Phase 2 Study of Ficlatuzumab (AV-299), an Anti-Hepatocyte Growth Factor Monoclonal Antibody, in Combination With Gefitinib in Asian Patients With Non–Small Cell Lung Cancer

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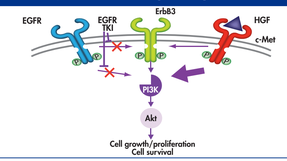
Background

- Hepatocyte growth factor (HGF) is the soluble ligand for the c-Met tyrosine kinase receptor (**Figure 1**), which is normally expressed by epithelial cells and frequently overexpressed in non–small cell lung cancer (NSCLC)
- High levels of HGF and intratumoral c-Met expression have been associated with more aggressive disease and a lower survival rate in NSCLC
  - The survival rate of patients with both intratumoral c-Met–positive and stromal HGF-positive tumors is significantly lower than for patients with tumors positive for only 1 or with tumors negative for both
  - HGF/c-Met pathway alterations may confer a substantial growth advantage and invasive potential to NSCLC cells
- In addition, recent studies have demonstrated that targeted c-Met inhibition by different therapeutic strategies, including small interfering RNA, small molecules, and specific antibodies, leads to decreased NSCLC cell growth and viability
- Ficlatuzumab (AV-299, formerly SCH 900105) is a humanized anti-HGF IgG1 monoclonal antibody with potent anti-tumor effects in vitro (**Table 1**) and in xenograft mouse models through:
  - Binding and neutralization of free HGF
  - Inhibition of c-Met phosphorylation
  - Inhibition of proliferation, apoptosis, angiogenesis, and invasion and motility
  - Ficlatuzumab has demonstrated inhibition of tumor growth in HGF autocrine and paracrine xenograft models

Figure 1. HGF/c-Met and EGFR pathways.



HGF, hepatocyte growth factor; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; PI3K, phosphoinositide kinase-3.

HGF/c-Met and Epidermal Growth Factor Receptor Pathway Dysregulation in NSCLC

HGF/c-Met pathway

- HGF was detectable in all NSCLC lysates tested; high HGF predicted poor prognosis[2]
- c-Met was expressed in 50% to 100% NSCLC tissue; high c-Met predicted poor prognosis[3]
- p-Met activation was observed in 22% to 72% NSCLC, highest among 5 major cancer types[4]
- c-Met and HGF reside on chromosome 7, c-Met focal amplification or chromosome 7 polysomy was observed in 10% to 30% NSCLC
- HGF hypersensitive juxtamembrane (JM) domain c-Met mutation was observed in 1% to 2% NSCLC
- c-Met genetic alteration is mutually exclusive with K-ras mutations

HGF/c-Met and epidermal growth factor receptor pathway crosstalk

- c-Met and epidermal growth factor receptor (EGFR) amplification and expression levels correlate
- EGFR or c-Met activation can account for 95% of Akt activation in lung adenocarcinoma
- HGF/c-Met pathway upregulation (c-Met amplification and/or high HGF) may result in EGFR tyrosine kinase inhibitor (TKI) resistance and vice versa
- HGF can accelerate EGFR TKI resistance by promoting clonal selection of subpopulation with c-Met amplification[5]
- EGFR TKI resistance caused by c-Met amplification or HGF upregulation can be overcome by dual c-Met and EGFR inhibition[6]

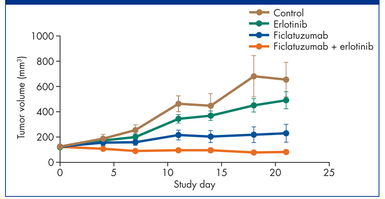
Ficlatuzumab Prevents HGF-induced EGFR TKI Resistance

- HGF decreases the sensitivity of HCC827 cells (EGFR Ex19del) to erlotinib by 50-fold
- Ficlatuzumab can restore erlotinib sensitivity in vitro (**Figure 2**)[7]
- Other growth factors tested—insulin-like growth factor (IGF), fibroblast growth factor (FGF)-2, macrophage-stimulating protein (MSP), and neuregulin—do not alter HCC827 sensitivity to erlotinib

Ficlatuzumab Potently Inhibits Tumor Growth of NCI-H596 Paracrine Xenograft in huHGF-Ki Mice

- NCI-H596 carries a c-Met JM mutation and wild-type EGFR and K-ras, and is hypersensitive to HGF
- The xenograft only grows in mice engineered to produce human HGF as a paracrine growth factor
- Ficlatuzumab in combination with erlotinib is more potent than either agent alone (**Figure 3**)[8]

Figure 3. Ficlatuzumab + erlotinib in NCI-H596 huHGF-transgenic mice.[8]



