Safety, Pharmacokinetics, and Pharmacodynamics of the Insulin-Like Growth Factor Type 1 Receptor Inhibitor Figitumumab (CP-751,871) in Combination with Paclitaxel and Carboplatin

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Introduction: This phase 1 study was conducted to determine the recommended phase 2 dose of the selective insulin-like growth factor type 1 receptor (IGF-IR) inhibitor figitumumab (F, CP-751,871) given in combination with paclitaxel and carboplatin in patients with advanced solid tumors.

Methods: Patients received paclitaxel 200 mg/m^2, carboplatin (area under the curve of 6), and F (0.05–20 mg/kg) q3 weeks for up to six cycles. Patients with objective response or stable disease were eligible to receive additional cycles of single agent F until disease progression. Safety, efficacy, pharmacokinetic, and pharmacodynamic endpoints were investigated.

Results: Forty-two patients, including 35 with stages IIIB and IV non-small cell lung cancer (NSCLC), were enrolled in eight dose escalation cohorts. A maximum tolerated dose was not identified. Severe adverse events possibly related to F included fatigue, diarrhea, hyperglycemia, gamma glutamyl transpeptidase elevation, and thrombocytopenia (one case each). F plasma exposure parameters increased with dose. Fifteen objective responses (RECIST) were reported, including two complete responses in NSCLC and ovarian carcinoma. Notably, levels of bioactive IGF-1 seemed to influence response to treatment with objective responses in patients with a high baseline-free IGF-1 to IGF binding protein-3 ratio seen only in the 10 and 20 mg/kg dosing cohorts.

Conclusions: F was well tolerated in combination with paclitaxel and carboplatin. Based on its favorable safety, pharmacokinetic, and pharmacodynamic properties, the maximal feasible dose of 20 mg/kg has been selected for further investigation.

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The insulin-like growth factor (IGF) system comprised the IGF ligands (IGF-1 and IGF-2), the IGF binding proteins (IGFBPs 1–6) that regulate their bioactivity, and the cell surface receptors IGF-1R and IGF-2R.[1] Signaling through the IGF-1R plays important roles in normal growth and development and in cancer progression.[1] In NSCLC, the IGF-1R has been shown to be frequently expressed in tumor tissue and to mediate the proliferation of lung cancer cell lines.[2] Also, high IGF-1 and low IGFBP-3 levels have been associated with a higher incidence and severity of the disease.[3] These data suggest that targeting the IGF-1R could be a viable approach in the treatment of NSCLC.

Figitumumab (F) is a selective inhibitor of the IGF-1R, which has been well tolerated in initial studies. F increases the tumor growth inhibition activity of chemotherapy and targeted agents in preclinical models.[4] This phase 1b study was conducted to define the recommended phase 2 dose (RP2D) of F when given in combination with standard doses of paclitaxel and carboplatin in patients with advanced solid tumors.

PATIENTS AND METHODS

Patient Selection

Patients with advanced tumors in whom the combination of paclitaxel and carboplatin was a reasonable treatment option were candidates for this study. Additional eligibility criteria included: age ≥18 years; Eastern Cooperative Oncology Group performance status ≤1; recovery from any prior treatment toxicity to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (CTCAE 3.0) grade ≤1; adequate hematopoietic (ANC ≥1500/μL, platelets ≥100,000/μL), hepatic (total bilirubin ≤1.5 normal, aspartate aminotransferase and alanine aminotransferase <5 times normal), and renal (serum creatinine ≤1.5 times normal or calculated creatinine clearance ≥60 mL/min) function; serum albumin ≥2.7 g/dl; 12-lead electrocardiogram with normal tracing, or nonclinically significant changes that would not require medical intervention. Enrollment exclusions included evidence of moderate or severe mitral valve regurgitation on transthoracic Doppler echocardiogram; females of childbearing potential who refused adequate methods of contraception; active gastrointestinal abnormalities; symptomatic brain metastasis (patients with brain metastases were enrolled if stable); coexisting uncontrolled medical condition; neuropathy >grade 1; known hypersensitivity to Cremophor; and major surgical procedure or radiation therapy within 4 weeks or 1 week, respectively, before study drug administration. The protocol was conducted in accordance with Good Clinical Practice guidelines. All patients provided written informed consent.

