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Phase I ficlatuzumab monotherapy or with erlotinib for refractory advanced solid tumours and multiple myeloma

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Background: Ficlatuzumab, a humanised hepatocyte growth factor (HGF) IgG1κ inhibitory monoclonal antibody, was evaluated for recommended phase II dose (RP2D), safety, pharmacokinetics (PKs), antidrug antibody (ADA), pharmacodynamics (PDs) and antitumour activity as monotherapy or combined with erlotinib.

Methods: Patients with solid tumours received ficlatuzumab 2, 5, 10 or 20 mg kg⁻¹ intravenously every 2 weeks (q2w). Additional patients were treated at the RP2D erlotinib.

Results: Forty-one patients enrolled at doses ≤20 mg kg⁻¹. Common adverse events (AEs) included peripheral oedema, fatigue and nausea. Three patients experienced grade ≥3 treatment-related hyperkalaemia/hypokalaemia, diarrhoea or fatigue. Best overall response (44%) was stable disease (SD); median duration was 5.5 months (0.4–18.7 months). One patient has been on therapy with SD for >4 years. Pharmacokinetics of ficlatuzumab showed low clearance (0.17–0.26 ml h⁻¹ kg⁻¹), a half-life of 6.8–9.4 days and dose-proportional exposure. Ficlatuzumab/erlotinib had no impact on the PK of either agent. No ADAs were detected. Ficlatuzumab increased serum HGF levels.

Conclusions: Recommended phase II dose is 20 mg kg⁻¹ q2w for ficlatuzumab monotherapy or with erlotinib. Preliminary antitumour activity and manageable AEs were observed. Pharmacokinetics were dose-proportional and consistent with other IgG therapeutics. Ficlatuzumab was not immunogenic, and serum HGF was a potential PD marker.

Hepatocyte growth factor (HGF) is the only known ligand for the c-Met receptor tyrosine kinase (Bottaro *et al*, 1991; Weidner *et al*, 1993; Zhang *et al*, 2010; Yap *et al*, 2011). Hepatocyte growth factor stimulation of c-Met results in activation of key oncogenic signalling pathways that increase cell proliferation, survival,

migration and invasion (Birchmeier *et al*, 2003). Hepatocyte growth factor-mediated autocrine and paracrine activation loops are found in a number of human cancers, including breast, lung, bladder, gastric, head and neck, and brain cancers, as well as multiple myeloma (Christensen *et al*, 2005; Gherardi *et al*, 2012).

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Further, HGF expression is a predictor of poor prognosis (Trusolino and Comoglio, 2002; Birchmeier *et al*, 2003; Betsunoh *et al*, 2007; Drebber *et al*, 2008; Sasaki *et al*, 2008; Ponzo *et al*, 2009; Pour *et al*, 2010; Gherardi *et al*, 2012).

Targeting both HGF/c-Met and epidermal growth factor receptor (EGFR) signalling pathways may be an effective antitumour strategy (Guo *et al*, 2008). In studies of breast, squamous cell carcinoma of head and neck, pancreatic, and non-small cell lung cancer (NSCLC) cancer models, tumour growth was synergistically inhibited by HGF/c-Met pathway inhibitors in combination with EGFR inhibitors (Tang *et al*, 2008; Seiwert *et al*, 2009; Zhang *et al*, 2010; Xu *et al*, 2011). c-Met amplification promotes resistance to the EGFR tyrosine kinase inhibitors erlotinib and gefitinib in NSCLC tumours with EGFR-activating mutations (Bean *et al*, 2007; Engelman *et al*, 2007). The clinical activity of combining HGF/c-Met pathway inhibitors onartuzumab with erlotinib was demonstrated in a randomised phase II NSCLC trial in patients with high c-Met levels. Therefore, evaluation of HGF/c-Met and EGFR inhibitors is warranted.

Ficlatuzumab is a potent, humanised HGF IgG1 κ inhibitory monoclonal antibody that neutralises HGF/c-Met binding, thus inhibiting HGF-induced c-Met phosphorylation, cell proliferation, cell invasion and cell migration (Birchmeier *et al*, 2003). Ficlatuzumab inhibits growth of HGF/c-Met-dependent tumours in autocrine or paracrine pre-clinical xenograft models, such as glioblastoma (GBM) (Meetze *et al*, 2009a), NSCLC (Meetze *et al*, 2009b) and pancreatic cancer (Meetze *et al*, 2009c), making it a candidate for the treatment of multiple cancer types (Patnaik *et al*, 2010; Tan *et al*, 2011). Ficlatuzumab demonstrated synergistic activity in combination with the EGFR pathway inhibitors erlotinib and cetuximab and achieved nearly complete tumour regression with cetuximab in a paracrine NSCLC xenograft model (Meetze *et al*, 2009c). Ficlatuzumab also demonstrated additive antitumour activity when combined with chemotherapy in GBM intracranial models (Meetze *et al*, 2009a).

This first-in-human phase I study of ficlatuzumab evaluated doses from 2 to 20 mg kg⁻¹ as monotherapy in patients with advanced solid tumours or multiple myeloma, and in combination with erlotinib in patients with advanced solid tumours (NCT00725634).

