Phase 1b Study of Ficlatuzumab (AV-299), an Anti-Hepatocyte Growth Factor Monoclonal Antibody, in Combination With Gefitinib in Asian Patients With NSCLC

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Background

- Ficlatuzumab (AV-299) is a highly potent humanized IgG1κ anti-hepatocyte growth factor (HGF) monoclonal antibody that
  - Neutralizes several important biological activities of HGF, such as HGF/c-Met binding, HGF-induced c-Met phosphorylation, cell proliferation, invasion, and migration[1]
  - Inhibits tumor growth in autocrine and paracrine xenograft models

HGF/c-Met and Epidermal Growth Factor Receptor Pathway Dysregulation in Non–small Cell Lung Cancer

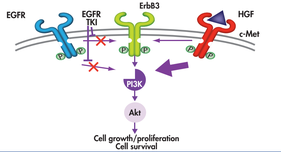
HGF/c-Met pathway

- HGF was detectable in all non–small cell lung cancer (NSCLC) lysates tested; high HGF levels are predictive of poor prognosis[2]
- c-Met was expressed in 50% to 100% of NSCLC tissue, with high c-Met predictive of poor prognosis[3]
- p-Met activation was observed in 22% to 72% of NSCLCs, the 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% of NSCLCs
- HGF hypersensitive juxtamembrane domain c-Met mutation is observed in 1% to 2% of NSCLCs
- c-Met genetic alteration is mutually exclusive with K-ras mutations

HGF/c-Met and epidermal growth factor receptor pathway cross-talk (Figure 1)

- 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 levels) may result in EGFR tyrosine kinase inhibitor (TKI) resistance and vice versa
- HGF can accelerate EGFR TKI resistance by promoting clonal selection of the 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[6,7]

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.

Objectives

Primary Objective

- To determine the safety, tolerability, dose-limiting toxicity (DLT), and recommended dose of ficlatuzumab in combination with gefitinib for the subsequent phase 2 study

Secondary Objectives

- To characterize the pharmacokinetic (PK) profiles of ficlatuzumab and gefitinib in combination
- To explore biomarkers in serum and tumor tissue in relationship to the antitumor activity of ficlatuzumab in combination with gefitinib

Methods

Key Eligibility Criteria

Inclusion criteria

- Asian ethnicity
- Eastern Cooperative Oncology Group Performance Status of 0 to 2
- Diagnosis of unresectable NSCLC with or without prior therapy, or other advanced solid tumor that progressed after standard therapy
- Adequate hematologic, hepatic, and renal function, and coagulation parameters
- No active central nervous system metastases

Exclusion criteria

- 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 higher or active inflammatory bowel disease
- Diagnosis of interstitial lung disease

Study Design

- This study used a standard 3 + 3 dose escalation design
- Patients received ficlatuzumab 10 or 20 mg/kg intravenously every 2 weeks plus gefitinib 250 mg orally once daily in continuous 28-day cycles
- Dose escalation criteria
  - A minimum of 3 patients were enrolled per dose level
  - The starting dose was ficlatuzumab 10 mg/kg intravenously every 2 weeks and gefitinib 250 mg orally once daily
  - If 1 of 3 patients experienced a DLT during Cycle 1, that dose level was expanded to 6 patients
  - If 0 of 3 or no more than 1 of 6 patients experienced a DLT during Cycle 1, dose escalation to ficlatuzumab 20 mg/kg plus gefitinib 250 mg occurred
  - If 2 or more of 6 patients experienced a DLT during Cycle 1 at ficlatuzumab 20 mg/kg, the cohort at 10 mg/kg will be expanded, if necessary, to a total of 6 patients to establish the recommended phase 2 dose (RP2D)
- The RP2D for ficlatuzumab in combination with gefitinib was defined as the highest dose level at which no more than 1 of 6 patients experienced a DLT during Cycle 1 (28 days after first dose of ficlatuzumab)
- After the initial 6 patients completed Cycle 1 in the RP2D cohort, an additional 6 patients were enrolled at the RP2D for an expanded assessment of safety and PK profile