Study Design and Treatment Plan

The primary objective of the study was to determine the RP2D of F in combination with standard doses of paclitaxel and carboplatin. Toxicities were assessed using the National Cancer Institute CTCAE 3.0. Dose-limiting toxicities (DLTs) included grade ≥4 treatment-related neutropenia (ANC <500 cells/mm^3) lasting >7 days, complicated by fever and/or requiring hospitalization; grade 4 thrombocytopenia (platelets <25,000 cells/ mm^3); ≥grade 3 gastrointestinal toxicity despite optimal intervention and/or prophylaxis; any other F-related ≥grade 3 nonhematological toxicity; and any structural and/or functional changes in transthoracic Doppler echocardiography parameters. Patients received paclitaxel 200 mg/m^2 intravenously (IV) more than 3 hours and carboplatin at an area under the curve (AUC) of 6, IV more than 15 to 60 minutes every 3 weeks. In the original protocol, F was administered IV after chemotherapy administration at doses of 0.05 to 10 mg/kg according a dose-doubling dose escalation schema.[5] Based on the favorable safety profile of F in three ongoing dose escalation trials,[6,7] this study protocol was amended to omit the 0.2 and 0.4 mg/kg F dose escalation cohorts, and only two patients were enrolled at the 0.1 mg/kg dosing cohort. Furthermore, based on the favorable safety and tolerability profile observed at the 10 mg/kg cohort, an additional cohort investigating the F dose of 20 mg/kg was introduced by protocol amendment. A dose of 30 mg/kg given every 3 weeks as a single agent was investigated in another study, not yet reported, and found to be not well tolerated. Consequently, doses higher than 20 mg/kg were not considered for testing in this study. Patients were eligible to receive up to six cycles of chemotherapy combined with F unless disease progression or unacceptable toxicity developed. On completion or early discontinuation of chemotherapy, patients were eligible to receive additional cycles of single agent F at a dose found to be well tolerated in two phase I dose escalation studies of single agent F conducted in parallel to this trial.[6,7] To open a new dosing cohort, one patient in the previous cohort had to complete at least 3 weeks, and two additional patients at least 2 weeks, of safety follow-up without identification of DLTs. The 10 and 20 mg/kg cohorts were empirically extended to 17 and 7 patients, respectively, to obtain further safety and pharmacodynamic information.

Safety Parameters

Before enrollment, at each treatment visit and either at the completion of the study or premature discontinuation, patients underwent safety laboratory testing (blood chemistry, hematology, and urinalysis) and were queried for adverse events and concomitant medication use. Doppler echocardiograms were recorded at baseline, end of cycles 1 and 6, or at premature discontinuation. Plasma samples for detection of antidrug antibodies were collected at baseline, end of cycles 1 and 6, and 150 days from the last F infusion.

TABLE 1. Demographics Characteristics

Treated patients (*N*)	42
Gender	
Male	24
Female	18
Age (yr)	
Median (range)	60.5 (26–80)
>65 (%)	37
ECOG PS	
0	12
1	30
Race	
White	38
Black	1
Asian	3
NSCLC histology	38
Stage	
IIA	1
IIIA	2
IIIB	6
IV	29
Adenocarcinoma	25
Squamous cell	6
Large cell/NOS	7
Other histologies[a]	5

[a] Histologies other than NSCLC includeovarian carcinoma stage IIIC (n = 1); colorectal carcinoma stage IV (1); hormone refractory prostate cancer (1); and hepatocellular carcinoma (1).

ECOG PS, Eastern Cooperative Oncology Group performance status; NOS, not otherwise specified.

Pharmacokinetics

All patients had pharmacokinetic (PK) blood samples taken 30 minutes before each infusion,1 hour after the end of infusion during cycles 1 to 4, and 1, 3, and 7 days after the end of infusion at cycles 1 and 4. Additionally, PK samples were collected 30 minutes before infusion in cycles 5 and 6, at the end of study, and at 150 days after the last F dose. Plasma concentrations of F were analyzed as described previously.[7]

Pharmacodynamics

Biomarkers investigated included the enumeration of circulating tumor cells (CTCs), CTCs expressing the IGF-1R and circulating endothelial cells (CECs).[8] Additional biomarkers included the measurement of plasma levels of the circulating cleaved soluble IGF-1R extracellular domain (sIGF-1R), free (bioactive) IGF-1 (fIGF-1), and IGF binding protein 3 (IGFBP-3) using enzyme linked immune assays (DSL, Webster, TX). Blood samples for the determination of CTCs and serum markers were collected before dosing at each treatment cycle. Additional samples were collected on day 8 and at the end of the study.

Clinical Responses

Tumor assessments were conducted at baseline and repeated every 6 weeks until disease progression. Disease status was assessed by investigator according to RECIST.