PATIENTS AND METHODS

Study design. This study was performed in accordance with the principles outlined in the Declaration of Helsinki. The primary study objectives were to determine the safety, tolerability, dose-limiting toxicities (DLTs) and recommended phase II dose (RP2D) of ficlatuzumab as monotherapy in patients with relapsed or refractory solid tumours, lymphoma or multiple myeloma, and in combination with erlotinib in patients with relapsed or refractory solid tumours. Secondary objectives included characterisation of the pharmacokinetic (PK) profiles of ficlatuzumab with and without erlotinib; evaluation of preliminary antitumour activity; and evaluation of the effects of ficlatuzumab on exploratory biomarkers in blood and bone marrow (BM).

Patients. All patients were aged ≥ 18 years and signed an institutional review board-approved consent form before starting the clinical trial. Eligible patients had advanced refractory solid tumour malignancies. Patients with multiple myeloma must have satisfied standard published requirements (Durie *et al*, 2006). Enrolment criteria for all cohorts are provided in Supplementary Appendix Table A1 (online only). Pertinent eligibility included written informed consent before study entry, Eastern Cooperative Oncology Group performance status of 0 or 1, and no radiotherapy within 3 weeks before the first study drug infusion. All patients were required to have adequate blood, kidney and liver laboratory

parameters. Other than patients with GBM, who could enrol in the safety expansion cohort or in the erlotinib combination cohort, patients with central nervous system disease were excluded.

Patients with grade ≥ 2 diarrhoea at baseline, inflammatory bowel disease, or acute onset of new or progressive pulmonary symptoms within 4 weeks before first study treatment were not eligible for the erlotinib combination cohort.

Escalating doses of intravenous (IV) ficlatuzumab at 2, 5, 10 or 20 mg kg⁻¹ over 60 min once per 14-day cycle were administered in 3 + 3 design (Storer, 1989). Dose-limiting toxicities were defined as any of the following drug-related toxicities occurring during the first two cycles of treatment: toxicity that resulted in dose reduction or interruption of treatment for > 2 weeks; pertinent grade 3 haematologic or nonhaematologic toxicity; grade 3 neutropaenia lasting ≥ 5 days; grade 4 thrombocytopenia associated with bleeding; and grade 4 haematologic or nonhaematologic toxicity of any duration.

Up to 12 additional patients per arm could subsequently be enrolled to receive ficlatuzumab at the RP2D in the safety expansion cohort (patients with solid tumours) or the multiple myeloma cohort ($n = 4$, methods described in Supplementary Appendix Tables A2 and A3).

Patients in the erlotinib combination cohort were administered ficlatuzumab at the RP2D plus erlotinib 150 mg day⁻¹ on day 1 of each cycle. No dose escalation was planned, but the dose of ficlatuzumab and/or erlotinib could be decreased stepwise. Dose-limiting toxicities for the combination excluded grade 3 rash lasting ≤ 48 h. A summary of cohort design and observed DLTs is provided in Supplementary Appendix Table A4.

Drug administration. The required dose of ficlatuzumab was admixed with 0.9% normal saline for a final concentration of 1.0 to 10.0 mg ml⁻¹ given by IV administration over 60 min. Pre-medication for nausea/vomiting or hypersensitivity reactions was permitted following any observed reactions after the first dose.

Safety evaluations. Patients were seen weekly during the first two cycles for a physical examination and routine laboratory tests and at the start of each subsequent cycle. Adverse events (AEs) were graded for severity according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0; Bethesda, MD, USA). Patients who received at least one treatment dose of ficlatuzumab were evaluable for safety analyses.

Efficacy evaluations. Patients had radiologic scans at baseline and every four cycles (8 weeks) for response assessments. After 1 year, scans were performed every six cycles (12 weeks). The guidelines of the Response Evaluation Criteria in Solid Tumors, version 1.0 (Brussels, Belgium) were used to assess efficacy in patients with solid tumours. For multiple myeloma patients, response was assessed according to the International Myeloma Working Group uniform response criteria (Durie *et al*, 2006). Efficacy parameters included objective response rate (complete response (CR) + partial response (PR)), duration of response, duration of stable disease (SD) and time to progression. All subjects who completed 8 weeks of treatment (i.e., four or more cycles) with a disease assessment were evaluable for response.

Pharmacokinetic evaluations. Patients who received at least one dose of ficlatuzumab or erlotinib and had at least one measurable post-dose concentration were considered evaluable for PK analyses. Samples for PK analysis of ficlatuzumab and/or erlotinib were collected pre-dose, immediately after infusion, and at 1, 3, 6, 8, 24, 48 and 72 h and 1-week post-dose in cycle 1; pre-dose, immediately after infusion, and at 2 h and 1-week post-dose in cycle 2; pre-dose and immediately after infusion in cycle 3; at 1 to 2 weeks post-dose in cycle 4; and pre-dose for each subsequent cycle through cycle 52 (details in the Supplementary Material).

Serum ficlatuzumab levels were quantified by a validated enzyme-linked immunosorbent assay (ELISA) (PPD, Richmond, VA, USA). Ficlatuzumab was captured from serum by recombinant human HGF (R&D Systems, Minneapolis, MN, USA) bound to a microtiter plate. Captured ficlatuzumab was then detected with polyclonal rabbit anti-human IgG-horseradish peroxidase (Dako Cytomation, Glostrup, Denmark). The range of detection was 2 to 150 $\mu\text{g ml}^{-1}$. Assay accuracy and precision were <20% as expressed by intraday and interday percentage error.

