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Pharmacodynamic–pharmacokinetic study of ficlatuzumab, a monoclonal antibody directed to the hepatocyte growth factor (HGF), in patients with advanced solid tumors who have liver metastases

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Abstract

Background: Ficlatuzumab is a humanized IgG1 mAb directed to HGF that inhibits activation of the c-Met receptor and has potential anti-tumor activity. This study defined the optimal dose using pharmacodynamic and pharmacokinetic (PK) assessments.

Methods: Patients (pts) with solid tumors and liver metastases and with phospho (p)-Met expression were sequentially enrolled to receive 2, 10, or 20 mg/kg (RP2D, defined in a previous study) of intravenous (IV) ficlatuzumab every 2 weeks (wks) and were evaluated every 8 wks for response using Response Evaluation Criteria In Solid Tumors (RECIST) 1.1. Target pathway modulation was assessed by measuring the following pharmacodynamic markers by immunohistochemistry (IHC) in biopsies of liver metastases: p-Met, p-Akt, p-ERK, p-S6K, HGF, c-Met, Ki67, cleaved caspase-3, and CD31. Pharmacodynamic-evaluable pts had measurable p-Met at Cycle 1, Day 1 pre-dose, and at least one post-dose time point. Serum was collected to measure ficlatuzumab, anti-drug antibodies (ADAs), s-Met, HGF, and HGF/ficlatuzumab complex levels by enzyme-linked immunosorbent assay (ELISA).

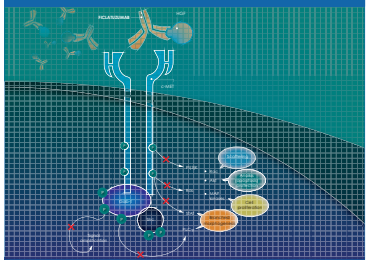
Results: Nineteen pts received ficlatuzumab: 15 men/4 women; mean age 60 years; Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0/1 (8/11 pts). The most frequent treatment-emergent adverse events (TEAEs) were asthenia (32%), peripheral edema (32%), hepatic pain (32%), and cough (26%). There were no dose-limiting toxicities (DLTs) or ADAs. Serum albumin decreased to below normal for the majority of pts at end of treatment and trended toward recovery at the follow-up visit. Best overall response was stable disease (SD) (5/18 pts) and disease progression (13/18 pts), and median duration of treatment was 6 wks (range 2-59). PK analysis revealed dose-proportional drug exposure with a low systemic clearance leading to a terminal half-life of 7.4 to 10.0 days and a low volume of distribution approximating the plasma volume. Ficlatuzumab treatment increased the total serum HGF and HGF/ficlatuzumab complex levels. Increasing dose of ficlatuzumab resulted in progressive decreases in p-Met and p-Akt. At RP2D, the majority of pts experienced ≥25% decrease from baseline in p-Met, p-Akt, p-ERK, Ki67, and CD31.

Conclusions: Ficlatuzumab is well tolerated in this population. The PK of ficlatuzumab in this study was consistent with that reported previously. Increase in post-dose serum HGF and HGF/ficlatuzumab complex levels indicates target engagement. At RP2D, a majority of pts experienced decreases in key cell signaling pharmacodynamic markers. This study supports the selection of the 20-mg/kg ficlatuzumab dose as RP2D.