RESULTS

Patient Characteristics

A total of 43 patients were enrolled between February 2005 and December 2007. One patient discontinued protocol before receiving treatment. The rest of the patients received F alone or in combination with paclitaxel and carboplatin for a median of five cycles. Demographic characteristics, performance status, disease stage, and tumor histologies are described in Table 1. Table 2 summarizes the treatments administered. No apparent dose-effect of F on the cumulative dose of chemotherapy was observed. Two study discontinu-

TABLE 2. Dosing Summary

Dose Cohort (mg/kg)	No. of Patients	Figitumumab Cycles/ Patient (Median)	Figitumumab Cycles/ Patient (Range)	Cumulative Dose (mg), Median	Cumulative Dose (mg), Range
0.05[a]	3	10	2 to 68+	1175	7–37,644
0.1[b]	2	5	4–7	259	30–489
0.8[c]	4	3	2–9	277	54–95
1.5	3	1	1–4	142	129–416
3[d]	3	7	2–9	2490	288–3118
6[c]	3	3	1–10	1754	362–11,115
10	17	6	1–12	3188	470–8018
20	7	4	1–15	7436	1300–16,438
		Paclitaxel Cycles/Patient (Median)	**Paclitaxel Cycles/Patient (Range)**		
0.05	3	6	2–6	—	—
0.1	2	5	4–6	1785	1400–2170
0.8	4	3	2–6	1418	397–2132
1.5	3	1	1–4	406	366–1460
3	3	3	2–6	1124	536–1988
6	3	3	1–6	1234	342–1240
10	17	5	1–6	1510	300–2632
20	7	4	1–6	1322	348–2088
		Carboplatin Cycles/ Patient (Median)	**Carboplatin Cycles/ Patient (Range)**		
0.05	3	6	2–6	5232	1,680–6025
0.1	2	5	4–6	3197	2985–3410
0.8	4	3	1–6	1972	642–3600
1.5	3	1	1–4	750	603–3000
3	3	3	2–6	1634	715–3289
6	3	3	1–5	2310	869–4475
10	17	5	1–6	2591	540–5946
20	7	4	1–6	2303	660–4456

[a] One patient received maintenancetherapy with F single agent at 3 mg/kg (eight cycles) and 10 mg/kg (54 cycles).
[b] One patient received maintenancetherapy with F at 6 mg/kg.
[c] One patient received maintenancetherapy with f at 10 mg/kg.
[d] Two patients received maintenancetherapy with F at 10 mg/kg.

ations due to combined treatment were reported and are described later. Paclitaxel was dose reduced in seven patients, six at the 10 mg/kg cohort ($n = 17$), and one at the 20 mg/kg cohort ($n = 7$). Carboplatin was dose reduced in three patients, two at the 10, and one at the 3 mg/kg ($n = 3$) dosing cohorts. Dose reductions were attributed to neutropenia, weight loss, and creatinine increase. Seventeen patients received single agent F on discontinuation of chemotherapy. Median and range of F single agent therapy were three and 1–62 cycles, respectively. One patient has received a total of 68 cycles, approximately 4 years, of F treatment (Table 2).

Safety Profile

One patient died of disease progression while receiving study treatment with chemotherapy and 20 mg/kg of F. Table 3 summarizes all adverse events with a frequency higher than 5% and any ≥CTCAE grade 3 event reported by investigator as possibly related to F. Seventy-one adverse events possibly related to F were reported in 28 study subjects. Five of these events were grade 3 and included fatigue, diarrhea, hyperglycemia, gamma glutamyl transpeptidase (GGT) elevation, and thrombocytopenia (one case each). All of them were reported in patients enrolled in the 10 mg/kg dosing cohort. The grade 3 events of GGT elevation and thrombocytopenia were attributed to the combination regimen and resulted in treatment discontinuation. The event of hyperglycemia was manageable with antidiabetic medication. No DLT was reported at the 20 mg/kg cohort. Grade 2 events included arthralgia, weight loss, and anemia. Cardiac function was monitored using Doppler echocardiogram. Ninety-one Doppler echocardiograms were conducted without treatment related findings reported. No quantifiable antidrug antibodies were detected.

TABLE 3. Treatment-Related Adverse Events

	Grade 1 (*n*)	Grade 2 (*n*)	Grade 3 (*n*)	Grade 4 (*n*)	All Grades
Figitumumab related					
Fatigue	7	5	1		13
Diarrhea	6	6	1		13
Dysgeusia	3	1	0		4
Arthralgia	2	2	0		4
Hyperglycemia	1	0	1		2
GGT elevation	0	0	1		1
Thrombocytopenia	0	0	1		1
All causality					
Fatigue	14	10	5	0	29
Alopecia	10	17	0	0	27
Diarrhea	14	7	1	0	22
Nausea	10	6	3	0	19
Neuropathy	10	6	3	0	19
Arthralgia	9	9	0	0	18
Pain	6	6	2	0	14
Anorexia	8	5	0	0	13
Vomiting	7	4	2	0	13
Dysgeusia	8	3	0	0	11
Hyperglycemia	8	1	2	0	11
Hypertension	6	3	2	0	11
Anemia	3	5	3	0	11
Cough	8	2	0	0	10
Neutropenia	3	3	3	2	9
Weight loss	3	5	1	0	9
Headache	5	1	1	0	7
Chest pain	2	4	1	0	7
Vision blurred	5	0	1	0	6
Confusion	3	1	1	0	5
Thrombocytopenia	1	0	2	0	3
Infection	0	2	1	0	3
Hypotension	1	1	1	0	3

GGT, gamma glutamyl transpeptidase.