Plasma erlotinib levels were quantified by a validated, high-performance liquid chromatography with tandem mass spectrometry (MS-MS) assay (PPD). Plasma erlotinib was extracted with 50% acetonitrile containing internal standard (erlotinib-d6) followed by centrifugation. The supernatant was further diluted with 50% acetonitrile and analysed by liquid chromatography/MS-MS (Applied Biosystems, Grand Island, NY, USA). The range detection of the assay was between 10 and 10 000 ng ml^{-1} . Assay accuracy and precision were <15% as expressed by intraday and interday percentage error.

Pharmacokinetic parameters were calculated by noncompartmental analysis using Phoenix WinNonLin, version 6.2 (Pharsight Corporation, Mountain View, CA, USA).

Ficlatuzumab antidrug antibody (ADA) analyses. Serum samples were collected before and after ficlatuzumab dosing at screen or pre-dose cycle 1 day 1 (C1D1), pre-dose C3D1 and subsequent odd cycles, as well as at 1-month follow-up. Antidrug antibody was detected using a pair of biotinylated and SULFO-TAG labelled (Mesoscale Discovery, Rockville, MD, USA) ficlatuzumab in a bridging electrochemiluminescence (ECL) method (detail provided in Supplementary Material).

Biomarker analyses. Serum samples were collected before and after ficlatuzumab dosing ranging from 2 h to 50 days after dose (Supplementary Table A5). Serum HGF levels were measured using an ELISA detection kit (R&D Systems) as per the manufacturer's instruction and validated by PPD. Serum c-Met concentrations were determined by ECL detection using an anti-c-Met polyclonal antibody targeting the extracellular domain labelled with biotin and SULFO-TAG (Mesoscale Discovery; experiment details are provided in Supplementary Material).

Twenty-nine of the 37 solid tumour patients enrolled (monotherapy or erlotinib combination) provided archival tissues for biomarker analysis using immunohistochemistry (IHC) for HGF and c-Met. As no paired samples from pre- and post-ficlatuzumab treatment were available, HGF pathway modulation by ficlatuzumab treatment was not evaluated.

Bone marrow aspirates were collected from the four subjects with multiple myeloma before and 2 to 3 days after treatment. Bone marrow cell pellet was collected and lysed in lysis buffer. Hepatocyte growth factor was measured by ELISA (R&D Systems), whereas c-Met and p-Met were measured by multiplex ELISA using ECL detection (Mesoscale Discovery), as per the manufacturer's instruction.

Statistical methods. Data were summarised using descriptive statistics using number of patients, mean, median, s.d. and range for continuous variables and using frequency and percentages for discrete variables.

Descriptive statistics for PK parameters were calculated using R (version 2.11.1, The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients. Between September 2008 and September 2010, 41 patients were enrolled at three sites; 37 patients had a solid tumour

and four patients had multiple myeloma. Twenty-three subjects (56%) were female, and 18 (44%) were male, with a mean age of 60.7 years (range, 18–87 years). Most subjects were white (38 subjects, 93%). Twenty-four subjects received ficlatuzumab as monotherapy (2 mg kg^{-1} , $n=3$; 5 mg kg^{-1} , $n=3$; 10 mg kg^{-1} , $n=3$; 20 mg kg^{-1} , $n=15$), and 13 subjects received the ficlatuzumab/erlotinib combination. Only one of the patients on the combination therapy had received a prior EGFR inhibitor (erlotinib).

Tumour types varied widely, with the most common (defined as being diagnosed in two or more patients) being ovarian ($n=4$), GBM ($n=3$) and mesothelioma ($n=3$). Two patients with lung cancer participated (non-small cell not otherwise specified and squamous cell), both of whom were enrolled in the erlotinib combination cohort. All patients had prior surgery, radiotherapy and/or systemic treatment. Demographic and baseline disease characteristics for all solid tumour cohorts are summarised in Table 1.

Determination of the RP2D of ficlatuzumab. No DLTs occurred in any dose-escalation cohort or the safety expansion cohort. Based on the absence of DLTs, the highest administered dose, ficlatuzumab 20 mg kg^{-1} once every 2 weeks (q2w), was determined to be the RP2D. The ficlatuzumab 20 mg kg^{-1} dose-escalation cohort ($n=4$) and the safety expansion cohort ($n=11$) were combined for all subsequent analyses of ficlatuzumab at the RP2D as monotherapy.

Determination of the RP2D of ficlatuzumab plus erlotinib. One patient in the combination cohort experienced a DLT (grade 3 mucositis during cycle 2), which the investigator considered to be related to both agents and which required concurrent medication and erlotinib interruption. The combination cohort was expanded to 13 patients, and the RP2D was determined to be ficlatuzumab 20 mg kg^{-1} q2w plus erlotinib 150 mg day^{-1} continuously.

Treatment exposure. In the monotherapy RP2D cohort, the median administered dose was ficlatuzumab 20 mg kg^{-1} (range, 16–21), with a median duration of 8.1 weeks (range, 2–102). In the erlotinib combination cohort, patients received median doses of ficlatuzumab 20.0 mg kg^{-1} and erlotinib 150 mg day^{-1} ; 11 of 13 combination patients had $\geq 90\%$ relative dose intensity. The median treatment duration in the combination cohort was 4 weeks. Of the patients who withdrew from the study, the most common reasons were disease progression (monotherapy RP2D, $n=8$; erlotinib combination, $n=8$) and treatment failure (monotherapy RP2D, $n=5$; erlotinib combination, $n=3$). Patient disposition and treatment for all solid tumour cohorts are summarised in Supplementary Table A6.