Background

- Ficlatuzumab (AV-299, formerly SCH 900105) is a humanized HGF IgG1 inhibitory monoclonal antibody that
  - Neutralizes all HGF biological activities tested, such as HGF/c-Met binding, HGF-induced c-Met phosphorylation, cell proliferation, invasion, and migration[1]
  - Inhibits tumor growth in autocrine and paracrine HGF-driven tumor models[2-4]
- HGF/c-Met pathway dysregulation is an important driver of cancer and contributes to resistance to targeted anti-cancer agents
  - Activation of HGF/c-Met pathway may lead to tumorigenesis, invasive growth, angiogenesis, and is frequently observed in a variety of human malignancies, including colorectal, pancreatic, gastric, and breast cancers[5]
  - The HGF/c-Met pathway is upregulated in liver metastasis compared with primary tumors and correlated with poor prognosis[6-9]
  - HGF upregulation has been shown to induce resistance to a panel of targeted therapies, such as epidermal growth factor receptor (EGFR) and B-Raf kinase inhibitors[10-13]
- Previous phase 1 studies have determined that the maximum administered dose of ficlatuzumab (ie, 20 mg/kg) was well tolerated as monotherapy as well as in combination with EGFR tyrosine-kinase inhibitors[12,13] without reaching the maximum tolerated dose
  - This finding is consistent with other HGF/c-Met inhibitory antibodies in development, such as onartuzumab and rilotumumab
- Establishing the proper dose for optimal anti-tumor activity can be challenging
  - A rilotumumab gastric cancer trial demonstrated that higher drug exposure resulted in higher anti-tumor effects, but it was not clear if an optimal anti-tumor effect was reached with the maximum dose administered[14]
  - There are no pharmacodynamic data available regarding HGF/c-Met pathway modulation in the tumor for this class of antibodies
  - This study aims to establish whether ficlatuzumab can inhibit HGF/c-Met and downstream signaling in the tumor

Figure 1. Ficlatuzumab's Mechanism of Action[1-5]



Study Objectives

Primary objective

- Evaluate the safety and tolerability of ficlatuzumab and investigate the effect of ficlatuzumab on exploratory pharmacodynamic markers in the serum and within the tumor

Secondary objective

- Evaluate the PK profile of ficlatuzumab and study the preliminary anti-tumor activity of ficlatuzumab

Study Design

- A single-center, open-label study
- Ficlatuzumab was administered as a 30-minute IV infusion once per cycle (1 cycle=14 days)
- Pts were sequentially enrolled into cohorts of 2 mg/kg (n=6); 10 mg/kg (n=7); and 20 mg/kg (n=6), which was the RP2D defined in a previous study
- Target pathway modulation was assessed by measuring the following pharmacodynamic markers by IHC in biopsies of liver metastases: p-Met, p-Akt, p-ERK, p-S6K, HGF, c-Met, Ki67, cleaved caspase-3, and CD31
- Serum was collected to measure ficlatuzumab, ADAs, s-Met, and HGF levels by ELISA

Key Inclusion Criteria

- Advanced metastatic colorectal, breast, gastric/esophageal, or pancreatic cancer that has recurred, progressed, or was intolerant to standard therapies
- Liver metastases that are amenable to biopsy
- Man or woman ≥18 years of age
- ECOG PS of 0-1
- Measurable p-Met by IHC (H-score ≥30) in archived or otherwise available tumor sample

Key Exclusion Criteria

- Known active hepatitis B or C
- Inability to comply with the protocol requirements, including inability to undergo liver biopsies

Results

- The most common primary disease diagnosis was colorectal cancer (79%); other diagnoses included pancreatic (11%), breast (5%), and esophageal (5%) cancers

Table 1. Patient Demographic and Disease Characteristics at Baseline

	2 mg/kg n=6	10 mg/kg n=7	20 mg/kg n=6	Total n=19
Male, n (%)	5	5	5	15 (79)
Female, n (%)	1	2	1	4 (21)
Mean age, years (range)	57 (46-68)	59 (46-65)	63 (52-74)	60 (46-74)
Caucasian, n (%)	6	7	6	19 (100)
ECOG PS, n (%)				
0	1	3	4	8 (42)
1	5	4	2	11 (58)
No. of target lesions, n (%)				
2-3	3	5	5	13 (68)
>3	3	2	1	6 (32)

ECOG PS=Eastern Cooperative Oncology Group Performance Status.

Table 2. TEAEs Occurring in ≥3 Pts

	2 mg/kg n=6	10 mg/kg n=7	20 mg/kg n=6	Total (%) n=19
Asthenia	2	3	1	6 (32)
Hepatic pain	2	3	1	6 (32)
Peripheral edema	1	3	2	6 (32)
Cough	1	2	2	5 (26)
Abdominal distension	1	2	1	4 (21)
Abdominal pain	1	2	1	4 (21)
Increased blood bilirubin	3	1	0	4 (21)
Constipation	0	2	1	3 (16)
Decreased appetite	1	2	0	3 (16)
Dyspnea	0	2	1	3 (16)
Anemia	0	2	1	3 (16)
Increased gamma-glutamyl transferase (GGT)[a]	3	0	0	3 (16)

[a]No patient experienced GGT laboratory abnormality of Grade >2.

