Efficacy analysis of gefitinib +/- ficlatuzumab in serum proteomic-based subgroups of patients with previously untreated lung adenocarcinoma

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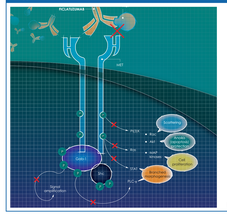
Background

Ficlatuzumab

- Ficlatuzumab is a monoclonal antibody that targets the Hepatocyte Growth Factor (HGF) and inhibits the MET pathway (**Figure 1**)
- Demonstrated efficacy in preclinical models as monotherapy and in combination with other therapies, including epidermal growth factor receptor (EGFR) inhibitors[1,2]
- Established pharmacodynamic profile and clinical activity in patients with solid tumors, including adenocarcinoma[3,4]
- A randomized Phase 2 study (P6162) was designed to compare the combination of ficlatuzumab + gefitinib with gefitinib alone in treatment-naïve Asian patients with adenocarcinoma (**Figure 2**)
  - There was no significant difference in tumor response rate, progression-free survival (PFS) and overall survival (OS) between ficlatuzumab + gefitinib and gefitinib alone in the intent-to-treat (ITT) population (**Figure 3**)
  - ORR of 43% (95% CI: 32–53%) versus 40% (95% CI: 30–51%) for ficlatuzumab + gefitinib versus gefitinib alone

Figure 1. Ficlatuzumab and HGF/MET Pathway Inhibition.



HGF, hepatocyte growth factor.

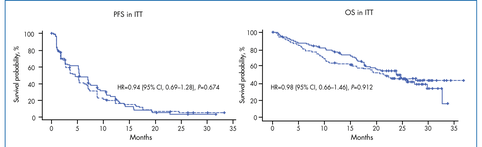
Ficlatuzumab:

Humanized IgG1κ Inhibitory Antibody of HGF (the only known ligand for the MET receptor)

Figure 2. Study Design of the Randomized Phase 2 Study (P6162).

- Primary objective
  - Objective response rate (ORR)
- Key secondary objectives
  - Compare duration of response, progression-free survival (PFS), overall survival (OS) in intent-to-treat, and in biomarker-defined subgroups (MET, HGF, EGFR)

Figure 3. Lack of Treatment Benefit in ITT Population.



	Median	95% CI
Combination G+F	5.6	5.4–7.9
Monotherapy G	4.7	2.8–7.1

	Median	95% CI
Combination G+F	24.7	18.0–29.8
Monotherapy G	21.8	16.3–NA

Combination G+F ——— Monotherapy G

F, ficlatuzumab; G, gefitinib.

VeriStrat

- VeriStrat® (VS) is a multivariate serum protein classifier
- Based on 8 features observed in matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectra[5,6] from patient serum
  - Some of the spectral regions analyzed by VS contain isoforms of acute phase reactants (eg, serum amyloid A)
  - Categorizes samples into "Good" or "Poor" subgroups; the selected spectral features are relatively elevated in samples testing "Poor"
  - Has shown prognostic/predictive significance independent of other known prognostic/predictive biomarkers
- VS appears to measure a host inflammatory state that may stimulate tumors via alternative pathways including HGF secretion, leading to resistance to EGFR tyrosine kinase inhibitor (TKI) therapy
- The PROSE prospective randomized study (NCT00989690) confirms that VS is predictive of a differential survival benefit between erlotinib and chemotherapy treatments for patients with advanced non–small cell lung cancer in second-line setting: VS-Poor patients have better outcomes on chemotherapy than erlotinib[7]

Study Objective

- The objective of this retrospective exploratory analysis was to evaluate the effect of ficlatuzumab + gefitinib in patient subgroups defined by VS and EGFR TKI-sensitizing mutations (EGFRsm) status

Methods

- Clinical data were extracted from the database of P6162
- 188 pretreatment serum samples were analyzed for VS classification
  - Serum samples were blinded for VS testing using approved procedures for MALDI-TOF in the Biodesix CLIA-certified Laboratory
  - VS labels of "Good" or "Poor" were successfully generated for 180 patients
  - Results were unblinded and merged with clinical data and EGFR mutation status for statistical analyses

Results

Patient Demographics

- Patient demographics were balanced between the two study arms (**Table 1**)
  - 58% and 56% of patients in the combination and gefitinib arm had EGFRsm, respectively
  - Of the patients who had VS classification successfully assigned, 145 (81%) were VS Good (VSG) and 35 (19%) were VS Poor (VSP)