Safety and tolerability. All 41 enrolled patients were included in the safety population. The most commonly occurring (five or more patients) all-grade treatment-emergent AEs (TEAEs) in the monotherapy solid tumour patients ($n=24$), regardless of relationship, were peripheral oedema ($n=12$), fatigue ($n=11$), nausea ($n=7$) and headache ($n=6$), as well as dyspnoea, vomiting and hypomagnesaemia (each $n=5$). The majority of events were grade 1 or 2. Treatment-related AEs included two patients enrolled in the 5 and 10 mg kg^{-1} monotherapy cohorts (grade 3 diarrhoea and grade 3 fatigue, which both resolved) as well as one patient in the 20 mg kg^{-1} RP2D cohort with grade 4 episodes of hypokalaemia followed by a subsequent serious AE of hyperkalaemia. The most frequent TEAEs are summarised by cohort in Table 2.

Nine of 24 patients receiving ficlatuzumab monotherapy required treatment interruption because of an AE. Two of the nine patients had grade 3 events (pneumonia and anaemia) that were reported as serious but unlikely related to study treatment. No patient required dose reduction (Supplementary Table A7).

The most commonly occurring (four or more patients) all grade TEAEs in the erlotinib combination cohort ($n=13$) were maculopapular rash ($n=8$), diarrhoea ($n=6$), and dermatitis

Table 1. Patient demographic and baseline disease characteristics

Characteristic	Monotherapy cohorts				
	2 mg kg ⁻¹ (n = 3)	5 mg kg ⁻¹ (n = 3)	10 mg kg ⁻¹ (n = 3)	RP2D 20 mg kg ^{-1a} (n = 15)	Erlotinib combination cohort (n = 13)
Sex, n female/male	2/1	1/2	1/2	10/5	7/6
Median age (range), years	64 (44–84)	80 (58–84)	71 (54–72)	62 (19–87)	61 (18–78)
Race, n					
White	3	1	3	14	13
Other	0	2	0	1	0
ECOG performance status, n					
0	0	0	0	4	6
1	3	3	3	11	7
Prior treatment					
Surgery, radiotherapy, systemic therapy	3	3	3	15	13
Disease stage, n					
II	0	0	0	1	0
III	0	0	0	0	2
IV	3	3	3	14	11

Abbreviations: ECOG = Eastern Cooperative Oncology Group; RP2D = recommended phase II dose.
^aThe monotherapy RP2D cohort includes the 20 mg kg⁻¹ dose-escalation cohort and the safety expansion cohort.

Table 2. TEAEs occurring in ≥20% of patients in the monotherapy RP2D or the erlotinib combination cohort

TEAE, all grades/grade ≥3, n	Monotherapy					Erlotinib combination cohort (n = 13)
	2 mg kg ⁻¹ (n = 3)	5 mg kg ⁻¹ (n = 3)	10 mg kg ⁻¹ (n = 3)	RP2D 20 mg kg ^{-1a} (n = 15)	All monotherapy (n = 24)	
Fatigue	1/0	2/0	3/1	5/0	11/1	4/0
Peripheral oedema	1/0	2/0	1/1	8/1	12/2	1/0
Nausea	0/0	2/0	1/0	4/0	7/0	3/0
Diarrhoea	1/0	1/1	0/0	1/0	3/1	6/0
Hypokalaemia	1/0	0/0	0/0	4/4	4/4	4/0
Rash, maculopapular	0/0	0/0	0/0	0/0	0/0	8/0
Vomiting	0/0	0/0	0/0	5/1	5/1	3/0
Hypomagnesaemia	1/0	0/0	1/0	3/0	5/0	2/0
Headache	0/0	1/0	2/0	3/0	6/0	1/0
Dyspnoea	0/0	1/0	1/0	3/1	5/1	1/0
Pruritus	0/0	1/0	1/0	0/0	2/0	3/0
Urinary tract infection	0/0	0/0	1/0	3/0	4/0	1/1
Dermatitis acneiform	0/0	0/0	0/0	0/0	0/0	4/0
Dysphonia	0/0	0/0	0/0	3/0	3/0	0/0

Abbreviations: RP2D = recommended phase II dose; TEAE = treatment-emergent adverse event.
^aThe monotherapy RP2D cohort includes the 20 mg kg⁻¹ dose-escalation cohort and the safety expansion cohort.

acneiform, fatigue and hypokalaemia (each $n = 4$). With the exception of a patient who withdrew from treatment because of a grade 3 urinary tract infection resulting in hospitalisation that was unlikely related to treatment, the most frequent events were grade 1 or 2. One patient in this cohort experienced grade 3 mucosal

inflammation that was determined to be related to both agents and required temporary interruption of erlotinib; this patient also had recurrent grade 2 mucosal inflammation that required erlotinib dose reduction. No other treatment modifications were required in the combination cohort (Supplementary Table A3).