Table 3. All TEAEs ≥ Grade 3

	2 mg/kg n=6	10 mg/kg n=7	20 mg/kg n=6	Total (%) n=19
Asthenia	0	0	1	1 (5)
Dyspnea	0	0	1	1 (5)
Hyperbilirubinemia[a]	1	0	0	1 (5)
Hypoalbuminemia	0	1	0	1 (5)
Hypokalemia	0	1	0	1 (5)
Proteinuria	1	0	0	1 (5)
Respiratory failure	0	0	1	1 (5)

[a]Likely related to liver metastasis biopsy procedures.

Table 4. Lab Abnormalities ≥ Grade 3

	2 mg/kg n=6	10 mg/kg n=7	20 mg/kg n=6	Total (%) n=19
Uric acid	2	2	1	5 (26)
Alkaline phosphatase	1	1	2	4 (21)
Hypoalbuminemia[a]	0	1	1	2 (11)
Hyperglycemia	1	0	0	1 (5)
Hypocalcemia	0	0	1	1 (5)
Total bilirubin[b]	1	0	0	1 (5)

[a]Serum albumin decreased to below normal for the majority of pts at end of treatment and trended toward recovery at the follow-up visit.
[b]Likely related to liver metastasis biopsy procedures.

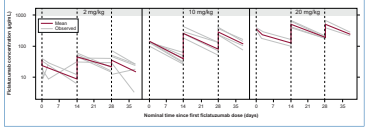
Table 5. Efficacy

	2 mg/kg n=6[a]	10 mg/kg n=7	20 mg/kg n=6
ORR (CR+PR)	0	0	0
SD (%)	3 (60)	2 (29)	0
Progressive disease (%)	2 (40)	5 (71)	6 (100)
DCR, CR+PR+SD (%)	3 (60)	2 (29)	0

[a]One patient was not evaluable for efficacy parameters.
CR=complete response; DCR=disease control rate; ORR=overall response rate; PR=partial response; SD=stable disease.

- The best response was SD in this refractory population, with 28% of patients achieving SD for a median duration of 2.6 months (range 0.6-13.7 months)
- One pt with pancreatic cancer in the 2-mg/kg cohort maintained SD >12 months
  - The pt experienced similar durations of SD with prior therapies because of slow growing tumors; therefore, the duration of SD on this study may not be solely attributable to study drug

Figure 2. Concentration Versus Time Profiles of Ficlatuzumab



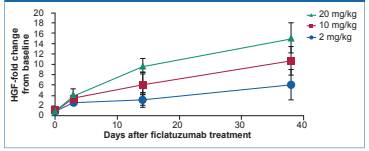
- PK profiles for ficlatuzumab are depicted in Figure 2 and showed a clear relationship in drug levels versus dose
- The PK of ficlatuzumab was characterized by low clearance (CL) ranging from 0.178 to 0.261 mL/hr/kg, a long half-life ($t_{1/2}$) ranging from 7.4 to 10 days, and V_d ranging from 61 to 75 mL/kg
- There were no statistically significant changes in CL or $t_{1/2}$ with dose. C_{max} and area under the curve (AUC) increased in an approximately dose-proportional manner
- There was evidence of accumulation between Cycle 1 and 2

Table 6. PK Parameters of Ficlatuzumab by Treatment Group in Cycle 1

Parameter	C_{max} (µg/mL)	t_{max} (h)[a]	$AUC_{0-\infty}$ (mg•h/mL)[b]	CL (mL/h/kg)[b]	$t_{1/2}$ (h)[b]	V_d (mL/kg)[b]
2 mg/kg						
n	6	6	4	4	4	4
Mean (SD)	39.1 (14.0)	1.5 (0.58-3.5)	8.38 (1.59)	0.245 (0.0484)	178 (32.7)	61.3 (4.16)
%CV	36	NA	19	20	18	6.8
10 mg/kg						
n	7	7	6	6	6	6
Mean (SD)	173 (39.9)	1.5 (0.58-3.6)	40.52 (11.24)	0.261 (0.0637)	207 (46.1)	75.4 (15.1)
%CV	23	NA	28	24	22	20
20 mg/kg						
n	6	6	4	4	4	4
Mean (SD)	443 (111)	1.0 (0.5-1.5)	117.0 (27.76)	0.178 (0.0398)	239 (43.3)	61.2 (17.8)
%CV	23	NA	24	22	18	29

