A Pharmacodynamic/Pharmacokinetic Study of Ficlatuzumab in Patients With Advanced Solid Tumors and Liver Metastases

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STATEMENT OF TRANSLATIONAL RELEVANCE

Dysregulation of the hepatocyte growth factor (HGF)/c-Met signaling pathway is observed in many malignancies and associated with progression of primary solid tumors to metastatic disease, including with presence of liver metastases. Thus, inhibition of the HGF/c-Met pathway may be therapeutically beneficial for some cancer patients. Ficlatuzumab is a humanized HGF inhibitory monoclonal antibody that neutralizes HGF/c-Met binding and HGF-induced c-Met phosphorylation. In addition to evaluation of the safety, tolerability, pharmacokinetic profile, and preliminary antitumor activity of ficlatuzumab in patients with advanced solid tumors and liver metastases, this clinical study investigated the pharmacodynamic effects of ficlatuzumab treatment in patients’ serum and tumors. Mean serum HGF levels increased with ficlatuzumab dose and number of treatment cycles. At 20 mg/kg, ficlatuzumab was well tolerated and decreases in tumor p-Met, p-Erk, and p-Akt and an increase in HGF were observed, suggesting ficlatuzumab can modulate HGF/c-Met pathway and downstream signaling in the tumor.
ABSTRACT

Purpose: This study evaluated the safety, tolerability, pharmacodynamics, pharmacokinetics, and antitumor activity of ficlatuzumab, a humanized hepatocyte growth factor (HGF) inhibitory monoclonal antibody, as monotherapy in patients with advanced solid tumors and liver metastases.

Patients and Methods: Patients with p-Met–positive tumors enrolled in 3 dose-escalation cohorts, receiving ficlatuzumab 2, 10, or 20 mg/kg once per 14-day cycle. Pharmacodynamic changes in liver tumor biopsies and serum, pharmacokinetics, safety, and clinical activity were assessed.

Results: No dose-limiting toxicities occurred in the 19 patients enrolled (n=6, 2 mg/kg; n=7, 10 mg/kg; n=6, 20 mg/kg). The most frequent diagnosis was colorectal cancer (n=15; 79%). The most common treatment-emergent adverse events were asthenia, peripheral edema, hepatic pain (32% each), and cough (26%). Laboratory abnormalities of decreased serum albumin were present in all patients. Ficlatuzumab at 20 mg/kg lowered median levels of tumor p-Met (−53%), p-ERK (−43%), p-Akt (−2%), and increased median HGF levels (+33%), at the last on-study time point relative to baseline. Mean serum HGF levels increased with ficlatuzumab dose and number of treatment cycles. Ficlatuzumab exhibited linear pharmacokinetics and long terminal half-life (7.4 to 10 days). Best overall response was stable disease (SD) in 28% of patients, including 1 pancreatic cancer patient with SD >1 year.

Conclusions: Ficlatuzumab exhibited good safety/tolerability and demonstrated ability to modulate the HGF/c-Met pathway and downstream signaling in the
tumor in patients with advanced solid tumors. Safety, pharmacodynamic, and pharmacokinetic data for ficlatuzumab confirmed the recommended phase 2 dose of 20 mg/kg once per 14-day cycle.
INTRODUCTION

Activation of the receptor tyrosine kinase c-Met via its ligand, hepatocyte growth factor (HGF) (1, 2), mediates proliferation, motility, and differentiation in several different cell types (3). Dysregulation of the HGF/c-Met signaling axis can lead to aberrant cell proliferation and drug resistance and promote cell migration, invasive growth, and angiogenesis (3-9), and is observed in many malignancies, including those of the pancreas, lung, stomach, breast, and kidney (3, 5, 10-16).

c-Met pathway activation has been associated with progression from primary to metastatic disease, particularly with liver metastasis (17-22). Serum HGF levels are elevated in breast cancer patients with malignant liver lesions (18), and have been correlated with liver metastases versus metastases at other sites (21). Dysregulation of c-Met is associated with the presence of liver metastases in patients with gastric (17) and colorectal cancer (22). These findings suggest that targeting the HGF/c-Met pathway may be beneficial for patients with advanced solid tumors and liver metastases; in addition, patients with liver metastases are likely to have detectable p-Met, making it possible to evaluate the p-Met changes in liver metastases after treatment.

Ficlatuzumab (AV-299, formerly SCH 900105) is a humanized HGF inhibitory monoclonal antibody that neutralizes HGF/c-Met binding and HGF-induced c-Met phosphorylation (23). Ficlatuzumab inhibits HGF-dependent growth of tumors in preclinical tumor xenograft models of glioblastoma (24) and non-small cell lung
cancer (NSCLC) (25). In a first-in-human dose-escalation study, ficlatuzumab 20 mg/kg once every 14-day cycle was established as the recommended phase 2 dose (RP2D) (26). Ficlatuzumab is in development for the treatment of solid tumors, including a phase 1b/2 study in NSCLC (27, 28).

