Phase 1 Study of SCH 900105, an Anti-Hepatocyte Growth Factor Monoclonal Antibody, as a Single Agent and in Combination with Erlotinib in Patients with Advanced Solid Tumors

Amita Patnaik[1], Glen J. Weiss[2], Kyriakos P. Papadopoulos[1], Raoul Tibes[2], Tara Iyengar[2], Anthony W. Tolcher[1], Francis C. Payumo[3], Monette M. Cotreau[3], Jaroslaw Jac[3], May Han[3], Pankaj Bhargava[3], William Slichenmyer[3], Randi E. Isaacs[4], Yali Zhu[4], Ramesh K. Ramanathan[2]
[1]South Texas Accelerated Research Therapeutics (START), San Antonio, TX; [2]Virginia G. Piper Cancer Center & TGEN, Scottsdale, AZ; [3]AVEO Pharmaceuticals, Cambridge, MA; [4]Merck Research Laboratories, Kenilworth, NJ

Abstract #2525

Abstract

Background: SCH 900105 (**SC**; formerly AV-299) is a humanized anti-hepatocyte growth factor (HGF) IgG1 monoclonal antibody (Mab) with potent anti-tumor effects in vitro and in xenograft models. The HGF/c-Met pathway mediates cell proliferation, angiogenesis, survival, migration and invasion. Preclinical studies indicate potent additivity when combined with EGFR inhibitors.

Methods: A Phase 1 study (3+3 design) evaluated the safety, tolerability, recommended Phase 2 dose (RP2D), pharmacokinetics (PK) and pharmacodynamics (PD) of **SC**. Monotherapy **SC** was given IV over 30-60 min, at 2, 5, 10 or 20 mg/kg once every 2 weeks. At the RP2D of **SC**, erlotinib (**E**) at a dose of 150 mg/d was evaluated. At RP2D, cohorts were expanded to a total of 12 pts.

Results: 37 pts (16M/21F, median age 62, range 18-87 years, ECOG PS 0/1/2:10/26/1) have been enrolled. 24 pts with monotherapy **SC** were treated at 2 (n=3), 5 (n=3), 10 (n=3), or 20 mg/kg (n=15). 13 pts received the combination of SC 20mg/kg and E 150 mg/d. Most common tumors were sarcoma (8), ovarian (4), mesothelioma (3), and GBM (3). There were no dose-limiting toxicities (DLTs) in the monotherapy arm. No maximum tolerated dose was defined. One DLT of G3 mucositis was observed in combination, resulting in expansion initially to 6 pts and further expansion at the **SC** RP2D of 20 mg/kg q2wks and E at 150 mg/d. In the monotherapy arm, treatment-related G1/2 toxicities were fatigue (33.3%), peripheral edema (16.7%), headache (16.7%), hematologic (12.5%) and pruritus (12.5%). G3 non-DLTs were fatigue and diarrhea (4.2% each). In combination, common AEs were rash (53.8%) and diarrhea (46.1%). Pts have received 1-26 doses of **SC**. Stable disease (SD) has been seen in 11/22 monotherapy pts. Longest duration of SD has been observed in pts with papillary thyroid cancer (53.7 weeks) and mixed mesodermal ovarian tumor (56 wks as of 22March10 - ongoing). The t½ of single agent **SC** is estimated to be 15 days. Serum HGF levels are increased after **SC** treatment compared with pre-dose levels. No changes in serum s-Met levels were observed after **SC** dosing. No HAHA to **SC** were detected.

Conclusions: The RP2D for monotherapy **SC** and in combination with **E** is 20 mg/kg IV every 2 weeks. This dose appears to be well-tolerated in combination with standard dose **E** (150 mg/d). Phase 2 studies are planned.

Introduction

Targeting the HGF/c-Met Signaling Pathway

- HGF is the soluble ligand for the c-Met receptor tyrosine kinase.
- Dysregulation of HGF/c-Met signaling has emerged as a crucial feature of many human malignancies and drug resistance.
- High HGF levels suggest poor prognosis in a wide variety of human malignancies including gastric, breast, lung, and multiple myeloma

SCH 900105

- Is a highly potent anti-HGF monoclonal antibody.
- Potently neutralizes several important biological activities of HGF, such as HGF/c-Met binding, HGF-induced c-Met phosphorylation, cell proliferation, invasion, and migration.