Results

Patients

- A total of 15 patients were enrolled in the dose-escalation study, including 3 patients who received ficlatuzumab 10 mg/kg plus gefitinib and 12 who received ficlatuzumab 20 mg/kg plus gefitinib (**Table 1**)

Table 1. Patient Demographic and Baseline Characteristics

Characteristic	Ficlatuzumab 10 mg/kg plus gefitinib 250 mg (n = 3)	Ficlatuzumab 20 mg/kg plus gefitinib 250 mg (n = 12)	Total (N = 15)
Median age (range), y	59 (54–60)	61 (46–76)	60 (46–76)
Gender, n (%)			
Female	2 (67)	8 (67)	10 (67)
Male	1 (33)	4 (33)	5 (33)
Median no. of prior oncology therapies (range)	3 (1–4)	2 (1–4)	2 (1–4)
Prior EGFR TKI therapy, n (%)			
Yes	3 (100)	7 (58)	10 (67)
No	0	5 (42)	5 (33)
Tumor histopathology, n (%)[a]			
NSCLC adenocarcinoma	1 (33)	10 (83)	11 (73)
NSCLC non-adenocarcinoma	1 (33)	2 (17)	3 (20)
Lymphoepithelial carcinoma	1 (33)	0	1 (7)
Race, n (%)			
Asian	3 (100)	12 (100)	15 (100)

[a]Percentages may not total to 100.0% due to rounding.
EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; NSCLC, non–small cell lung cancer.

Safety and Tolerability

- The most commonly reported adverse event was dermatitis acneiform (67%), followed by cough (53%), decreased appetite (47%), and diarrhea (40%) (**Table 2**)

Table 2. Treatment-emergent Adverse Events Reported by ≥20% of Patients

Adverse event, n (%)	Ficlatuzumab 10 mg/kg plus gefitinib 250 mg (n = 3)	Ficlatuzumab 20 mg/kg plus gefitinib 250 mg (n = 12)	Total (N = 15)
Dermatitis acneiform	1 (33)	9 (75)	10 (67)
Cough	2 (67)	6 (50)	8 (53)
Decreased appetite	1 (33)	6 (50)	7 (47)
Diarrhea	1 (33)	5 (42)	6 (40)
Abdominal distension	2 (67)	3 (25)	5 (33)
Fatigue	1 (33)	4 (33)	5 (33)
Paronychia	0	5 (42)	5 (33)
Hemoptysis	1 (33)	3 (25)	4 (27)
Peripheral edema	1 (33)	3 (25)	4 (27)
Pruritis	0	4 (33)	4 (27)
Back pain	1 (33)	2 (17)	3 (20)
Dizziness	1 (33)	2 (17)	3 (20)
Dry skin	0	3 (25)	3 (20)
Dyspnea	0	3 (25)	3 (20)
Gingival bleeding	0	3 (25)	3 (20)
Nausea	0	3 (25)	3 (20)
Chest pain (non-cardiac)	0	3 (25)	3 (20)
Pyrexia	0	3 (25)	3 (20)
Vomiting	0	3 (25)	3 (20)

- Only 4 grade 3/4 treatment-related adverse events were reported during the study (**Table 3**)

Table 3. Grade 3/4 Treatment-related Adverse Events

Adverse event	Serious adverse event	Severity	Relationship to study treatment[a]
Paronychia	No	Severe (grade 3)	Possible
Edema peripheral	No	Severe (grade 3)	Possible
Dermatitis acneiform	No	Severe (grade 3)	Probable
Diffuse alveolar damage[b]	Yes	Life-threatening (grade 4)	Possible

[a]Assessed as related to either study drug, ficlatuzumab and/or gefitinib.
[b]Assessed as related to gefitinib by the investigator and listed as per product label.

