1198P

A randomized phase 2 study with exploratory biomarker analysis of ficlatuzumab, a humanized hepatocyte growth factor (HGF) inhibitory monoclonal antibody, in combination with gefitinib versus gefitinib alone in Asian patients with lung adenocarcinoma

T.S.K. Mok[1], K. Park[2], S.L. Geater[3], S. Agarwal[4], M. Han[4], P. Komarnitsky[4], M. Credi[4], K. McKee[4], N. Kuriyama[4], W. Slichenmyer[4], E.H. Tan[5]

[1]State Key Laboratory of Southern China, the Chinese University of Hong Kong, Hong Kong; [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [3]Songklanagarind Hospital, Thailand; [4]AVEO Oncology, Cambridge, Massachusetts, United States; [5]National Cancer Centre, Singapore

Abstract

Background: HGF/c-Met pathway activation has been implicated in epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor (TKI) resistance in lung adenocarcinoma. Ficlatuzumab is an HGF IgG1κ inhibitory monoclonal antibody (mAb) that prevents c-Met receptor activation by blocking its only known ligand, HGF. This study compared ficlatuzumab with gefitinib in treatment-naïve patients (pts) with high incidence of sensitizing EGFR mutation (SM+) and explored other biomarkers.

Methods: This was a multicenter, open-label, randomized phase 2 study in Asian pts with lung adenocarcinoma. Pts received either gefitinib (250 mg daily) or ficlatuzumab (20 mg/kg intravenous every 2 weeks [wks]) plus gefitinib (250 mg daily). Pts receiving gefitinib were allowed to cross over to ficlatuzumab plus gefitinib upon disease progression. Primary endpoint was overall response rate (ORR). The secondary endpoints included progression-free survival (PFS), overall survival (OS), and correlation of biomarkers with clinical activity. Biomarker analysis included EGFR mutation status, c-Met, and HGF expression levels, and EGFR and c-Met gene copy number.

Results: One hundred eighty-eight pts were randomized, 94 (19 men/75 women) to ficlatuzumab plus gefitinib or gefitinib, respectively; median age (ficlatuzumab plus gefitinib: 58 years, gefitinib: 62 years); and Eastern Cooperative Oncology Group Performance Status (ECOG PS) was balanced between arms. Tumor tissue samples were analyzed from 144 of 188 pts. There was no statistically significant improvement in ORR and PFS in intent-to-treat (ITT). Notable difference was seen in low c-Met group, ORR (41% versus 22%), and median PFS (mPFS; 7.3 versus 2.8 months), favoring ficlatuzumab plus gefitinib. The difference can be mostly attributed to the SM+/c-Met low subset ORR (70% versus 44%) and mPFS (11.1 versus 5.5 months), favoring ficlatuzumab plus gefitinib. The low c-Met group may identify a subgroup in SM+ that had worse outcome by gefitinib (mPFS 5.5 versus 7.4 months in SM+ overall) and benefited from ficlatuzumab plus gefitinib treatment (11.1 months). Preliminary OS results favor ficlatuzumab plus gefitinib in pts with stromal HGF high (P=0.03), c-Met high (P=0.18), and SM- (P=0.25) biomarkers. Ficlatuzumab plus gefitinib demonstrated a manageable safety profile.

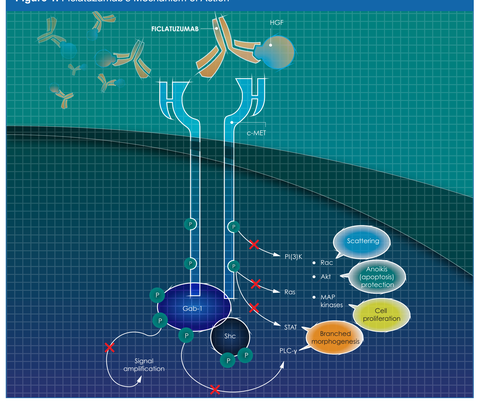
Conclusions: Ficlatuzumab plus gefitinib was well tolerated and showed clinical activity in biomarker subsets. However, the study results did not reach statistical significance. Ficlatuzumab plus gefitinib appears to improve mPFS in a subset of pts with SM+ and low c-Met expression, and prolong OS in pts with high stromal HGF and potentially other biomarker subsets such as high c-Met and SM-. These observations warrant further evaluation.