Six monotherapy patients died during the study or within 30 days after the last dose (one in the 2 mg kg⁻¹ cohort, two in the 10 mg kg⁻¹ cohort and three in the safety expansion cohort). Each of these deaths was considered a result of disease progression, with

the exception of one patient in the safety expansion cohort whose death was reported to be unlikely related to study drug and related to a grade 4 comminuted intertrochanteric fracture resulting in hospitalisation, treatment discontinuation and death. In the

Table 3. Best overall response (efficacy evaluable population)

Response, n ^a	Monotherapy				All monotherapy (n = 24)	Erlotinib combination cohort (n = 8)
	2 mg kg ⁻¹ (n = 3)	5 mg kg ⁻¹ (n = 3)	10 mg kg ⁻¹ (n = 3)	RP2D 20 mg kg ⁻¹ ^b (n = 13)		
Objective response ^c	0	0	0	0	0	0
Stable disease	1	3	1	7	12	2
Progressive disease	1	0	2	6	9	6

Abbreviation: RP2D = recommended phase II dose.

^aEight patients (three monotherapy/five erlotinib combination) were withdrawn from the study before completion of cycle 4 for reasons other than progressive disease and were not evaluable for response assessment.

^bThe monotherapy RP2D cohort includes the 20 mg kg⁻¹ dose-escalation cohort and the safety expansion cohort.

^cPartial or complete responses were to be confirmed by repeat assessments performed ≥4 weeks after the criteria for response were first met.

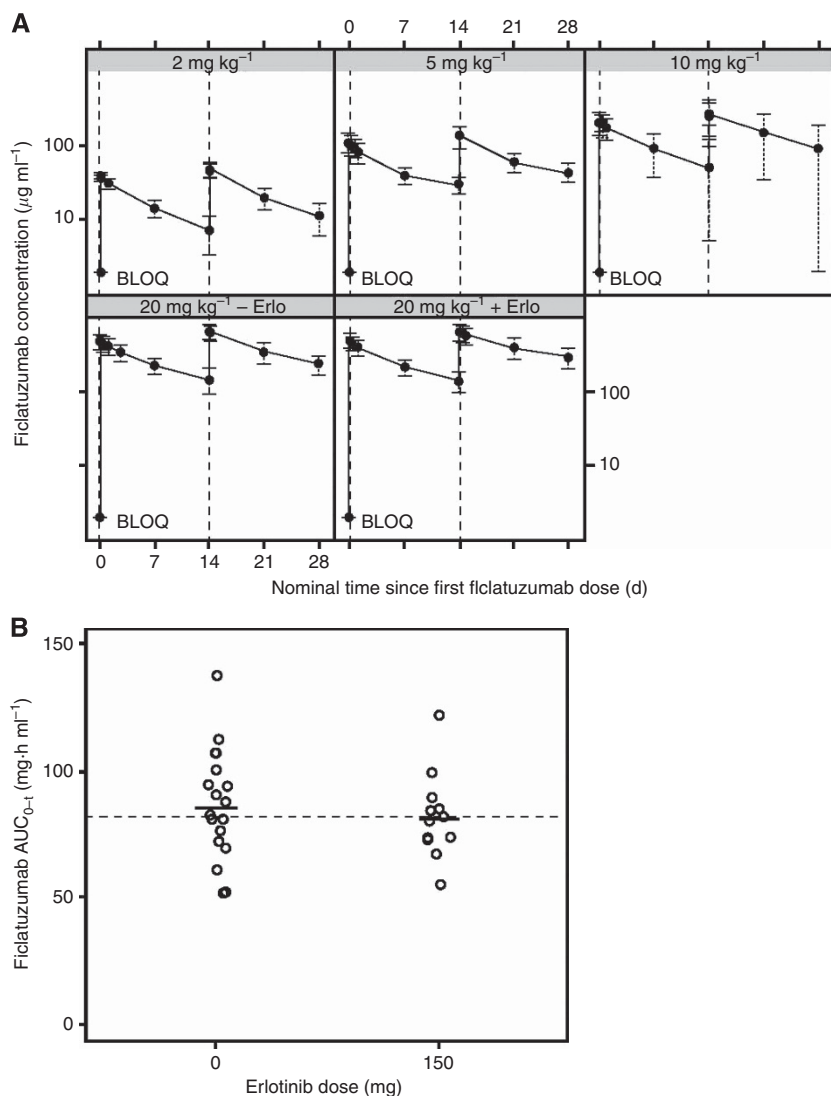


Figure 1. Ficlatuzumab exposure as a function of cycle 1 dose. (A) Ficlatuzumab concentration-time profiles by dose for cycle 1. (B) Comparison of ficlatuzumab AUC_{0→τ} in patients administered ficlatuzumab alone vs ficlatuzumab with concurrent erlotinib treatment in cycle 1. Abbreviations: AUC_{0→τ} = area under the concentration-time curve from time zero to immediately before the next dose; Erlo = erlotinib.

combination cohort, a rhabdomyosarcoma patient discontinued treatment and died because of respiratory distress secondary to disease progression.

Three patients discontinued the study because of an AE unlikely related to study drug; these were the two patients who died following the events of comminuted intertrochanteric fracture and respiratory distress described above and the patient in the combination cohort who discontinued owing to a urinary tract infection.

Antitumour activity. Best overall response (ficlatuzumab monotherapy or combination therapy) was SD (four cycles or 8 weeks) observed in 44% of evaluable patients. Among the evaluable ficlatuzumab monotherapy patients, 12 of 21 (57%) had SD, including 7 of 13 (54%) evaluable patients in the RP2D cohort. The disease control rate (DCR; CR + PR + SD \geq 8 weeks) for the RP2D cohort was 54% (95% confidence interval (CI): 25–81%). Best overall response by cohort is presented in Table 3. Stable disease of at least 16 weeks duration was observed in 14.7% (5 out of 34) of patients receiving either ficlatuzumab monotherapy or combination therapy.