Table 1. Patient Demographics

	Gefitinib Alone (n=94)	Ficlatuzumab + Gefitinib (n=94)
Sex, n (%)		
Male	19 (20)	19 (20)
Female	75 (80)	75 (80)
Median age, (range),years	62 (25, 84)	58 (35, 80)
Smoking, n (%)		
Yes	5 (5)	6 (6)
No	89 (95)	88 (94)
ECOG PS, n (%)		
0	26 (28)	27 (29)
1	65 (69)	64 (68)
2	3 (3)	3 (3)
EGFRsm status, n (%)		
Known status, n (% of total)	68 (72)	57 (61)
EGFRsm-, n (% of known)	30 (44)	24 (42)
EGFRsm+, n (% of known)	38 (56)	33 (58)
VeriStrat status, n (% of classified)		
Good (VSG)	76 (82)	69 (79)
Poor (VSP)	17 (18)	18 (21)
VeriStrat and EGFRsm (% of EGFRsm status)		
VSG/EGFRsm-	23 (77)	13 (54)
VSP/EGFRsm-	7 (23)	9 (38)
VSG/EGFRsm+	32 (84)	28 (85)
VSP/EGFRsm+	6 (16)	5 (15)

ECOG, Eastern Collaborative Oncology Group; EGFRsm; epidermal growth factor receptor tyrosine kinase inhibitor–sensitizing mutation; EGFRsm-, no EGFR TKI-sensitizing mutation; EGFRsm+, EGFR TKI-sensitizing mutation.

Tumor Response Rate

- There were no significant differences in ORR in the VSG subgroup for the combination vs gefitinib-alone treatment groups (42% vs 43%, *P*=0.87) (**Table 2**)
  - However, there was a potential benefit with the addition of ficlatuzumab in the VSP subgroup with a numerical improvement in ORR (56% vs 29%, *P*=0.12)

Table 2. Tumor Response Rate According to VeriStrat Status

	VSG n=145			VSP n=35		
	Gefitinib	Gefitinib + Ficlatuzumab	*P* Value	Gefitinib	Gefitinib + Ficlatuzumab	*P* Value
	n=76	n=69		n=17	n=18	
CR	0 (0%)	1 (1%)		0 (0%)	0 (0%)	
PR	33 (43%)	28 (41%)		5 (29%)	10 (56%)	
SD	27 (36%)	20 (29%)		9 (53%)	4 (22%)	
PD	13 (17%)	14 (20%)		3 (18%)	2 (11%)	
ORR[a]	33 (43%)	29 (42%)	0.866	5 (29%)	10 (56%)	0.118
DCR[b]	62 (82%)	52 (75%)		14 (82%)	15 (83%)	

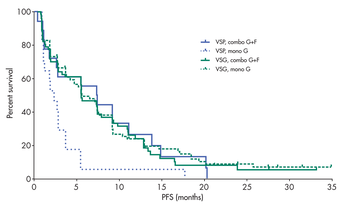
CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response.

[a]ORR = Confirmed CR + confirmed PR.
[b]DCR = Confirmed and unconfirmed CR + confirmed and unconfirmed PR + SD.

Progression-Free Survival

- Median PFS of the VSG and VSP subgroups is summarized in **Figure 4**
  - In the VSP subgroup, median PFS for the combination and gefitinib subgroups were 7.4 months and 2.3 months, respectively (HR=0.41, *P*=0.014)
  - There were no significant differences in median PFS in the VSG subgroup (5.6 months vs 5.6 months, HR=1.06, *P*=0.753)
  - Test of interaction between VS and treatment was significant, showing a differential benefit with the addition of ficlatuzumab to gefitinib between VSG and VSP patient groups (**Figure 4**)

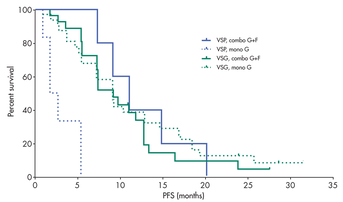
Figure 4. VeriStrat as a Predictive Biomarker for PFS.



PFS Medians, Months (95% CI)	Gefitinib	Ficlatuzumab + Gefitinib	Hazard Ratio (95% CI)	*P* Value
VSG	5.6 (3.8, 7.6) n=76	5.6 (3.6, 7.9) n=69	1.06 (0.74–1.51)	0.753
VSP	2.3 (1.1, 3.7) n=17	7.4 (2.6, 11.1) n=18	0.41 (0.20–0.86)	0.014
Interaction term (treatment and VS [G/P])			2.51	0.019

- 60 and 11 patients with EGFRsm were VSG and VSP, respectively
- Median PFS for both the combination and monotherapy was 9.2 months for the VSG subgroup, and 11.1 versus 2.3 for the VSP subgroup, respectively (**Figure 5**)

Figure 5. Predictive Effect of VeriStrat in the EGFR TKI-Sensitizing Mutation-Positive Population Treated With Ficlatuzumab/Gefitinib Combination (PFS).