This study reports the safety/tolerability, pharmacodynamic effects in tumors and serum, pharmacokinetic profile, and preliminary antitumor activity of ficlatuzumab monotherapy in patients who have solid tumors with liver metastases that express activated c-Met.

PATIENTS AND METHODS

Enrollment Criteria

All patients provided informed consent prior to enrollment. Patients were aged ≥18 years with histologically confirmed advanced unresectable colorectal, breast, gastric/esophageal, or pancreatic cancer with liver metastases amenable to biopsy. Patients had failed standard therapy, recurred/progressed following standard therapy, or had no standard therapeutic options, and were not currently amenable to curative surgical intervention. Key inclusion/exclusion criteria were: Eastern Cooperative Oncology Group performance status ≤1; measurable p-Met by immunohistochemistry of a tumor sample; and no previous use of anti–c-Met or anti-HGF therapy.
Patients should have had adequate hematologic (hemoglobin $\geq 9$ g/dL; white blood cell count $\geq 3,000$/mm$^3$; absolute neutrophil count $\geq 1,500$/mm$^3$; platelets $\geq 100,000$/mm$^3$), hepatic (serum bilirubin $\leq 1.5\times$ULN [upper limit of normal] except with Gilbert’s Syndrome; serum alanine and/or aspartate aminotransferase $\leq 5\times$ULN), renal (serum creatinine $\leq 1.5\times$ULN or calculated creatinine clearance $>60$ mL/min), and coagulation function (partial thromboplastin time $\leq 1.5\times$ULN; international normalized ratio $\leq 1.5\times$ULN). However, patients could not have persistent, unresolved grade $\geq 2$ drug-related toxicity (except alopecia, erectile dysfunction, hot flashes, decreased libido, and grade 2 sensory peripheral neuropathy), HIV infection or HIV-related malignancy, active hepatitis B or C, bleeding diathesis, hypersensitivity to any fczatuzumab components, active alcohol or illicit drug abuse, or any of the following events $\leq 6$ months prior to administration of study drug: serious/symptomatic active infection (or infection requiring antibiotics $\leq 14$ days prior to administration), myocardial infarction, severe/unstable angina, pectoris, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack, or seizure disorder. Those with any medical or psychiatric condition that might interfere with trial participation or interpretation of study results and those unable to comply with protocol requirements were also excluded. In addition, patients were excluded if they did not have adequate recovery from prior medical procedures, ie, major surgical procedure $\leq 4$ weeks prior to administration of study drug, radiotherapy $\leq 3$ weeks prior, and stem cell/bone marrow transplant $\leq 6$ months prior. Those with participation in any
other clinical trials involving therapeutic agents were also excluded. Female patients could not be pregnant or breast-feeding, and all women of childbearing potential and men with partners of childbearing potential were required to use effective contraception during the study and for 60 days after the last dose.

**Study Design**

Primary objectives of this phase 1, open-label, single-center study were to evaluate ficlatuzumab safety/tolerability and its effect on exploratory pharmacodynamic markers in patients with advanced solid tumors and liver metastases. Secondary objectives were to evaluate the pharmacokinetic profile and antitumor activity of ficlatuzumab.

Ficlatuzumab was administered once per 14-day cycle. A solution of ficlatuzumab (1.0-10.0 mg/mL) in 0.9% sodium chloride was administered as a 30-minute intravenous infusion through a low protein-binding, 0.22 μM in-line filter without premedication. The study was designed to include a minimum of 6 patients in each of the 3 cohorts (2, 10, and 20 mg/kg) for safety evaluation, which would also allow for a minimum of 3 fully evaluable patients to study dose-dependence of the pharmacodynamic changes.

Patients with intolerable grade 2 toxicity could have their dose reduced a level or treatment discontinued (if at the lowest dose level). Patients with grade 3/4...
toxicity requiring dose reduction could resume treatment at the lower dose after the adverse event (AE) resolved to grade 0/1 or baseline.

The study protocol was approved by the appropriate ethics committee and was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki.

**Safety Evaluations**

All patients who received ≥1 dose of ficlatuzumab were considered evaluable for safety analyses. AE reporting occurred at screening, during treatment, and 1 month after the final dose; other safety evaluations occurred at screening, the beginning of each treatment cycle, end of treatment (EOT), and 1 month after treatment discontinuation. Toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (29).