Background

- Ficlatuzumab (AV-299, formerly SCH 900105) is a humanized HGF IgG1 inhibitory monoclonal antibody that
  - Neutralizes all biological activities of HGF tested, such as HGF/c-Met binding, HGF-induced c-Met phosphorylation, cell proliferation, invasion, and migration[1]
  - Inhibits tumor growth in HGF-driven autocrine and paracrine xenograft models[2-4]
- HGF/c-Met dysregulation play an important role in non-small cell lung cancer (NSCLC)
  - HGF and c-Met are broadly expressed in NSCLC and high levels predict poor prognosis[5]
  - High HGF levels predicted anti-tumor activity of ficlatuzumab in preclinical models*
  - Phospho-Met activation was observed in 22% to 72% of NSCLCs, the highest among major cancer types[6]
  - HGF or c-Met amplification potently induces EGFR TKI resistance in EGFR- mutated NSCLC cells which can be reversed by the addition of ficlatuzumab or other c-Met inhibitors[7-10]
- Prior ficlatuzumab phase 1 clinical experience
  - Ficlatuzumab was well tolerated as monotherapy as well as in combination with EGFR TKIs[8,11]
  - Preliminary clinical activity was observed
  - Notably, the pt with the highest HGF in the single agent first-in-human trial (diagnosed with malignant mixed Mullerian tumor of the ovary) experienced SD >3 years and treatment is ongoing
  - Testing ficlatuzumab in combination with EGFR TKIs is warranted in NSCLC, particularly in NSCLC with EGFR mutations

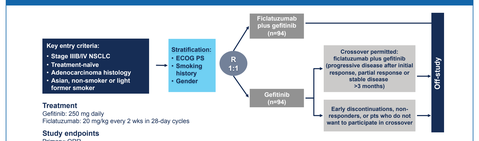
*Manuscript in preparation.

Figure 1. Ficlatuzumab's Mechanism of Action[1-4,12]



Study Design

Figure 2. Phase 2 Study Design: Ficlatuzumab Plus Gefitinib as First-Line Therapy in NSCLC



ECOG PS=Eastern Cooperative Oncology Group Performance Status; NSCLC=non-small cell lung cancer; ORR=overall response rate; OS=overall survival; PFS=progression-free survival.

Key Inclusion Criteria

- Asian ethnicity
- ECOG PS 0 to 2
- Confirmation of Stage IIIB/IV lung adenocarcinoma with at least 1 measurable lesion per Response Evaluation Criteria In Solid Tumors (RECIST) 1.1
- Non-smoker (<100 cigarettes in lifetime) or light former smoker (quit ≥15 years ago and smoked ≤10 pack years)
- Must have archived or otherwise available tumor tissue for determination of EGFR mutational status and immunohistochemistry (IHC) analysis*
- Adequate hematologic, hepatic function, renal function, and coagulation parameters
- No active central nervous system metastases

*Although the original protocol did not require archived or available tumor tissue for study entry, the protocol was modified November 17, 2010 (Amendment #02) adding the requirement to collect archived or available tumor tissue. All efforts were made to retrospectively collect archived or available tumor tissue for pts previously enrolled.