SCH 900105 in Combination with Erlotinib

- EGFR and HGF/c-Met pathways cooperate to activate Akt to sustain cell proliferation and survival. (Fig 1)
- Preclinical evidence shows inhibition of HGF/c-Met pathway and EGFR are additive. (Fig 2)
- HGF has been shown to be involved in intrinsic and acquired resistance to EGFR TKIs. *(Yano et al. Cancer Res. 2008, 68 (22): 8479.)*
- HGF induces resistance to EGFR inhibitors. (Fig 3)
- Inhibition of HGF/c-Met signaling could be important in optimizing therapy with EGFR inhibitors.

Figure 1. HGF/c-MET and EGFR Pathways

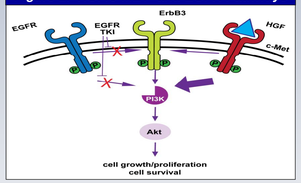


Figure 2. SC+E in NCI-H596 huHGF-transgenic Mice

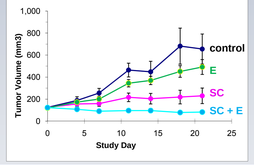
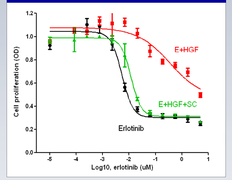


Figure 3. SC Prevents HGF-Induced EGFR TKI Resistance



Study Design

Objectives:

- To determine safety, tolerability, dose-limiting toxicities (DLTs) and recommended Phase 2 dose(s) (RP2D) of:
  - A. SCH 900105 administered IV in patients with relapsed or refractory solid tumors
  - B. SCH 900105 in combination with erlotinib in patients with relapsed or refractory solid tumors
- To characterize the pharmacokinetic (PK), pharmacodynamic (PD), and biomarker profiles of SCH 900105 and of erlotinib when dosed in combination.

Key Eligibility Criteria:

- Male or Female ≥ 18 years of age.
- Advanced malignancy, metastatic or unresectable, that has recurred or progressed following standard therapy or failed standard therapy.
- ECOG performance status of 0-1. Patients with PS of 2 considered after discussion between the investigator and medical monitor.
- Adequate organ function.

Dose-escalation Cohorts:

- Open-label, dose-escalation study
- 3+3 design.
- SCH 900105 administered IV over 60 min at doses of 2, 5, 10 or 20 mg/kg once every 2 weeks (1 Cycle = 14 days).

Table 1. Patient Characteristics

	Cohort 1 2mg/kg (n=3)	Cohort 2 5mg/kg (n=3)	Cohort 3 10mg/kg (n=3)	Cohort 4 20mg/kg (n=4)	Cohort 5 20mg/kg (n=11)	Cohort 6 (SC+E) 20mg/kg + 150mg/d (n=13)	Total (n=37)
Number of patients	3	3	3	4	11	13	37
Female/Male	2/1	1/2	1/2	2/2	8/3	7/6	21/16
Age, median (yrs)	64	80	71	57	62	61	62
Age, range (yrs)	44-84	58-84	54-72	19-87	46-69	18-78	18-87
ECOG Status(0/1/2)	0/3/0	0/3/0	0/2/1	1/3/0	2/9/0	7/6/0	10/26/1
Race: White/Other	3/0	1/2	3/0	4/0	10/1	13/0	34/3

Safety Expansion Cohort at RP2D:

- 11 additional patients were enrolled at the RP2D for an expanded safety assessment.