Dose limiting toxicities (DLTs) were defined as any of the following toxicities: grade 3 toxicities (except nausea or vomiting, diarrhea, fever without neutropenia, and alanine or aspartate aminotransferase abnormalities lasting ≤48 hours); grade 3 neutropenia with an absolute neutrophil count ≥500/mm³ and <1000/mm³ lasting ≥5 days; grade 3 thrombocytopenia associated with bleeding; grade 4 hematologic or non-hematologic toxicities; drug-related toxicities of any grade that occurred during the first 2 cycles and required a dose reduction during the next scheduled study drug administration; and drug-related toxicities of any
grade that resulted in interruption of treatment for >2 weeks. Accrual to the next cohort occurred if ≤1 of 6 patients experienced a DLT during the first 2 cycles; dose-escalation was terminated if ≥2 patients in a cohort experienced a DLT. Anti-drug antibodies (ADA) against ficlatuzumab were evaluated in serum at Cycle 1 Day 1 predose and at EOT using a validated bridging electrochemiluminescence assay. Briefly, biotinylated-ficlatuzumab and sulfo-tag ficlatuzumab (Meso Scale Discovery [MSD], Gaithersburg, MD) were added to diluted serum samples and incubated overnight. Samples were added to the wells of a streptavidin-coated plate (MSD) to capture the biotinylated-ficlatuzumab in the complex. Only samples containing antibody bound to both biotinylated-ficlatuzumab and sulfo-tag ficlatuzumab generated the electrochemiluminescence signal. The specificity of the ADA signal was verified by ficlatuzumab spike-in. If the reading was reduced by half and/or was below the assay cutpoint after spike-in, then the sample was considered positive for ADA.

**Pharmacodynamic Evaluations**

For pharmacodynamic biomarker analyses, a minimum of 3 patients per cohort had to meet the criteria for the pharmacodynamic evaluable population, defined as patients with p-Met-positive tumors (ie, H-score ≥30) by immunohistochemistry at baseline predose and with ≥1 postdose p-Met result. This threshold for p-Met positivity was selected conservatively, to minimize inclusion of false-positive patients (particularly as archival specimens were used...
for eligibility determination for several patients), and was based on prior observation that known low/negative tissue microarray samples typically score below this cutoff, while the rest score above it; of note, literature guides were not available for threshold determination at the time of study design.

Sequential tumor biopsies from liver metastases were collected at baseline predose, Cycle 1 Day 3-8, and Cycle 3 Days 8-14; archived tumor tissue was also collected. Tumor sample preparation has been described previously (30). Collected biopsies were fixed in 10% formalin for 12-16 hours followed by a series of alcohol, xylene, and paraffin solution exchanges until final embedding in a paraffin block. Expression of HGF, c-Met, p-Met, p-ERK, p-Akt, p-S6K, cleaved caspase-3, CD31, and Ki-67 in tumor samples was analyzed by immunohistochemistry, using automated staining system (Dako Autostainer and Dako Envision Flex Kit [K8012] detection system from Dako Colorado, Inc, Fort Collins, CO) and immunodetection with commercially available antibodies according to the manufacturer’s instructions (Appendix Table A1 [online only]). Percent positive cells were reported for Ki-67 and cleaved caspase-3; CD31 was quantified as percent positive area within tumor tissue per high power field. H-scores (31) were calculated for all other pharmacodynamic parameters using the formula: (% weak-stained cells) x 1 + (% intermediate-stained cells) x 2 + (% strong-stained cells) x 3. Results were presented as percent change from baseline, calculated as: [100 x (Cycle “X” value – baseline value)/baseline value].
Sequential blood samples were collected predose and at 3 hours postdose on Cycle 1 Day 1; Cycle 1 Day 3-4; predose and at 2 hours postdose on Cycle 2 Day 1; and on Cycle 3 Days 8-14. Serum HGF was measured using an enzyme-linked immunosorbent assay (ELISA; R&D Systems, Minneapolis, MN). c-Met levels were measured using a bridging electrochemiluminescence assay. Briefly, streptavidin-coated plates (MSD) were coated with a biotinylated goat polyclonal Met antibody (R&D Systems). c-Met present in serum samples was captured and subsequently detected using goat polyclonal c-Met antibody (R&D Systems) labeled with sulfo-tag (MSD). c-Met extracellular domain (R&D Systems) was used as a standard.

Tumor metabolic activity was followed by positron emission tomography (PET) computed tomography (CT) with [18F]fluorodeoxyglucose at baseline (Cycle 1 Day 1 pre-infusion and prior to the first liver biopsy), on Day 3 or 4 (48-72 hours after the first dose of study drug; only performed in patients with evaluable PET CT scan lesions clearly distinct from the biopsy site), and during Cycle 3 (at the time of the first disease assessment).

**Pharmacokinetic Evaluations**

Whole blood samples for serum evaluations were collected predose, immediately postdose, and at 1, 3, 6, and 8 hours postdose on Cycle 1 Day 1; Cycle 1 Day 3-4; predose, postdose, and at 2 hours postdose on Cycle 2 Day 1; predose and postdose on Cycle 3 Day 1; Cycle 3 Days 8-14; and EOT.
Ficlatuzumab serum concentrations were measured in serum using an ELISA method validated according to Good Laboratory Practice guidelines (with mean inter- and intra-assay precision of 9.99% and 6.27%, respectively). Briefly, ficlatuzumab was captured from serum samples by recombinant HGF (R&D Systems) bound on a microtiter plate, and captured ficlatuzumab was detected with peroxidase-labeled rabbit anti-human antibody (Dako) and tetramethylbenzidine as substrate.