Two monotherapy patients experienced prolonged SD (> 12 months). One patient with a papillary thyroid tumour in the ficlatuzumab 5 mg kg⁻¹ dose cohort had previous therapy of radioactive iodine and, before the study, had four cycles of doxorubicin/cisplatin before progressive disease occurred in the neck lymph nodes. On ficlatuzumab, this patient achieved SD for 54 weeks. A second patient with mixed mesodermal (Müllerian) tumour of the ovary who was enrolled in the 20 mg kg⁻¹ cohort (actual dose 16.5 mg kg⁻¹) had been treated with three prior lines of conventional therapy but still continued to demonstrate progression. This patient received an antineuropilin inhibitor for 3 months with clearly documented progression within the abdomen. On ficlatuzumab, this patient had had long-term SD and was still receiving treatment at the time of manuscript submission with maintenance of SD after > 5 years. This patient also has the highest tumour HGF levels among those who provided tissue for analysis (Supplementary Figure A1) and moderate levels of serum HGF (2.3 ng ml⁻¹) at C1D1 pre-dosing. The median time to progression for evaluable patients receiving ficlatuzumab

monotherapy in the RP2D cohort was 3.5 months (95% CI: 1.6 to > 36 months).

The best overall response observed in the combination cohort was also SD, with two of eight evaluable patients achieving SD (DCR 25%; 95% CI: 3.2–65.1%), each for 3.5 months. Median time to progression for this cohort was 1.3 months (95% CI: 0.9–3.5 months).

Pharmacokinetics. The PK of ficlatuzumab is characterized by low clearance (CL), long terminal half-life and volume of distribution (V_d) that approximates the plasma volume. The CL, half-life and V_d were 166 ml h⁻¹ kg⁻¹, 9.4 days and 49 ml kg⁻¹, respectively, in the monotherapy RP2D cohort, and these results were similar in comparison with the other dose groups. Examination of individual patient concentration-time profiles across treatment cohorts suggested two-compartment PK. The maximum serum concentration and area under the serum concentration-time curve increased proportionally with dose within the range studied (Figure 1A). There was clear evidence of drug accumulation from cycle 1 to cycle 2, but accumulation to steady-state levels could not be demonstrated on the basis of only two treatment cycles. There was no evidence of any impact of concurrent erlotinib treatment on the PK of ficlatuzumab; the serum profiles and exposure parameters obtained for ficlatuzumab monotherapy and in combination with erlotinib were virtually indistinguishable from one another (Figure 1A and B and Table 4). The PK of erlotinib was broadly comparable with reported values in the literature (Lu *et al*, 2005).

ADA analyses. Among the 41 subjects enrolled in the study, 29 had at least one post-dose sample tested for ADA. All samples tested were negative for ADA. The median follow-up for ADA was 68 days, ranging from 27 to 607 days. Ficlatuzumab did not appear to be immunogenic at the doses tested.

Biomarker analyses. Serum HGF and c-Met were evaluated at various time points before and after ficlatuzumab administration. Bone marrow was also collected before and after ficlatuzumab administration for the multiple myeloma cohort to measure HGF, c-Met and p-Met levels in the BM and to determine if ficlatuzumab can modulate p-Met in these patients.

Table 4. Summary of ficlatuzumab pharmacokinetic parameters for subjects by treatment group in cycles 1 and 2

Pharmacokinetic parameter ^a	Ficlatuzumab dose									
	2 mg	N	5 mg	N	10 mg	N	20 mg (monotherapy)	N	20 mg (+ erlotinib)	N
Cycle 1										
C_{max} (μ g ml ⁻¹)	40.63 (1.55)	3	111.3 (31.60)	3	214.0 (62.75)	3	488.3 (112.3)	18	512.8 (95.20)	12
T_{max} (h)	1.997 (1.709)	3	1.407 (0.5405)	3	4.717 (4.071)	3	2.714 (2.736)	18	4.888 (6.822)	12
$AUC_{0-\tau}$ (mg·h ml ⁻¹)	6.568 (1.776)	3	18.58 (7.585)	3	37.28 (16.45)	3	85.96 (21.82)	18	81.44 (16.92)	12
CL (ml h ⁻¹ kg ⁻¹)	0.2593 (0.09535)	3	0.2017 (0.07111)	3	0.2363 (0.1151)	3	0.1661 (0.06415)	18	0.1815 (0.04376)	11
$t_{1/2}$ (h)	164.0 (35.34)	3	202.3 (10.79)	3	193.0 (73.08)	3	225.0 (74.02)	18	206.6 (59.86)	11
V_d (ml kg ⁻¹)	58.27 (6.786)	3	59.00 (22.13)	3	57.80 (15.92)	3	49.39 (10.98)	18	51.52 (9.020)	11
Cycle 2										
C_{max} (μ g ml ⁻¹)	49.10 (9.777)	3	136.7 (44.82)	3	267.0 (137.4)	3	643.0 (138.6)	18	694.7 (120.3)	11
T_{max} (h)	1.520 (0.7472)	3	2.367 (1.097)	3	1.377 (0.2359)	3	1.848 (1.038)	18	4.029 (2.631)	11
$t_{1/2}$ (h)	160.9 (42.89)	3	220.8 (NC)	2	249.9 (NC)	1	255.4 (66.94)	11	225.8 (57.52)	10

Abbreviations: $AUC_{0-\tau}$ = area under the serum concentration-time curve from time zero to immediately before the next dose; CL = clearance; C_{max} = maximum (peak) observed serum concentration; NC = not calculable; $t_{1/2}$ = terminal elimination half-life; T_{max} = time to reach C_{max} following drug administration; V_d = volume of distribution.