Therapeutic Hypotheses for Ficlatuzumab and Gefitinib Combination in NSCLC

Ficlatuzumab in combination with gefitinib

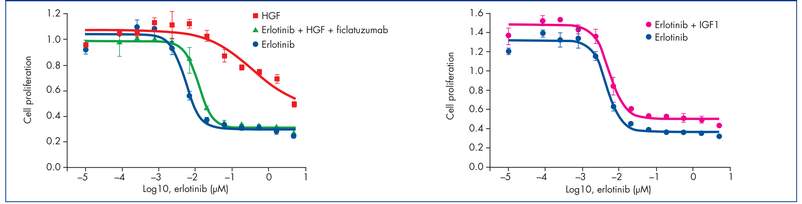
- May restore sensitivity to gefitinib in resistant population (intrinsic and acquired)
- May increase objective response rate (ORR) and prolong progression-free survival (PFS) to gefitinib in NSCLC patients with EGFR mutations
- May also be effective in patients with wild-type EGFR
- East Asian nonsmoker to light smoker population is an ideal setting to test the hypotheses in both EGFR mutated and wild-type molecular subtypes

Table 1. Ficlatuzumab Is a Highly Potent Anti-HGF Antibody[1]

mAb	K_D at 37°C	Neutralization of c-Met binding IC_{50}	Inhibition of c-Met phosphorylation IC_{50} in PC-3 cells	Inhibition of proliferation IC_{50} in 4MBr-5 cells	Maximum inhibition of invasion in MDA-MB-231 cells	Inhibition of scratch sealing in NCI-H441 cells	Inhibition of scatter at 0.5 µg/mL in MDCK cells
Ficlatuzumab	3	6.6 nM	0.58 nM	0.75 nM	93%	Yes	Yes

HGF, hepatocyte growth factor; mAb, monoclonal antibody; K_D, dissociation constant; IC_{50}, half-maximal inhibitory concentration.

Figure 2. Ficlatuzumab prevents HGF-induced EGFR TKI resistance.[7]



HGF, hepatocyte growth factor; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; IGF1, insulin-like growth factor 1.

Study Objectives

Primary Objective

- ORR of ficlatuzumab in combination with gefitinib in the study population

Secondary Objectives

- Safety and tolerability of the two-drug combination
- Response duration, PFS, and overall survival
- ORR in patients following cross-over from single-agent gefitinib
- Effect of the two-drug combination on exploratory biomarkers in peripheral blood mononuclear cells, body fluids, and/or tumor tissue
- Relationship between anti-tumor activity of the drug combination with baseline molecular markers, such as activating EGFR mutations; c-Met and EGFR gene copy numbers (fluorescence in situ hybridization [FISH] positivity); HGF, c-Met, and p-Met expression; HGF serum levels; and the anti-tumor activity of ficlatuzumab in combination with gefitinib
- Assess whether acquired resistance to gefitinib can be overcome with the addition of ficlatuzumab in patients following cross-over from single-agent gefitinib

Key Eligibility Criteria

Inclusion Criteria

- Asian ethnicity
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 2
- Confirmation of stage IIIB/IV lung adenocarcinoma with at least 1 measurable lesion per Response Evaluation Criteria In Solid Tumors (RECIST), version 1.1
- Never smoker (<100 cigarettes in lifetime) or light ex-smoker (quit ≥15 years ago and smoked ≤10 pack-years)
- Archived or otherwise available tumor tissue for determination of EGFR mutational status and immunohistochemistry (IHC) analysis
- Adequate hematologic, hepatic, and renal function, and coagulation parameters
- No active central nervous system metastases
- Enrollment and treatment in the gefitinib monotherapy arm with documented complete response, partial response, or stable disease for at least 12 weeks prior to disease progression in order to cross over into the gefitinib + ficlatuzumab arm
  - Upon progression in the gefitinib alone arm, patients who initially demonstrated disease control with single-agent gefitinib will be offered to receive the two-drug combination of ficlatuzumab and gefitinib upon sponsor approval, provided that safety is maintained and the patient continues to meet eligibility criteria

Exclusion Criteria

- Prior chemotherapy or prior treatment with an EGFR inhibitor, including both TKIs and monoclonal antibodies
- Myocardial infarction within 6 months prior to initiation of study treatment
- Thrombotic or embolic events, such as a stroke and transient ischemic attack, within the past 6 months
- Any condition that impairs absorption of oral agents or the patient's ability to swallow whole pills
- Diarrhea grade ≥2 or active inflammatory bowel disease
- Diagnosis of interstitial lung disease