Pharmacokinetic parameters calculated for ficlatuzumab included minimum and maximum plasma concentration ($C_{\text{min}}$, $C_{\text{max}}$), time to peak plasma concentration ($t_{\text{max}}$), area under the plasma concentration-time curve from time ($AUC_{0\rightarrow\infty}$), clearance, half-life ($t_{1/2}$), apparent volume of distribution ($V_d$), and percent coefficient of variation ($\%CV$), using non-compartmental analysis (Phoenix® WinNonLin® version 6.2; Pharsight Corporation, Mountain View, CA).

**Tumor Response Evaluations**

The efficacy evaluable population included those who received $\geq 3$ cycles of ficlatuzumab or were withdrawn due to progressive disease before completing Cycle 3. Disease and tumor response were assessed using Response Evaluation Criteria In Solid Tumors, version 1.1 (32), at screening, the Cycle 3 Day 8-14 visit, and approximately every 6 weeks thereafter. Efficacy parameters included overall response rate, duration of response, and time to progression.
(TTP). Time-to-event endpoints were estimated using Kaplan-Meier methodology.

RESULTS

Patients

From August 2009 to March 2011, 19 patients were enrolled across 3 dose cohorts: n=6, 2-mg/kg cohort; n=7, 10-mg/kg cohort; and n=6, 20-mg/kg cohort (baseline characteristics in Table 1). The most common primary diagnosis was colorectal cancer (79%). All patients had stage IV disease with measurable target lesions at screening, including in the liver; all had ≥1 nontarget lesion.

Median (range) treatment duration was 6 (2-59) weeks. Fifteen patients (79%) received ficlatuzumab for 2 weeks to 2 months, 3 patients (16%) for >2 to 6 months, and 1 patient (5%) for >6 months. All patients discontinued: 18 patients (95%) for progressive disease and 1 patient (5%) for grade 4 AE (hyperbilirubinemia; unlikely related to treatment).

Safety and Tolerability

The safety population included all patients. No DLTs were reported. Eighteen patients (95%) experienced ≥1 treatment-emergent AE (TEAE), including 1 considered possibly drug-related (grade 1 pyrexia during Cycle 1 in the 2-mg/kg cohort). The most common TEAEs were asthenia, peripheral edema, hepatic pain, and cough (Table 2). Four patients (21%) experienced grade 3/4 unrelated
TEAEs. Grade 3 TEAEs included asthenia, hypoalbuminemia, hypokalemia, proteinuria, and dyspnea (n=1 each). Albumin level in the patient with grade 3 hypoalbuminemia was 26.9 g/L at screening (grade 2) and decreased throughout the study. Grade 4 TEAEs included hyperbilirubinemia associated with worsening liver metastasis resulting in discontinuation and respiratory failure due to disease progression (n=1 each). Five patients (26%) had 1 dose delay each for AE management.

Laboratory abnormalities reported as TEAEs (all grades) included hypokalemia, hypomagnesemia, hypoalbuminemia, anemia, leukopenia, hypocalcemia, hyponatremia, proteinuria, hyperglycemia, increased gamma-glutamyl transpeptidase, and neutropenia. One patient had an abnormal change in urinalysis results (epithelial cells) considered clinically significant.

Five patients (26%) experienced serious unrelated AEs: hyperbilirubinemia (n=1, 2 mg/kg); fatigue and intestinal obstruction (n=1 each; 10 mg/kg), gastrointestinal hemorrhage (n=1, 20 mg/kg), and intestinal obstruction, hepatic pain, and respiratory failure (n=1, 20 mg/kg). The last patient died due to grade 4 respiratory failure considered related to disease progression.

The most frequently occurring laboratory abnormalities were hepatobiliary events; average levels of lactate dehydrogenase, alkaline phosphatase (AP), alanine aminotransferase, and aspartate aminotransferase were high at baseline
and throughout the study. Grade 3 abnormalities included elevated AP for 4 patients (21%) and elevated total bilirubin for 1 patient (5%), which worsened to grade 4 (Table 2). Other changes in laboratory parameters included grade 2 increased lymphocytes, partial thromboplastin time, and potassium, and grade 3 increased blood glucose and decreased albumin.

In a retrospective analysis, serum albumin levels decreased in all patients to below the lower limit of normal by study completion. Mean (standard deviation [stdv]) albumin levels decreased from 36.8 (4.46) to 30.5 (6.70) g/L during treatment, reaching minimum levels at EOT. Three patients (n=1, 10 mg/kg; n=2, 20 mg/kg) experienced serum albumin decreases to grade 3 at the end of Cycle 2, coinciding with EOT for all 3 patients. Mean (stdv) albumin level increased during the 30-day follow-up period for all cohorts to 31.1 (4.67) g/L but remained below normal.

Anti-drug antibodies were measured for 13 patients at the EOT and ficlatuzumab was not immunogenic. No patient had clinically significant abnormal electrocardiograms. Changes in body mass index were small and not clinically meaningful.

**Pharmacodynamic Analyses**

The tumor pharmacodynamic evaluable population comprised 12 patients (n=4, 2 mg/kg; n=3, 10 mg/kg; n=5, 20 mg/kg). All patients had measurable baseline p-
Met by immunohistochemistry (H-score ≥30); median (range) H-score was 115 (40-260).