Key Exclusion Criteria

- Prior chemotherapy or prior treatment with EGFR inhibitor, including both TKIs and mAbs
- Myocardial infarction within 6 months prior to initiation of study treatment
- A serious active infection (> Grade 2) within 14 days of starting treatment; uncontrolled infection requiring antibiotics, antivirals, or antifungals
- Known human immunodeficiency virus (HIV) infection
- Thrombotic or embolic events such as a stroke and transient ischemic attack within the past 6 months
- Diarrhea ≥ Grade 2 or active inflammatory bowel disease
- Diagnosis of interstitial lung disease

Primary Objective

- Compare the ORR in Asian pts with previously untreated lung adenocarcinoma receiving either ficlatuzumab plus gefitinib or gefitinib alone

Secondary Objectives

- Evaluate the safety and tolerability of ficlatuzumab combined with gefitinib
- Compare the response duration, PFS, and OS in pts treated with a combination of ficlatuzumab plus gefitinib or gefitinib alone
- Investigate the effect of the 2-drug combination on exploratory biomarkers in peripheral blood mononuclear cells, serum, body fluids, and/or tumor tissue
- Investigate the relationship between baseline molecular markers such as activating EGFR mutations, HGF expression, c-Met expression, HGF serum levels, and the anti-tumor activity of ficlatuzumab in combination with gefitinib
- Determine the ORR with a combination of ficlatuzumab plus gefitinib following progression in pts who initially demonstrated disease control with single-agent gefitinib
- Assess whether acquired resistance to gefitinib can be overcome with the addition of ficlatuzumab in pts who progressed after initially demonstrating disease control in the gefitinib-alone arm

Statistical Methods

- The study was designed to enroll an estimated 170 evaluable pts (85 pts per treatment arm). For the ITT population, the ORR of each treatment arm was compared using a one-sided Fisher's exact test (α=0.05; power=0.80) to detect an improvement in response rate from 40% to 60%
- PFS and OS between ficlatuzumab plus gefitinib and gefitinib arms were compared using Kaplan-Meier survival analysis (P-values derived by unstratified log rank test) and hazard ratios (HRs) were determined using univariate Cox proportional hazards regression
- Pts with available tumor tissue were analyzed for EGFR mutation status. Additionally, HGF levels and c-Met levels were detected by IHC. ORR, PFS, and OS were analyzed in each biomarker-defined subpopulation using the same methods as for the ITT population. No multiplicity adjustments were introduced in these analyses
- Pts crossed over to ficlatuzumab plus gefitinib arm are analyzed in the gefitinib-alone arm

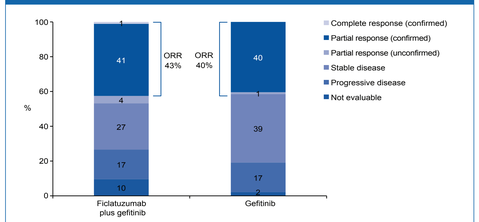
Results

- Demographics and tumor molecular markers were balanced between arms

Table 1. Key Patient Demographics

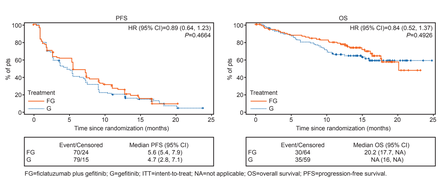
	Ficlatuzumab plus gefitinib n=94	Gefitinib alone n=94
Male, n (%)	19 (20)	19 (20)
Female, n (%)	75 (80)	75 (80)
Median age, years (range)	58 (35, 80)	62 (25, 84)
Smoking, n (%)		
Yes	6 (6)	5 (5)
No	88 (94)	89 (95)
ECOG PS, n (%)		
0	27 (29)	26 (28)
1	64 (68)	65 (69)
2	3 (3)	3 (3)

Figure 3. Best Overall Response (ITT)



ITT=intent-to-treat; ORR=overall response rate.

Figure 4. PFS and OS (ITT)



FG=ficlatuzumab plus gefitinib; G=gefitinib; ITT=intent-to-treat; NA=not applicable; OS=overall survival; PFS=progression-free survival.