[a]Median (minimum, maximum) presented for t_{max}.
[b]Only pts with PK profiles evaluable for complete non-compartmental analysis were included.
$AUC_{0-\infty}$=area under the concentration-time curve extrapolated to infinite time; CL=clearance; C_{max}=maximum plasma concentration; h=hour; NA=not applicable; SD=standard deviation; t_{max}=time to maximum plasma concentration; $t_{1/2}$=terminal elimination half-life; V_d=volume of distribution; %CV=percent coefficient of variation.

Figure 3. Change in Serum HGF Levels from Baseline



- Ficlatuzumab increased the total serum HGF levels in a dose- and time-dependent manner

Figure 4. Tumor Pharmacodynamic Analyses

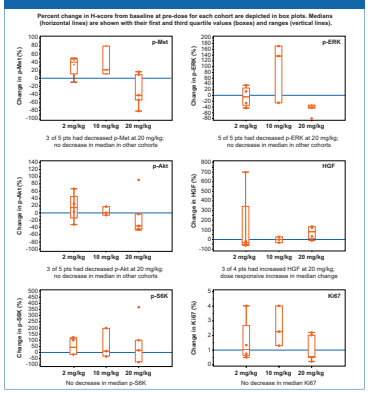
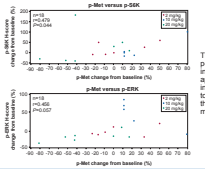
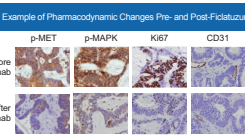


Figure 5. Correlations Between Percent Changes in p-Met Versus p-S6K and p-ERK



Three pts experienced decreases in p-S6K and had the strongest decrease in p-Met. Pts with p-Met decreases appeared to have less of an increase in p-S6K. Correlation between p-Met to p-S6K and p-ERK suggests that these downstream signaling changes may result from changes in p-Met.

Figure 6. Example of Pharmacodynamic Changes Pre- and Post-Ficlatuzumab Treatment



- The pt was diagnosed with advanced colorectal carcinoma with lung and liver metastasis
- The pt experienced pharmacodynamic changes in nearly all the markers tested
- Pt received 3 cycles of ficlatuzumab at 20 mg/kg and had progressive disease due to suspected new liver lesion by CT; however, the new lesion was not detected with PET

Summary of Results

- The most frequent TEAEs were asthenia (32%), peripheral edema (32%), hepatic pain (32%), and cough (26%)
- There were no DLTs or ADAs detected
- The best overall response was SD (5/18 pts) and disease progression (13/18 pts), and median duration of treatment was 6 wks (range 2-59)
- The PK of ficlatuzumab was characterized by low CL and a long $t_{1/2}$ of 7 to 10 days; ficlatuzumab exhibited linear PK across all dose levels tested
- Ficlatuzumab treatment resulted in dose- and time-dependent increase in serum HGF
- At 20 mg/kg, the majority of pts experienced ≥25% decrease from baseline in p-Met, p-ERK, p-Akt, Ki67, and CD31 and increased HGF in the tumor
- All pts treated with 20 mg/kg ficlatuzumab had a decrease of p-ERK in the tumor biopsies post-treatment
- Changes in p-Met were correlated with changes in p-S6K and p-ERK

Conclusions

- Ficlatuzumab was well tolerated in this study population
- Ficlatuzumab treatment at 20 mg/kg, but not at 2 and 10 mg/kg, demonstrated pharmacodynamic modulation in the tumor by inhibiting HGF/c-Met pathway and downstream signaling for cell proliferation, survival, and angiogenesis in majority of the pts treated
- Ficlatuzumab treatment also resulted in increased HGF in both tumor and serum, suggesting ficlatuzumab may stabilize tumor HGF and/or induce a compensatory increase in HGF production
- The PK was consistent with that of other ficlatuzumab trials and with other humanized IgG1 antibodies[12,13]
- The PD analysis confirmed the validity of 20 mg/kg every 2 wks as RP2D for ficlatuzumab

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