H-score changes from baseline for selected pharmacodynamic markers are shown in Fig 1 (marker summary in Appendix Table A2 [online only]). More pronounced and consistent decrease in p-Met from baseline was apparent at the RP2D (20 mg/kg) of ficlatuzumab versus lower doses. At Cycles 1 and 3, respectively, median (range) relative changes were: at 20 mg/kg, −21% (−42-17) and −53% (−81-9); at 10 mg/kg, 11% (11-11) and 22% (11-80); and at 2 mg/kg, 40% (0-50) and −17% (−23 to −9; Fig 1A). Similarly, at 20 mg/kg there was a decrease in p-ERK with median (range) change of −38% (−59 to −34) and −43% (−78-15) and to lesser extent p-Akt, with a median (range) change of −40% (−48-91) and −2% (−45-12) at both time points (Fig. 1B, C). At 20 mg/kg, there was an increase in tumor HGF level with median (range) change of 17% (0-125) and 33% (−10-138) at the same time points (Fig. 1D). Increased serum HGF levels were also observed in a time- and dose-dependent manner (Fig 1E; Appendix Table A3 [online only]). At 10 mg/kg, there was an increase in median change p-Met and p-ERK at both time points for reasons unknown. Further, changes in p-ERK expression correlated with changes in tumor p-Met (Spearman correlation coefficient r=0.48, P=0.044; n=18; Fig 1F), suggesting that changes in p-ERK could result from changes in HGF/c-Met signal transduction. No dose- or time-dependent pattern could be identified in the changes in CD31-positive
microvessel density upon initiation of treatment with ficlatuzumab (Appendix Table A2). No changes in serum c-Met levels were observed postdose.

All patients who had PET CT scans performed had [18F]fluorodeoxyglucose avid tumors at baseline, consistent with metabolically active neoplastic disease. Fourteen patients had both a baseline and Cycle 3 PET CT scans and were evaluable for pharmacodynamic analyses; the remaining 5 patients did not have a Cycle 3 PET CT scan. Among these 14 evaluable patients, 4 patients had stable disease (SD), and 10 patients had increased [18F]fluorodeoxyglucose uptake consistent with progression at Cycle 3. Of note, 1 patient had a decrease in [18F]fluorodeoxyglucose update after 3 days of ficlatuzumab, which correlated with decreased p-Met, p-MAPK, Ki-67, CD31, and tumor HGF expression as assessed by immunohistochemistry staining; however, this patient had disease progression by the first tumor evaluation and was withdrawn from the study before the Cycle 4 dose.

One patient with colorectal carcinoma had dramatic decreases in nearly all pharmacodynamic markers (Fig 2A-D) and an increase in HGF (Fig 2E). This patient received 3 treatment cycles and was withdrawn from the study due to a new lesion observed by CT (negative by PET).
**Pharmacokinetic Analyses**

Pharmacokinetic parameters are listed by dose cohort in Table 3. Ficlatuzumab exposure (assessed by C\text{\text{max}} and AUC) increased in an approximately dose-proportional manner (Fig 3). No significant changes in the mean clearance and t_{1/2} across doses was observed (P=0.092 and 0.167, respectively, by analysis of variance), suggesting linear pharmacokinetics for the 2-20 mg/kg dose range. Ficlatuzumab exhibited low clearance (0.178-0.261 mL/h/kg) leading to a long terminal t_{1/2} (7.4-10 days), with significant accumulation of ficlatuzumab from Cycle 1 to Cycle 3. Mean (stdv) V_d ranged from 61 (18) to 75 (15) mL/kg, suggesting limited distribution of ficlatuzumab to the extravascular compartment (33).

**Antitumor Activity**

Eighteen patients were evaluable for efficacy (n=5, 2 mg/kg; n=7, 10 mg/kg; n=6, 20 mg/kg); no patient had an objective response. Five patients (28%) achieved SD; median duration was 2.6 months (95% confidence interval [CI]: 1.5-13.7). Four of these patients had colorectal adenocarcinoma with SD duration from 1.5 to 2.7 months, and 1 patient had pancreatic acinar cell carcinoma with SD lasting 13.7 months (this particular tumor type usually has a more indolent course than pancreatic ductal adenocarcinoma). Median TTP was 1.4 months (95% CI: 1.3-1.5). No significant relationship was found between TTP and maximum percent change from baseline for any measured pharmacodynamic marker.
DISCUSSION

In a previous ficlatuzumab phase 1 study in patients with advanced solid tumors, the recommended treatment dose was 20 mg/kg once every 2 weeks (14-day cycle) (34). In this study, the same ficlatuzumab regimen was well-tolerated without DLTs; ficlatuzumab modulated HGF/c-Met pathway pharmacodynamic markers in the tumor and serum, and had a good pharmacokinetic profile that was consistent with a previous study (34).

