10 mg/kg group this corresponded to decreases in Ki67 staining and increases in caspase-3 staining within the 72 hr time period

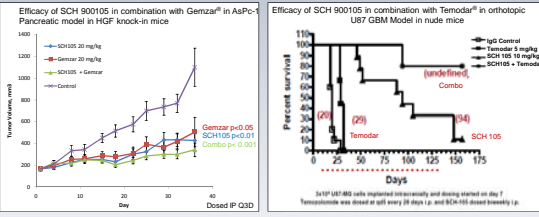


Combination Studies in Autocrine and Paracrine Models

SCH 900105 demonstrates additive activity in combination with ERGFR inhibitors in H596 NSCLC model in mice engineered to express human HGF



SCH 900105 demonstrates additive activity in combination with chemotherapeutics in multiple models



Summary

- SCH 900105 exhibited significant efficacy in the autocrine U87 GBM model resulting in complete regressions even after withdrawal of treatment.
- In the U87 model SCH 900105 had a half life of 9 days, however the most efficacious schedule for dosing was the shortest interval of every 3 days in mice.
- Several paracrine models demonstrated enhanced growth when host animals were engineered to supply human HGF. (Poster #6276)
- SCH 900105 demonstrated efficacy in several paracrine models in the HGF mice.
- SCH 900105 treatment resulted in dose dependent decreases in p-Met, p-Akt, and Ki67 as well as increases in caspase-3.
- Combinations of SCH900105 with EGFR inhibitors and chemotherapeutics demonstrated additive efficacy in vivo.