Phase 1b Evaluation of SCH 900105 in Combination with Erlotinib

- 13 patients were evaluated at the RP2D in combination with erlotinib for assessment of safety and tolerability

Results - Safety and Activity

Table 2. Common (>15%) Treatment-Emergent Adverse Events

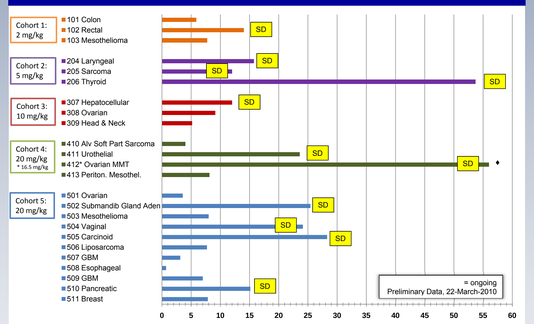
Adverse Event	Total (n = 37)	Cohort 1 (2mg/kg) (n = 3)	Cohort 2 (5mg/kg) (n = 3)	Cohort 3 (10mg/kg) (n = 3)	Cohort 4 (20mg/kg) (n = 4)	Cohort 5 (20mg/kg) (n = 11)	Cohort 6 (SC+E Combo) (n = 13)
Rash	16 (43.2%)	1	1	1	1	1	11
Fatigue	13 (35.1%)	1	2	3	1	4	2
Nausea	10 (27.0%)	-	2	1	-	4	3
Diarrhea	9 (24.3%)	1	1	-	1	-	6
Edema	8 (21.6%)	1	1	-	2	3	1
Hypokalemia	8 (21.6%)	-	-	-	-	4	4
Vomiting	7 (18.9%)	-	-	-	1	3	3
Headache	7 (18.9%)	1	1	2	1	2	-
Abdominal Pain	6 (16.2%)	-	1	2	-	1	2

Table 3. Related Grade 3-4 Adverse Events and Serious Adverse Events

Patient[a]	Adverse Event	Grade	SAE?
206	Diarrhea	3	No
307	Temporary Vision Loss – Left Eye	1	Yes
308	Fatigue	3	No
505	Hypokalemia / Hyperkalemia	4	Yes
602	Mucositis[b]	3	No

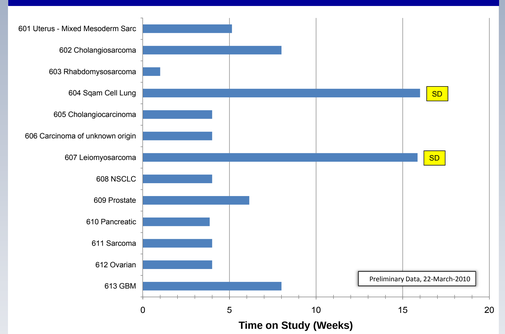
[a] Patients who have received at least 1 dose of SC
[b] DLT; also considered to be related to erlotinib

Figure 4. Responses and Time on Study (SCH 900105 Monotherapy)



Best Response: Stable Disease (SD); Average time on study = 14.9 wks (± 14.4)

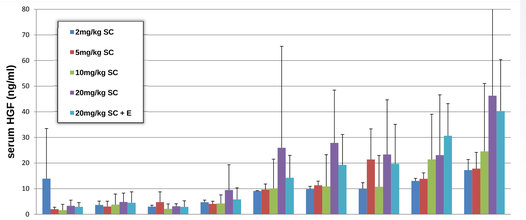
Figure 5. Responses and Time on Study (SCH 900105 + Erlotinib Combo)



Best Response: Stable Disease (SD); Average time on study = 6.5 wks (± 4.6)

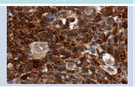
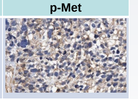
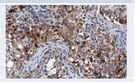
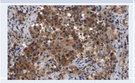
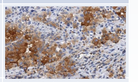
Results – Pharmacodynamics / Immunohistochemistry

Figure 6. Serum HGF Levels by Dose Level



The average baseline HGF levels in study patients are 6-fold higher versus normal donors ($p < 0.0001$). There are no statistically significant correlations between baseline serum HGF levels and the duration of the treatment.