The overall safety profile of ficlatuzumab observed in this study, characterized by peripheral edema, hypoalbuminemia, cough, and gastrointestinal AEs, matches that observed for other antibodies targeting the HGF/c-Met pathway (ie, rilotumumab, onartuzumab, TAK701) (35-37). Edema was also among the most common AEs observed for the ALK/c-Met inhibitor crizotinib (38). Slow recovery of albumin levels after EOT is consistent with the long half-life of ficlatuzumab. In the current study, gastrointestinal AEs (eg, abdominal pain, abdominal distention, and constipation), were among the most common TEAEs, consistent with the disease state.

The pharmacokinetics of ficlatuzumab was characterized by low clearance and a long half-life (7.4-10 days), consistent with the previous phase 1 study (34) and the profile of other humanized IgG1 antibodies (38). Ficlatuzumab exhibited linear pharmacokinetics across all dose levels tested.
A maximum tolerated dose was not reached with ficlatuzumab, making the determination of the RP2D challenging; this is similar to reports of other HGF/c-Met inhibitory antibodies, including onartuzumab (37), rilotumumab (35), and TAK701 (36). The objective of this study was to determine if ficlatuzumab treatment could result in pharmacodynamic target modulation in the tumor to maximize antitumor activity at the doses tested.

Activation of the c-Met pathway, indicated by p-Met levels, tends to increase with disease progression (17-22), and tends to be higher in liver metastases than in the primary tumor site. In the current study, ficlatuzumab inhibition of p-Met and subsequent downstream signaling was investigated in patients with advanced tumors with liver metastases accessible to repeat biopsies. Patients with positive p-Met in archival tumor biopsies were also enrolled. Pre-dose baseline liver tumor biopsies for all patients had measurable p-Met. Ficlatuzumab treatment led to consistently decreased levels of p-Met only at 20 mg/kg, confirming that it can modulate HGF/c-Met pathway function in the tumor at the RP2D of 20 mg/kg. These findings support a mechanism proposed by previous in vitro and in vivo studies (23-25), in which ficlatuzumab inhibits c-Met signaling.

The observed decrease in p-Akt and p-ERK only at 20 mg/kg suggests that ficlatuzumab may decrease cellular proliferation and survival signals at RP2D. Changes in p-ERK that correlated with changes in p-Met suggested that changes
observed in p-ERK may indeed result from changes in p-Met following fclatuzumab treatment.

Treatment with 20 mg/kg fclatuzumab also resulted in mild increases in HGF levels in liver metastases (17%-33%) and more pronounced increases in serum (4.0-fold by Cycle 1, Days 3-4). While no measurable increase in tumor HGF expression levels was observed for the 2- or 10-mg/kg cohorts, the increase was observed in serum by 2.66- and 3.51-fold respectively by the same time postdose. Increased serum HGF post-fclatuzumab administration, indicating target engagement, is consistent with previous observations (26). The increase in HGF in tumor and more pronounced and consistent increase in serum is likely due to the stabilization of HGF upon complex formation with fclatuzumab and/or compensatory increase in HGF production (39).

Similarly, decreased HGF/c-Met pathway–related signaling, as indicated by reductions in p-Met and p-ERK, was more pronounced in the 20-mg/kg cohort, despite a high fclatuzumab serum trough concentration (mean $C_{\text{min}}$: 7.15, 40.7, and $128 \mu g/mL$ at 2, 10, and 20 mg/kg, respectively) in all cohorts well exceeding the $IC_{50}$ of approximately $1 \mu g/mL$ in most cellular assays (23). This discrepancy between tumor and serum pharmacodynamic marker modulations is likely due to limited antibody penetration into the tumor milieu, emphasizing the importance of establishing an effective dosing regimen using paired predose and postdose tumor biopsies rather than solely relying on exposure in the serum.
Given the small number of patients at each dose and time point, the results need to be interpreted with caution. However, collectively, at 20 mg/kg ficlatuzumab, there is decrease in median tumor p-Met, p-Erk, and p-Akt, and an increase in HGF at both time points; this pattern is consistent with the mechanism of action of an anti-HGF antibody. These changes likely indicate that ficlatuzumab 20 mg/kg induced pharmacodynamic modulation of HGF/c-Met pathway and downstream signaling.

Overall, ficlatuzumab monotherapy was well tolerated in patients with solid tumors and liver metastases. The study confirmed the validity of 20 mg/kg as the appropriate RP2D for ficlatuzumab based on pharmacodynamic target modulation in the tumor. These results support the clinical evaluation of ficlatuzumab for treating patients with advanced solid tumors. A randomized phase 1b/2 trial exploring ficlatuzumab in combination with gefitinib (27, 28) is ongoing.
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hepatocyte growth factor and interleukin-6 levels can distinguish patients with
primary or metastatic liver tumors from those with benign liver lesions.