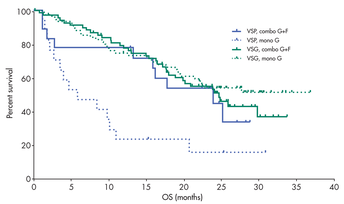
PFS Medians, Months (95% CI)	Gefitinib	Ficlatuzumab + Gefitinib	Hazard Ratio (95% CI)	*P* Value
VSG	9.2 (7.2, 12.9) n=32	9.2 (7.3, 12.8) n=28	1.19 (0.68–2.11)	0.538
VSP	2.3 (1.8, 5.5) n=6	11.1 (7.4, 20.2) n=5	–*	–*

*All of the patients in the gefitinib group progressed before the first event occurred in the ficlatuzumab+gefitinib group.

Overall Survival

- Median OS of the VSG and VSP subgroups is summarized in **Figure 6**
  - There were no significant differences in median OS in the VSG subgroups (HR=1.18, 95% CI, 0.74–1.88)
  - In the VSP subgroup, median OS for the combination and monotherapy subgroups was 23.9 months and 5.8 months, respectively (HR=0.41, 95% CI, 0.18–0.95; *P*=0.032)
  - Test of interaction between VS and treatment was significant, showing a differential benefit with the addition of ficlatuzumab to gefitinib between VSG and VSP patient groups

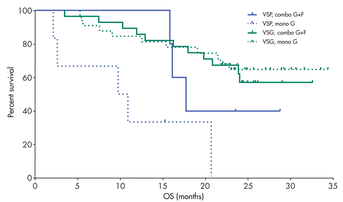
Figure 6. VeriStrat as a Predictive Biomarker for OS.



OS Medians, Months (95% CI)	Gefitinib	Ficlatuzumab + Gefitinib	Hazard Ratio (95% CI)	*P* Value
VSG	NR (19.5, NR) n=76	24.7 (18.0, NR) n=69	1.18 (0.74–1.89)	0.492
VSP	5.8 (2.7, 11.0) n=17	23.9 (15.9, NR) n=18	0.41 (0.18–0.95)	0.032
Interaction term (treatment and VS [G/P])			3.31	0.013

- Median OS was not reached for either the combination or gefitinib alone in the VSG subgroup, and was 17.8 versus 10.4 months for the VSP subgroup (*P*=0.09) (**Figure 7**)

Figure 7. Predictive Effect of VeriStrat in the EGFR TKI-Sensitizing Mutation-Positive Population Treated With Ficlatuzumab/Gefitinib Combination (OS).



OS Medians, Months (95% CI)	Gefitinib	Ficlatuzumab + Gefitinib	Hazard Ratio (95% CI)	*P* Value
VSG	NR (22.8, NA) n=32	NR (20.9, NA) n=28	1.15 (0.50–2.66)	0.737
VSP	10.4 (2.7, 20.7) n=6	17.8 (15.9, NA) n=5	0.30 (0.07–1.31)	0.093

- Key baseline characteristics were balanced among the VSP and VSG subgroups (**Table 3**)

Table 3. Baseline Characteristics Among the Subgroups

Demographic	VSP		VSG	
	Gefitinib	Ficlatuzumab + Gefitinib	Gefitinib	Ficlatuzumab + Gefitinib
ECOG 0/1/2	1/14/2	2/14/2	25/50/1	22/46/1
Median age	69	59	62	59
Male/Female	4/13	4/14	15/61	15/54
Past/Nonsmoker	1/16	3/15	4/72	3/66
EGFR NA/sm+/sm-/Unknown	1/6/7/3	2/5/9/2	5/32/23/16	9/28/13/19

ECOG, Eastern Collaborative Oncology Group; EGFR, epidermal growth factor receptor; EGFRsm-, no EGFR TKI-sensitizing mutation; EGFRsm+, EGFR TKI-sensitizing mutation; NA, not applicable.

Conclusions

- Although no statistically significant differences were observed in ORR, there was a potential signal of benefit with the addition of ficlatuzumab in the VSP subgroup
- Addition of ficlatuzumab to gefitinib improves PFS and OS in the VSP subgroup
- PFS and OS of the EGFRsm+VSP patients treated with gefitinib alone (2.3 and 10.4 mo respectively) are worse than expected (median PFS and OS for EGFRsm+VSP patients on gefitinib from the IPASS study were 9.6 and 21 mo, respectively[8]); ORR and PFS for the P6162 study ITT population were similar to the ITT population results in IPASS
- VS may be predictive of clinical benefit with ficlatuzumab + gefitinib compared with gefitinib alone
- A prospective confirmatory study using a VS-based predictive biomarker test for the combination of ficlatuzumab + EGFR-TKI in EGFRsm-positive patients is planned

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