Study Design

- Multi-center, randomized, open-label, phase 2 study of the two-drug combination of ficlatuzumab + gefitinib versus gefitinib alone (**Figure 4**)
- Approximately 170 evaluable patients from 25 to 30 sites in 7 Asian countries: Hong Kong, Malaysia, Philippines, Singapore, South Korea, Taiwan, and Thailand
- After a screening period of 28 days, patients will be randomized to receive either gefitinib monotherapy (250 mg daily) or ficlatuzumab 20 mg/kg every 2 weeks in combination with gefitinib 250 mg daily
- Patients will be enrolled sequentially in order of confirmation of eligibility, and randomization will be stratified by ECOG Performance Status (0–1 vs 2), smoking status (nonsmoker vs light ex-smoker), and gender
- Patients will be treated in continuous 28-day cycles, during which all patients will receive gefitinib daily and patients assigned to the two-drug combination arm will also receive ficlatuzumab on Days 1 and 15 of each cycle
  - Each patient should receive the assigned treatment for at least 1 cycle
  - Study drug may continue to be administered in the absence of progressive disease, unacceptable toxicity, or other criteria for withdrawal
- Patients will be monitored throughout treatment and for a follow-up period of 1 month (30 ± 3 days after the last dose of ficlatuzumab or gefitinib, whichever occurs later) for occurrence of adverse events, as well as for changes in clinical status, vital signs, and laboratory data

Study Endpoints and Evaluations

Disease Assessment for Primary Endpoint

- Response will be determined radiographically using standard RECIST criteria, version 1.1
- Imaging assessments (type and location) should be consistent for each patient throughout the study
- Imaging assessment time points
  - Screening
  - Every 4 weeks for first 4 cycles: end of Cycles 1, 2, 3, and 4
  - Approximately every 8 weeks thereafter: end of Cycles 6, 8, 10, etc
  - The last disease/response assessment should be performed after last dosing with either agent and on/before the 1-month follow-up visit
  - As clinically indicated

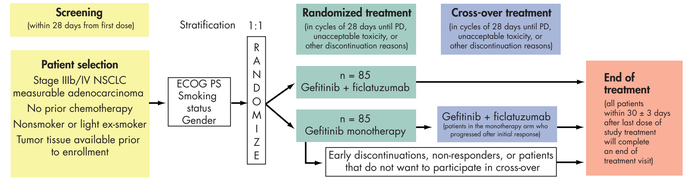
Assessment of Biomarkers

- The effect of the two-drug combination on exploratory biomarkers will be assessed in tumor and blood samples (**Table 2**)

Statistical Methods

- Estimated 170 evaluable patients enrolled (85 patients per treatment arm)
- Three study populations will be used in the analysis of data (**Table 3**)
- The ORR of each treatment arm will be compared using a 1-sided Fisher exact test (α = 0.05; power = 0.80) to detect an improvement in response rate (RR) from 40% to 60%
- Two subpopulations will be defined by the EGFR mutation status (wild-type and mutated). Differences in RR are expected across these subpopulations
  - At least 120 patients with tumor tissue analyzed for EGFR mutation status and c-Met expression by IHC will be enrolled in order to estimate the treatment effect in each subpopulation
  - For evaluation of the overall treatment effect, the ORR of each treatment arm in each subpopulation will be compared using a 1-sided Fisher exact test (α = 0.2) to detect improvements in ORR of 0.05 to 0.20 (power = 0.60) for wild-type and 0.65 to 0.85 (power = 0.80) for mutated EGFR, assuming 60% of patients with mutated EGFR and 40% with wild-type EGFR. No adjustments will be made for multiplicity

Figure 4. Study design.



PD, progressive disease; NSCLC, non–small cell lung cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Table 2. Assessment of Biomarkers

Tumor biomarkers to be investigated: ≥60% of patients expected to provide tumor samples
- EGFR mutation status
- c-Met, HGF, p-Met IHC
- c-Met/CEP7 FISH
- p-Akt, p-S6, pERK, CD31 IHC

Serum biomarkers to be investigated: 100% of patients expected to provide pre-dose and post-dose serum samples
- HGF (target engagement)
- sMet, angiogenic, inflammation markers
- Other markers (pharmacodynamic assessments)

All tumor assays use formalin-fixed, paraffin-embedded slides.

Table 3. Study Populations

Intent-to-treat population
- All randomized patients
- Population for analysis of the primary endpoint

Evaluable population
- All patients who
  - Complete the first efficacy evaluation (Cycle 1, Days 25–28), OR
  - Experience progressive disease prior to the first scheduled efficacy evaluation, confirmed by imaging studies
- Secondary population for analysis of efficacy endpoints

Safety population
- All randomized patients who received ≥1 dose of either study drug
- Treatment assignment will be designated according to the actual study treatment received

Discussion

- **A phase 1b study of ficlatuzumab in combination with gefitinib in NSCLC demonstrated safety and activity of the regimen[9]**
- **This phase 2 trial will further evaluate the efficacy, safety, and tolerability of ficlatuzumab combined with gefitinib versus gefitinib alone in Asian patients with advanced NSCLC**
- **As of April 2011, 174 patients have been randomized and the study is ongoing**
- **The study may also provide important information on the relationship between molecular markers and anti-tumor activity of ficlatuzumab combined with gefitinib**

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