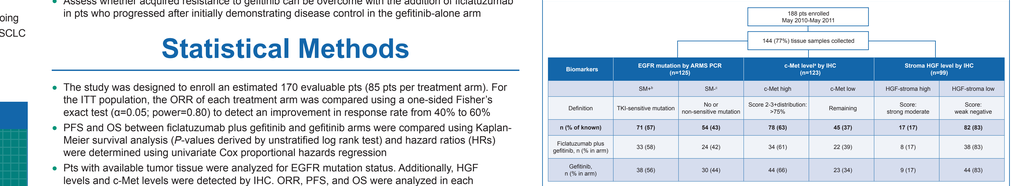
Efficacy in the ITT Population

- There was no statistically significant difference in the ORR (primary endpoint) between treatment arms
  - 43% ORR (95% confidence interval [CI] 32%, 53%) in ficlatuzumab plus gefitinib versus 40% (95% CI 30%, 51%) in gefitinib arm
- PFS HR was 0.89 (95% CI 0.64,1.23) for ficlatuzumab plus gefitinib versus gefitinib
  - Median PFS was 5.6 versus 4.7 months in ficlatuzumab plus gefitinib and gefitinib arms, respectively (P=0.47)
- Preliminary OS HR was 0.84 (95% CI 0.52,1.37) for ficlatuzumab plus gefitinib versus gefitinib
  - With only 32% of events recorded in the ficlatuzumab plus gefitinib arm, and 37% recorded in the gefitinib arm, the OS data are not yet fully mature

Pharmacodynamics

- HGF serum increases were observed post-ficlatuzumab administration. This is likely because of induction and/or increased stability of HGF when bound to ficlatuzumab. This finding is consistent with other pharmacodynamic studies of ficlatuzumab[8,11]

Figure 5. Biomarker Analyses



Biomarkers	EGFR mutation by ARMS PCR (n=125)		c-Met level[a] by IHC (n=123)		Stroma HGF level by IHC (n=99)	
	SM+[b]	SM-[c]	c-Met high	c-Met low	HGF-stroma high	HGF-stroma low
Definition	TKI-sensitive mutation	No or non-sensitive mutation	Score: 2-3+distribution: >75%	Remaining	Score: strong moderate	Score: weak negative
n (% of known)	71 (57)	54 (43)	78 (63)	45 (37)	17 (17)	82 (83)
Ficlatuzumab plus gefitinib, n (% in arm)	33 (58)	24 (42)	34 (61)	22 (39)	8 (17)	38 (83)
Gefitinib, n (% in arm)	38 (56)	30 (44)	44 (66)	23 (34)	9 (17)	44 (83)

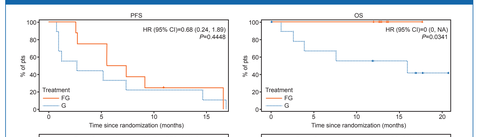
[a]120 of 123 pts had detectable c-Met, 3 of 123 were negative. All analysis were performed on polytetrafluoroethylene-coated slides.
[b]SM+: TKI-sensitive mutations included 36 pts with exon 19 deletion, 32 pts with L858R, 1 pt each; G719X, L861Q, exon19 del/L858R double mutation.
[c]SM-: No or non-sensitive mutation included 51 pts with no mutation detected, 1 pt each; L858R/T790M double mutation, G719X/S768I double mutation, exon 20 insertion.
ARMS PCR=amplification refractory mutation system polymerase chain reaction; IHC=immunohistochemistry; TKI=tyrosine-kinase inhibitor.

Table 2. PFS and OS in ITT and Biomarker Subsets

		PFS			OS		
Population	n	HR	95% CI	*P* Value	HR	95% CI	*P* Value
ITT	188	0.89	0.64, 1.23	0.47	0.84	0.52, 1.37	0.49
SM+	71	0.83	0.48, 1.45	0.51	0.72	0.28, 1.87	0.50
SM-	54	0.83	0.47, 1.47	0.51	0.62	0.28, 1.40	0.25
c-Met high	78	0.88	0.52, 1.48	0.62	0.57	0.25, 1.32	0.18
c-Met low	45	0.63	0.33, 1.21	0.16	0.79	0.33, 1.92	0.61
SM+/c-Met low	19	0.50	0.18, 1.35	0.16	0.93	0.15, 5.67	0.94
SM+/c-Met high	50	0.97	0.48, 1.94	0.92	0.54	0.16, 1.81	0.31
HGF-stroma high	17	0.68	0.24, 1.89	0.45	0	0, NA	0.03
HGF-stroma low	82	0.94	0.57, 1.54	0.80	1.19	0.59, 2.40	0.63