Serum levels of hepatocyte growth factor/scatter factor in patients with liver

proto-oncogene and insulin-like growth factor binding protein 3 overexpression
correlates with metastatic ability in well-differentiated pancreatic endocrine


Table 1. Patient Demographic and Disease Characteristics at Baseline

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<td>15 (79)</td>
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<td>Caucasian race, n (%)</td>
<td>6 (100)</td>
<td>7 (100)</td>
<td>6 (100)</td>
<td>19 (100)</td>
</tr>
<tr>
<td>Mean BMI (range), kg/m²</td>
<td>26 (24-28)</td>
<td>24 (20-28)</td>
<td>26 (22-31)</td>
<td>25 (20-31)</td>
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<tr>
<td>ECOG PS, n (%)</td>
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<td>1</td>
<td>3</td>
<td>4</td>
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<td>5</td>
<td>4</td>
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<td>11 (58)</td>
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<td>Median no. prior antitumor therapies</td>
<td>4</td>
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<td>Cancer diagnosis (%)</td>
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<td>Breast</td>
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<tr>
<td>Esophageal adenocarcinoma</td>
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<td>0</td>
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<td>1 (5)</td>
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<tr>
<td>No. of target lesions, n (%)</td>
<td></td>
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</tr>
<tr>
<td>2-3</td>
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<td>5</td>
<td>13 (68)</td>
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<tr>
<td>&gt;3</td>
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<td>Target lesion location, n (%)</td>
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<tr>
<td>Liver</td>
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<td>19 (100)</td>
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<tr>
<td>Lung</td>
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<td>3</td>
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<td>8 (42)</td>
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<tr>
<td>Lymph nodes</td>
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<td>Abdomen</td>
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<td>Other</td>
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<td>No. of non-target lesions, n (%)</td>
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<td>0</td>
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<td>4</td>
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<td>&gt;3</td>
<td>0</td>
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<td>0</td>
<td>2 (11)</td>
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<tr>
<td>Non-target lesion location, n (%)</td>
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<tr>
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<td>14 (74)</td>
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<td>Lymph nodes</td>
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<td>8 (42)</td>
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<tr>
<td>Othera</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>3 (16)</td>
</tr>
</tbody>
</table>

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

aOther target lesion locations included the following: 2 mg/kg, mediastinum (aorta-lung window lymph node); 10 mg/kg, pancreas (local recurrence).
<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>2 mg/kg (n=6)</th>
<th>10 mg/kg (n=7)</th>
<th>20 mg/kg (n=6)</th>
<th>Total (n=19)</th>
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<tbody>
<tr>
<td><strong>TEAE</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Asthenia</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>6 (32)</td>
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<tr>
<td>Hepatic pain</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>6 (32)</td>
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<tr>
<td>Peripheral edema</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>6 (32)</td>
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<tr>
<td>Cough</td>
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<td>2</td>
<td>2</td>
<td>5 (26)</td>
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<td>Abdominal distension</td>
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<td>2</td>
<td>1</td>
<td>4 (21)</td>
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<td>Constipation</td>
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<td>2</td>
<td>1</td>
<td>3 (16)</td>
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<td>Decreased appetite</td>
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<td>2</td>
<td>0</td>
<td>3 (16)</td>
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<tr>
<td>Dyspnea</td>
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<td>2</td>
<td>1</td>
<td>3 (16)</td>
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<td>Increased GGT&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>0</td>
<td>0</td>
<td>3 (16)</td>
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<td><strong>Grade 3 laboratory abnormalities</strong></td>
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<tr>
<td>Hyperuricemia</td>
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<td>2</td>
<td>1</td>
<td>5 (26)</td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>4 (21)</td>
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<tr>
<td>Hypoalbuminemia&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>1</td>
<td>1</td>
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<tr>
<td>Hyperbilirubinemia&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>0</td>
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</tr>
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<td>Hyperglycemia</td>
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<td>0</td>
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<td>0</td>
<td>0</td>
<td>1 (5)</td>
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</tbody>
</table>

TEAE, treatment-emergent adverse event; GGT, gamma-glutamyl transferase; EOT, end of treatment.

<sup>a</sup>Grade 3/4 TEAEs included hypoalbuminemia and proteinuria (n=1 each) in the 2-mg/kg cohort; hypoalbuminemia and hypokalemia (n=1 each) in the 10-mg/kg cohort; and asthenia, dyspnea, and respiratory failure (n=1 each) in the 20-mg/kg cohort.

<sup>b</sup>No patient experienced a GGT laboratory abnormality of grade >2.

<sup>c</sup>Serum albumin decreased to below normal for the majority of patients by the EOT visit and trended toward recovery at the follow-up visit.

<sup>d</sup> Likely related to liver metastasis biopsy procedures.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (μg/mL)</th>
<th>t&lt;sub&gt;max&lt;/sub&gt; (h)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>AUC&lt;sub&gt;0→t&lt;/sub&gt; (mg•h/mL)</th>
<th>AUC&lt;sub&gt;0→∞&lt;/sub&gt; (mg•h/mL)</th>
<th>CL (mL/h/kg)</th>
<th>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</th>
<th>V&lt;sub&gt;d&lt;/sub&gt; (mL/kg)</th>
<th>C&lt;sub&gt;min&lt;/sub&gt; (μg/mL)</th>
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<tr>
<td>2 mg/kg</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4</td>
<td>4</td>
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<td>Mean (stdv)</td>
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<td>4.365</td>
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<td>0.2452</td>
<td>177.5</td>
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<tr>
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<td>61.3</td>
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<td>19.7</td>
<td>18.4</td>
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<td>10 mg/kg</td>
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<td>0.2610</td>
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<td>20 mg/kg</td>
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<td>4</td>
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<tr>
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<td>0.1780</td>
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<tr>
<td>%CV</td>
<td>22.7</td>
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<td>22.4</td>
<td>18.1</td>
<td>29.2</td>
<td>21.8</td>
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</table>