^aMeasures of pharmacokinetic parameters are mean and s.d.

Patients from the trial had higher pre-dose HGF levels at C1D1 than those measured in the serum of 36 healthy donors (samples purchased from Bioreclamation, Westbury, NY, USA) by Student's *t*-test (Figure 2A). This is consistent with the observation that serum HGF was elevated in many cancers (Christensen *et al*, 2005). The presence of ficlatuzumab does not interfere with HGF detection in the method used; therefore, the sum of free and ficlatuzumab-complexed HGF was measured. The pre-dose HGF level at C1D1 was used as baseline to derive fold increase in total HGF levels for each time point for each subject. The HGF fold increase over baseline was plotted as a function of time (Figure 2B). An increase in HGF levels compared with baseline was observed in all subjects tested, suggesting ficlatuzumab administration can increase total HGF levels, likely by stabilising HGF upon forming an HGF-ficlatuzumab complex and/or induction of HGF production. There was a statistically significant increase in serum total HGF at all post-dose time points, starting on C1D2 (or C1D3-4 for four multiple myeloma patients), with average fold increases of 2.0, 5.5, 8.0, 6.8, 6.2 and 12.3 at C1D2, C1D8, C2D1PRE, C2D1HR2, C2D8 and C4D8-14, respectively.

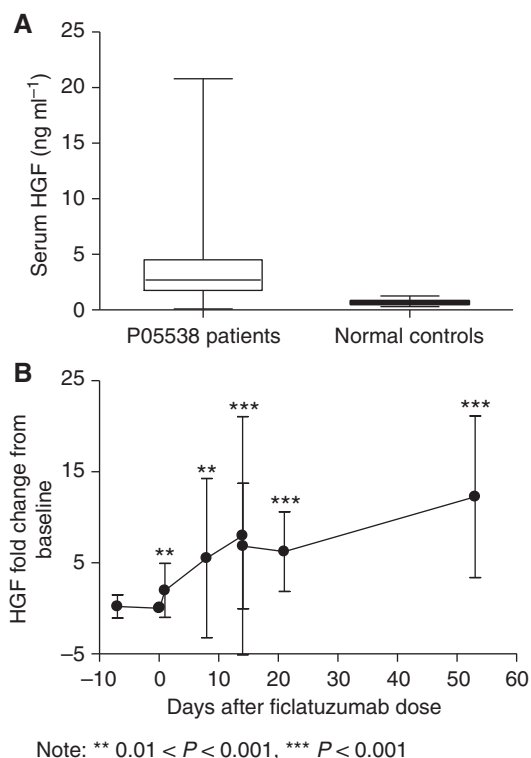


Figure 2. Serum HGF levels. Serum HGF levels were measured using validated ELISA assay (R&D Systems). **(A)** Higher HGF levels were observed in trial cancer patients than in normal controls. Pre-dosing HGF levels for P05538 patients were derived from the average of levels at screening and C1D1 pre-dosing. Hepatocyte growth factor levels from normal controls (41 cases) were measured using the same method. Median, quartile, maximum, minimum were indicated in the box plot. On average, cancer patients in P05538 have 5.8-fold higher HGF than normal control (3.93 vs 0.68 ng ml⁻¹), and the difference is statistically significant based on Student's *t*-test ($P < 0.001$). **(B)** Serum HGF levels increases after ficlatuzumab treatment. Hepatocyte growth factor fold change from baseline was derived from for each time point as follows: (HGF–HGF at C1D1-pre)/HGF at C1D1-pre. Average fold change at each time point from all cohorts were plotted as a function of time relative to the start of ficlatuzumab treatment. Abbreviations: C1D1 = cycle 1 day 1; HGF = hepatocyte growth factor.

Soluble *c*-Met (*s*-Met), most likely from extracellular domain shed from cell surface, was observed at high levels in all patients, with a median level of 92.4 ng ml⁻¹ (ranging from 40.0 to 202.1 ng ml⁻¹) at baseline during screening. There was a modest (13.5%) but significant ($P < 0.004$, by Student's *t*-test) increase in *s*-Met levels only after 50 days of ficlatuzumab exposure compared with baseline screening, but there was no increase observed in ficlatuzumab and erlotinib combination therapy cohort during the observation period.

Detectable HGF was observed in BM cell lysates of all four multiple myeloma patients at baseline. Ficlatuzumab treatment increased BM HGF in three of the four multiple myeloma patients. This is consistent with the increased serum HGF with ficlatuzumab treatment as previously described. There were detectable *c*-Met and *p*-Met levels in two of the four subjects at baseline. One patient experienced decreased *c*-Met (497–160 units, 68% decrease) and *p*-Met (200–153 units, 23% decrease) after ficlatuzumab treatment. It is not clear if this resulted from ficlatuzumab treatment or other factors, such as sample heterogeneity.