Efficacy

- Median duration of exposure was 4.0 weeks (range, 3.6–4.0 weeks) for patients in the first dose cohort and 14.0 weeks (range, 4.0–40.0 weeks) for those in the RP2D cohort
- Five patients in the RP2D cohort experienced a partial response, including 4 confirmed responses, for an overall objective response rate of 33% (**Table 4**)
- Four additional patients in the RP2D cohort experienced stable disease

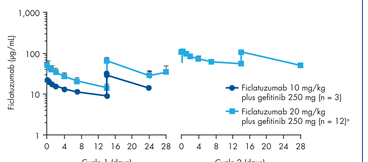
Table 4. Best Overall Response

Response, n (%)	Ficlatuzumab 10 mg/kg plus gefitinib 250 mg (n = 3)	Ficlatuzumab 20 mg/kg plus gefitinib 250 mg (n = 12)	Total (N = 15)
Objective response	0	5 (42)	5 (33)
Complete response	0	0	0
Partial response	0	5 (42)	5 (33)
Confirmed	0	4 (33)	4 (27)
Unconfirmed	0	1 (8)	1 (7)
Stable disease	0	4 (33)	4 (27)
Progressive disease	3 (100)	3 (25)	6 (40)
Not determined/not applicable/ not evaluable	0	0	0

Pharmacokinetics

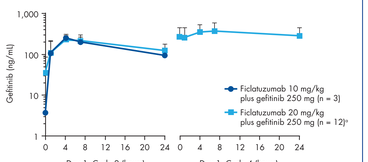
- Concentration-time profiles of ficlatuzumab and gefitinib are shown in **Figure 2** and **Figure 3**, respectively

Figure 2. Mean (+ SD) ficlatuzumab concentration-time profiles.



SD, standard deviation.
[a]n = 12 for Cycle 1 and n = 5 for Cycle 4.

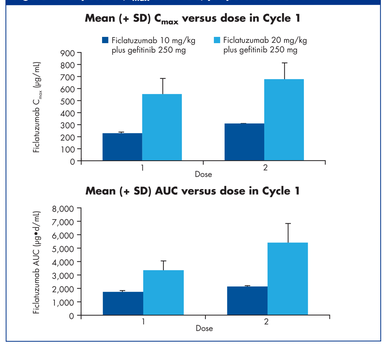
Figure 3. Mean (+ SD) gefitinib concentration-time profiles.



SD, standard deviation.
[a]n = 12 for Cycle 1 and n = 5 for Cycle 4.

- Consistent with previously reported data, drug exposure (maximal plasma concentration [C_{max}] and area under the curve [AUC]) was proportional to dose and nearly doubled after chronic dosing (**Figure 4**)[7]

Figure 4. Exposure (C_{max} and AUC) proportional to dose.



C_{max}, maximal plasma concentration; AUC, area under the curve; SD, standard deviation.
The first dose was given on Day 1, and the second dose was given on Day 15.

- The half-life ($t_{1/2}$) was approximately 11 to 23 days after the first dose, in the range expected for humanized monoclonal IgG antibodies (**Table 5**)[8]
- The $t_{1/2}$ was longer (32 days) after chronic dosing, indicating a likely decrease in drug elimination possibly due to gradual saturation of HGF increase after Cycle 1 as a result of ficlatuzumab treatment[7]
- The C_{max} was reached at or after the end of the intravenous drug infusion (**Table 5**)

Table 5. Mean (SD) PK Parameters of Ficlatuzumab

		$t_{1/2}$ (d)	C_{max} (μg/mL)		AUC (μg•d/mL)	
Ficlatuzumab dose	n	Day 1	Day 1	Day 15	Day 1	Day 15
10 mg/kg, Cycle 1	3	23 (14)	229 (9)	309 (1)	1,741 (96)	2,134 (71)
20 mg/kg, Cycle 1	12	11 (3)	544 (141)	677 (138)	3,339 (729)	5,400 (1,452)
20 mg/kg, Cycle 4	5[a]	32 (28)[b]	1,148 (123)	1,080 (143)[b]	7,798 (3,894)	NC[c]

SD, standard deviation; $t_{1/2}$, half-life; PK, pharmacokinetic; C_{max}, maximal plasma concentration; AUC, area under the curve; NC, not calculated.
[a]Only 5 patients enrolled in the 20 mg/kg dosage group were dosed in Cycle 4.
[b]n = 4.
[c]Not calculated due to limited sample collection.