C<sub>max</sub>, maximum plasma concentration; t<sub>max</sub>, time to plasma concentration; AUC<sub>0→t</sub>, area under the concentration-time curve from time zero to the end of the dosing interval; AUC<sub>0→∞</sub>, area under the concentration-time curve extrapolated to infinite time; CL, clearance; t<sub>1/2</sub>, half-life; V<sub>d</sub>, volume of distribution; C<sub>min</sub>, minimum plasma concentration; stdv, standard deviation; %CV, percent coefficient of variation.

Only patients with pharmacokinetic profiles evaluable for complete noncompartmental analysis were included.

<sup>a</sup>t<sub>max</sub> is reported as median (range).
FIGURE LEGENDS

**Fig 1. Pharmacodynamic analyses.** Median percent changes from baseline for p-Met (A), p-ERK (B), p-Akt (C), and HGF (D) H-scores in the tumor samples for each cohort are depicted in box plots. Medians (horizontal lines) are shown with their first and third quartile values (boxes) and ranges (vertical lines). Change in serum HGF levels from baseline over time for each cohort (E). Percent changes from baseline for p-ERK H-scores versus percent change from baseline for p-Met H-score are plotted for each cohort (F). Data points were offset slightly for improved visibility of the error bars. Abbreviations: p-Met, phosphorylated c-Met; p-ERK, phosphorylated extracellular-signal-regulated kinase; p-Akt, phosphorylated Akt; HGF, hepatocyte growth factor.

**Fig 2. Pharmacodynamic changes in liver tumor biopsies.** Liver biopsies from a single patient predose (left-hand side panels of A-E) and 3 days after fclatuzumab 20 mg/kg (right-hand side panels of A-E) to detect levels of p-Met (A), p-MAPK (B), Ki-67 (C), CD31 (D), and tumor HGF(E). Abbreviations: p-Met, phosphorylated c-Met; p-MAPK, phosphorylated mitogen-activated protein kinase; HGF, hepatocyte growth factor.

**Fig 3. Ficlatuzumab pharmacokinetics.** Concentration-time profiles (A). Serum concentrations of fclatuzumab are plotted as a function of treatment visit for each patient. Dashed lines indicate expected dosing times for Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 3 Day 1 (0, 14, and 28 doses since the first fclatuzumab dose,
respectively). Four patients who withdrew before their Cycle 2 dose were included up to their last recorded sample point. Ficlatuzumab \( C_{\text{max}} \) (B) and \( \text{AUC}_{0\rightarrow\infty} \) (C) as a function of Cycle 1 dose. Abbreviations: \( C_{\text{max}} \), maximum plasma concentration; \( \text{AUC}_{0\rightarrow\infty} \), area under the concentration-time curve extrapolated to infinite time.
Figure 1A.
Figure 1B.
Figure 1C.
Figure 1D.
Figure 1E.

Ficlatuzumab dose

- 2 mg/kg
- 10 mg/kg
- 20 mg/kg

Fold change in HGF from baseline

Time since ficlatuzumab treatment (d)
Figure 1F.

```
p-Met versus p-ERK

n = 18
r = 0.456
P = 0.057

p-ERK H-score change from baseline (%)

Ficlatuzumab dose  • 2 mg/kg  ■ 10 mg/kg  ▲ 20 mg/kg
```
Figure 3A.

Ficlatuzumab dose

<table>
<thead>
<tr>
<th>Ficlatuzumab dose</th>
<th>Nominal time since first ficlatuzumab dose (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mg/kg</td>
<td>0 7 14 21 28 35</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>0 7 14 21 28 35</td>
</tr>
<tr>
<td>20 mg/kg</td>
<td>0 7 14 21 28 35</td>
</tr>
</tbody>
</table>

Nominal time since first ficlatuzumab dose (d)

Ficlatuzumab concentration (µg/mL)

- 1,000
- 100
- 10

Mean

Individual
Figure 3B.

$r^2 = 0.87$

Ficlatuzumab $C_{\text{max}}$ (µg/mL) vs. Ficlatuzumab dose (mg/kg)
Figure 3C. Ficlatuzumab dose (mg/kg)

\[ r^2 = 0.853 \]

Ficlatuzumab AUC\(_{0-\infty}\) (mg • h/mL)

Ficlatuzumab dose (mg/kg)
Clinical Cancer Research

A Pharmacodynamic/Pharmacokinetic Study of Ficlatuzumab in Patients With Advanced Solid Tumors and Liver Metastases

Josep Tabernero, Maria Elena Elez, Maria Herranz, et al.

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