Figure 7. Immunohistochemical Staining of Archived Tumor Tissues

	HGF	c-Met	p-Met
Pt 412 Ovarian-MMT			
IHC Score:	3+ cytoplasmic	1+ cytoplasmic	1+ cyto/membranous
Pt 503 Mesothelioma			
IHC Score:	2+ to 3+ cytoplasmic	2+ cytoplasmic	2+ cyto/membranous

There are no statistically significant correlations among the three markers from archived tissue (HGF, c-Met or p-Met) or between any of the IHC scores and the duration of treatment.

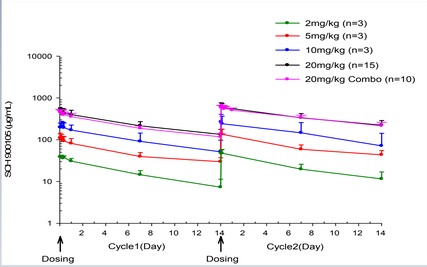
Results - Pharmacokinetics

Table 4. Mean SCH 900105 PK Parameters

Dose	N	Cmax (µg/ml)		AUC (µg·day/mL)	
		Cycle 1	Cycle 2	Cycle 1	Cycle 2
2 mg/kg	**3**	40.6 (4)	49.1 (20)	271 (27)	334 (27)
5 mg/kg	**3**	111 (28)	137 (33)	782 (39)	1170 (32)
10 mg/kg	**3**	214 (29)	267 (51)	1539 (43)	2139 (54)
20 mg/kg	**15**	490 (25)	641 (22)[a]	3561 (27)[a]	5566 (25)[a]
20 mg/kg SCH 900105+E	**10**	490 (15)	631 (13)[b]	3104 (14)[b]	5127 (9)[c]

a: n=14. Patient 508, Cycle 1 sample collection up to 24 hr post-dose only and no samples at Cycle 2.
b: n=9. Patient 603, Cycle 1 sample collection up to 24 hr post-dose only and no samples at Cycle 2.
c: n=7. Patient 601, Cycle 2 sample collection up to Day 8 post-dose only; Patient 603, no samples at Cycle 2; Patient 609, Cycle 2 sample collection up to 24 hr post-dose only.

Figure 8. Mean SCH 900105 Concentration-Time Profiles



Summary of Biomarker Findings:

1. Drug exposure (Cmax and AUC) are dose-proportional for dose levels tested.
2. The $t_{1/2}$ for SCH 900105 is estimated to be approximately 15-23 days after chronic dosing (n=2).
3. Patients had a higher average baseline concentration of HGF than normal donors.
4. Total HGF increased post-SCH 900105-dosing, likely due to HGF stabilization in the presence of SCH 900105.
5. Proportional increase in HGF/ SCH 900105 complex with increasing total HGF was also observed.
6. Target engagement is confirmed in patients.
7. No anti-drug antibody (HAHA) observed in any patient tested to date
8. No changes in soluble c-Met have been observed after dosing in any patient tested to date.
9. Patients receiving 20 mg/kg SCH 900105 + 150 mg/d erlotinib have the same serum HGF levels compared to those receiving 20 mg/kg SCH 900105 alone. (Fig 6)

Conclusions

- In this Phase 1 study, SCH 900105 appears to be well-tolerated as monotherapy at the 4 dose levels tested (2, 5, 10 or 20 mg/kg) and in combination with erlotinib (20 mg/kg SCH 900105 & 150 mg/d erlotinib).
- The maximum administered dose of 20 mg/kg SCH 900105 IV every 2 weeks as monotherapy and in combination with erlotinib (150 mg/d) was found to be well-tolerated and determined to be the RP2D for SCH 900105.
- Two monotherapy patients achieved prolonged SD (>12 months): #206 papillary thyroid (53.7 wks) and #412 MMT of the ovary (56.0 wks – ongoing as of 22 March 2010).
- Serum HGF increased post-SCH 900105-dosing, likely due to HGF stabilization in the presence of SCH 900105.
- SCH 900105 exposure is dose-proportional within the dose range evaluated.
- The $t_{1/2}$ for SCH 900105 is estimated to be approximately 15-23 days after chronic dosing (n=2).
- A Phase 2 study of SCH 900105 in combination with gefitinib in NSCLC is in progress.