- Gefitinib was slowly absorbed, with time to C_{max} (T_{max}) observed 4 to 7 hours after dosing (**Table 6**)
- Daily oral treatment with gefitinib resulted in a two-fold accumulation at steady state, as expected
- Gefitinib exposure (C_{max} and AUC) was similar in patients given ficlatuzumab 10 and 20 mg/kg (**Table 6**), indicating that the gefitinib PK parameters are unlikely to be altered by ficlatuzumab

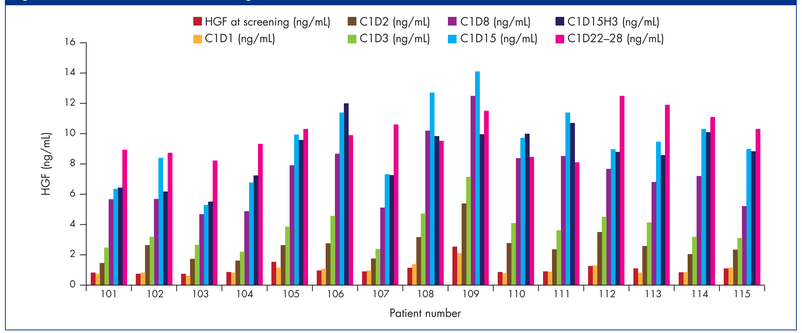
Table 6. Mean (SD) PK Parameters of Gefitinib

Ficlatuzumab dose	n	T_{max} (h)	C_{max} (ng/mL)	AUC (ng•h/mL)
10 mg/kg, Cycle 1	3	4 (0)	250 (44)	3,828 (1,040)
20 mg/kg, Cycle 1	12	5 (2)	245 (89)	4,109 (1,612)
20 mg/kg, Cycle 4	5[a]	7 (0)[b]	400 (243)	8,146 (4,994)

SD, standard deviation; PK, pharmacokinetic; T_{max}, time to C_{max}; C_{max}, maximal plasma concentration; AUC, area under the curve.
[a]Only 5 patients enrolled in the 20 mg/kg dosage group were dosed in Cycle 4.
[b]n = 4.

- All patients experienced increased levels of total HGF starting on Day 2 after ficlatuzumab administration (**Figure 5**)
  - Gradual increases were observed from Day 2 to Days 22 through 28
  - The observed increase is likely due to stabilization and/or induction of HGF as a result of ficlatuzumab treatment[9]

Figure 5. Serum HGF after ficlatuzumab + gefitinib treatment.



HGF, hepatocyte growth factor; C, cycle; D, day; H, hour.

Conclusions

- **The combination of ficlatuzumab and gefitinib was well tolerated**
- **The RP2D is ficlatuzumab 20 mg/kg intravenously every 2 weeks plus gefitinib 250 mg orally once daily**
- **Clinical activity was observed in patients with NSCLC**
- **The PK profiles of both ficlatuzumab and gefitinib were similar to previously reported values for each as monotherapy, and there was no indication of drug-drug interactions[7,10,11]**
- **All patients experienced the expected increase in total HGF levels upon ficlatuzumab administration, suggesting target engagement**
- **A phase 2, open-label, randomized trial is ongoing to compare ficlatuzumab plus gefitinib at the RP2D versus gefitinib alone as first-line treatment in Asian patients with lung adenocarcinoma (never smokers or former light smokers)[12]**

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