Tumor tissue samples were analyzed from 144 of 188 pts.
HR=hazard ratio; ITT=intent-to-treat; NA=not applicable; OS=overall survival; PFS=progression-free survival.

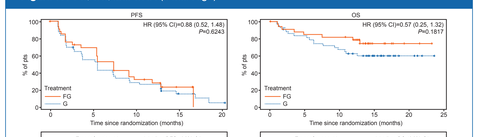
Figure 6. PFS, OS, and ORR (HGF-Stroma High)



EGFR=epidermal growth factor receptor; FG=ficlatuzumab plus gefitinib; G=gefitinib; NA=not applicable; ORR=overall response rate; OS=overall survival; PFS=progression-free survival.

Group	ORR, % (95% CI)
FG	50 (16, 84)
G	44 (14, 79)

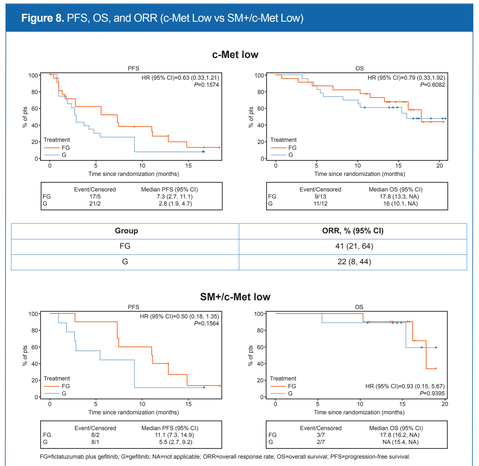
Figure 7. PFS, OS, and ORR (c-Met High)



FG=ficlatuzumab plus gefitinib; G=gefitinib; NA=not applicable; ORR=overall response rate; OS=overall survival; PFS=progression-free survival.

Group	ORR, % (95% CI)
FG	44 (29, 60)
G	30 (17, 45)

Figure 8. PFS, OS, and ORR (c-Met Low vs SM+/c-Met Low)



FG=ficlatuzumab plus gefitinib; G=gefitinib; NA=not applicable; ORR=overall response rate; OS=overall survival; PFS=progression-free survival.

Group	ORR, % (95% CI)
FG	41 (21, 64)
G	22 (8, 44)

Group	ORR, % (95% CI)
FG	70 (35, 93)
G	44 (14, 79)

Table 3. Overall Summary of AEs

	Ficlatuzumab plus gefitinib n=90		Gefitinib alone n=94	
	Pts n (%)	Events n	Pts n (%)	Events n
At least 1 treatment-related AE	84 (93)	851	85 (90)	642
At least 1 AE of Grade 3 or 4	40 (44)	94	35 (37)	63
At least 1 treatment-related AE of Grade 3 or 4	22 (24)	47	18 (19)	22
At least 1 SAE	32 (36)	45	25 (27)	47
At least 1 treatment-related SAE	7 (8)	10	3 (3)	3
At least 1 AE leading to study withdrawal	9 (10)	10	6 (6)	9
At least 1 treatment-related AE leading to study withdrawal	2 (2)	2	5 (5)	8
At least 1 AE with the outcome of death	5 (6)	5	7 (7)	7

AE=adverse event; SAE=serious AE.