DISCUSSION

Targeting the HGF/*c*-Met axis as an antitumour strategy is currently being pursued through multiple approaches, including HGF-neutralising monoclonal antibodies, such as ficlatuzumab and rilotumumab, recombinant protein competitive inhibitor of HGF, antibodies to *c*-Met, such as ornatumumab and *c*-Met small molecule inhibitors, such as crizotinib (Zhang *et al*, 2004; Imai and Takaoka, 2006; Comoglio *et al*, 2008; Knudsen and Vande Woude, 2008; Eder *et al*, 2009).

In this study, ficlatuzumab monotherapy was well tolerated in patients with solid tumours at 2, 5 or 10 mg kg⁻¹ or at the maximum administered dose of 20 mg kg⁻¹. No DLTs were reported, establishing the RP2D dose for ficlatuzumab as 20 mg kg⁻¹ IV once q2w. The most commonly observed toxicities were peripheral oedema, fatigue and nausea. Peripheral oedema, mostly grades 1–2, was also observed in trials with other HGF/*c*-Met targeting antibodies, such as rilotumumab and onartuzumab (Gordon *et al*, 2010; Spigel *et al*, 2011, 2012).

Pre-clinical studies (Zhang *et al*, 2010) and a clinical trial (Schiller *et al*, 2010; Mok *et al*, 2011) have demonstrated that targeting *c*-Met in combination with EGFR may result in antitumour activity. In the study reported here, ficlatuzumab at the RP2D in combination with the erlotinib dose of 150 mg day⁻¹ was found to be well tolerated in patients with advanced solid tumours, with only 1 of 13 patients in the combination cohort experiencing a DLT (grade 3 mucositis).

In addition, SD (≥ 8 weeks) was observed in 44% of evaluable patients (receiving ficlatuzumab monotherapy or combination therapy), including two patients who experienced prolonged disease control > 12 months. The ongoing patient with SD > 5 years has also demonstrated the highest tumour HGF.

The PK profile of ficlatuzumab was characterised by low CL and long half-life, consistent with that of other monoclonal antibodies. Accumulation was observed with subsequent treatment cycles, and exposure increased in a dose-proportional manner. The long half-life of approximately 9.4 to 10.6 days at the R2PD supports an every-2-week dosing schedule, with trough levels above the half maximal inhibitory concentration in pre-clinical models. The administration of erlotinib in combination with ficlatuzumab had no detectable impact on the PK of either agent. Ficlatuzumab was not immunogenic. Pre-treatment serum HGF levels were significantly higher in study patients than in healthy volunteers (Figure 2), consistent with observations of elevated HGF in many types of cancers (Christensen *et al*, 2005). Increased serum HGF levels compared with baseline were observed in all patients dosed

with ficlatuzumab, and the elevation was apparent as early as 1 day after dose and persisted through the observation period of approximately 50 days. Although increases were detectable following the lowest ficlatuzumab administered dose, the sample number was not large enough to determine a dose response. The increase was likely due to the stabilisation of HGF upon complex formation with ficlatuzumab and was not affected in the presence of erlotinib. In contrast, s-Met increase was not consistent, and a mild increase over baseline was only observed with prolonged exposure at approximately day 50. Although c-Met expression by IHC and/or fluorescence *in situ* hybridisation analysis was performed on archived formalin-fixed paraffin-embedded specimens, the data were not validated and therefore not reliable to present here. The increase in total HGF after ficlatuzumab administration indicates target engagement. Serum HGF increases after ficlatuzumab administration makes HGF the most robust and convenient pharmacodynamic marker for ficlatuzumab treatment. Despite the increase in total HGF, the level of ficlatuzumab ($\mu\text{g ml}^{-1}$) in the serum is still higher than the serum HGF level (ng ml^{-1}); therefore, most of the HGF is likely to be in the form of HGF-ficlatuzumab complex. These observations are consistent with those observed for other anti-HGF antibodies, such as rilotumumab (Gordon *et al*, 2010) and TAK701 (Jones *et al*, 2010), suggesting that increased HGF levels after anti-HGF antibody treatment is likely a class effect.

Specific antibodies for HGF and c-Met have demonstrated promising clinical activity in randomised phase II trials in c-Met biomarker selected patients (Spigel *et al*, 2011; Oliner *et al*, 2012) and are currently being evaluated in phase III trials in NSCLC and metastatic gastric or oesophagogastric junction cancer. Ficlatuzumab is a potent HGF antibody with demonstrated antitumour activity in pre-clinical models and preliminary clinical activity.

The findings from this study have supported the continued clinical development of ficlatuzumab, a member of a new class of anticancer agents. A randomised phase II study in first-line NSCLC patients treated with gefitinib with or without ficlatuzumab is ongoing (Mok *et al*, 2012). The phase II dose for that study was based on this study presented here, as well as on pre-clinical data obtained for ficlatuzumab.

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CONFLICT OF INTEREST

Other than research support paid to the institutions, the authors declare the following conflicts: GJW is on the speaker's bureau for Genentech, Pfizer, Celgene and Eli Lilly, and has received honoraria from Quintiles and Medscape; CCH has been on the speaker's bureau and advisory boards for Celgene, and AT has consulting and/or advisory agreements with Astellas. Employment conflicts are reported by the following authors: JJ and FCP are current employees of AVEO and, at the time the research was being performed, MH and MMC were employees of AVEO and RI was an employee of Schering Plough. In addition, MMC is a stock holder for AVEO. The remaining authors declare no conflict of interest.

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