Table 4. TEAEs With ≥10% Difference Between Treatment Groups

TEAE, n (%)	Ficlatuzumab plus gefitinib n=90		Gefitinib alone n=94	
	All grades	Grade 3	All grades	Grade 3
Paronychia	42 (47)	-	23 (25)	1 (1)
Acne	24 (27)	1 (1)	15 (16)	-
Peripheral edema	34 (38)	2 (2)	4 (4)	1 (1)
Dizziness	17 (19)	-	8 (9)	-
Eczema	15 (17)	2 (2)	7 (7)	-
Hypoalbuminemia	18 (20)	2 (2)	3 (3)	-
Gingival bleeding	11 (12)	-	1 (1)	-

TEAE=treatment-emergent adverse event.

Table 5. Grade 3 or Higher AE Occurring in ≥3 Pts

AE, n (%)	Ficlatuzumab plus gefitinib n=90	Gefitinib alone n=94
Alanine aminotransferase (increased)	5 (6)	10 (11)
Pneumonia	4 (4)	5 (5)
Aspartate aminotransferase (increased)	1 (1)	4 (4)
Hypokalemia	3 (3)	2 (2)
Activated partial thromboplastin time (prolonged)	4 (4)	0
Dyspnea	1 (1)	3 (3)
Deep vein thrombosis	0	3 (3)
Diarrhea	2 (2)	1 (1)
Hypocalcemia[a]	3 (3)	0
International normalized ratio (increased)	3 (3)	0
Peripheral edema	2 (2)	1 (1)
Pleural effusion	3 (3)	0
Weight (decreased)	2 (2)	1 (1)

[a]Based on uncorrected total calcium.
AE=adverse event.

Conclusions

- Addition of ficlatuzumab to gefitinib did not result in statistically significant improved ORR or PFS in the ITT population in Asian treatment-naïve NSCLC pts
- Ficlatuzumab and gefitinib combination demonstrated a trend for ORR and PFS improvement in a subset of pts with both EGFR-sensitizing mutations and low c-Met biomarker levels
- Preliminary OS results suggest that addition of ficlatuzumab to gefitinib may significantly prolong survival in pts with high stromal HGF (P=0.03)
- Trends for OS benefit in other biomarker subsets continue to be evaluated (patient follow-up is ongoing)
- Ficlatuzumab was well tolerated in combination with gefitinib
- These observations warrant further evaluation of ficlatuzumab in NSCLC

References

1. Han M, et al. Proceedings of the 98th Annual Meeting of the AACR. Los Angeles, CA: American Association of Cancer Research; 2007. Abstract 4887.
2. Meetze KA, et al. *Mol Cancer Ther.* 2009;8(suppl 12). Abstract C181.
3. Meetze KA, et al. *Mol Cancer Ther.* 2009;8(suppl 12). Abstract C173.
4. Meetze KA, et al. Proceedings of the 100th Annual Meeting of the AACR. Denver, CO: American Association of Cancer Research; 2009. Abstract 3184.
5. Spigel D, et al. *Ann Oncol.* 2010;21(suppl 8):viii7. Abstract LBA15.
6. Ma PC, et al. *Genes Chromosomes Cancer.* 2008;47(12):1025-37.
7. Engelman JA, et al. *Science.* 2007;316(5827):1039-43.
8. Patnaik A, et al. *J Clin Oncol.* 2010;28(15S). Abstract 2525.
9. Wilson TR, et al. *Nature.* 2012;487(7408):505-9.
10. Mok T, et al. *J Clin Oncol.* 2011;29(15 suppl). Abstract TPS213.
11. Tan E, et al. *J Clin Oncol.* 2011;29(15 suppl). Abstract 7571.
12. Christensen JG, et al. *Cancer Lett.* 2005;225(1):1-26.

Acknowledgements

AVEO Oncology would like to thank the patients and their families for participation in this study.
Editorial and writing assistance provided by Raffy M. Dakessian, PhD, and Christina Valentine-Leary from Scientific Connexions, funded by AVEO Oncology.

Corresponding author: Tony Mok (tony@clo.cuhk.edu.hk)

Presented at the European Society of Medical Oncology (ESMO) Annual Meeting; September 28-October 2, 2012; Vienna, Austria