PK Analysis

F plasma concentration-time data were available from 40 patients. One patient was excluded from the analysis because of incomplete data. Plasma concentrations of F decreased in a multiexponential manner after intravenous infusion (Figure 1). As shown in Table 4, the plasma concentration at the end of infusion ($C_{1\ hour}$) and the AUC within a cycle ($AUC_{0-day\ 22}$) increased with dose at both cycles 1 and 4. The increase in $AUC_{0-day\ 22}$ was approximately dose proportional at dose levels higher than 0.8 mg/kg. After repeated administration every 3 weeks, there was a moderate accumulation in plasma exposure of F at dose levels ≥3 mg/kg. Mean accumulation ratio reached approximately twofold at 10 and 20 mg/kg q3 weeks dosing (Figure 1 and Table 4), supporting an effective half-life approximating the 3-week dosing interval.[6,7]

Pharmacodynamic Analysis

The effects of F on CTCs, IGF-1R expressing CTCs and CECs were investigated. Thirty-one patients provided blood samples ($n = 674$) for the enumeration of these biomarkers, including 26 patients with NSCLC. Seventeen patients had detectable CTCs at some point during the study; however, only one to five cells were detected in most cases, with all but one of the patients with NSCLC having ≤10 CTCs at study entry. Because IGF-1R has been described as an upstream regulator of VEGF expression,[9] CECs were

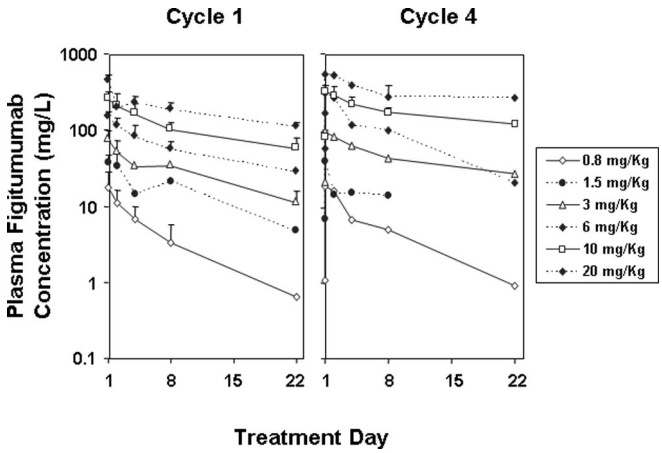

FIGURE 1. Mean (±SD) plasma concentration-time profiles of figitumumab (F) after cycles 1 and 3 of treatment.

TABLE 4. Figitumumab PK Parameters

Dose (mg/kg)	Cycle 1			Cycle 4				
	n	$C_{1\ h}$ (mg/L)	$AUC_{0–Day\ 22}$ (mg h/L)	*n*	$C_{1\ h}$ (mg/L)	$C_{Day\ 22}$ (mg/L)	$AUC_{0–Day\ 22}$ (mg h/L)	RAC
0.1	2	1.40, 1.51	—	2	4.36, 1.59	—	—	—
0.5	3	0.533 ± 0.212	112[a]	2	0.575, 0.412	0.034[a]	62.5[a]	0.56[a]
0.8	4	17.3, 10.3	1920 ± 1010	2	20.3, 18.0	0.926[a]	1790, 2790	0.61 ± 1.3
1.5	3	37.5 ± 9.0	4490, 5420[b]	1	40.7	—	5320	1.2[a]
3	3	75.2 ± 22.2	12,900 ± 5450	2	122, 79.4	33.6, 21.8	31,200, 14,900	1.8 ± 2.1
6	3	147 ± 27	25,600 ± 8830	1	327	21	44,600	1.3
10	16	255 ± 60	52,300 ± 14,700[c]	10	345 ± 70	108 ± 50[d]	87,000 ± 15,500[e]	1.9 ± 0.4[e]
20	5	443 ± 85	85,300 ± 26,000[f]	2	557 ± 611	357, 207	217,000, 138,000	2.2 ± 1.8

[a] $n = 1$; [b] $n = 2$; [c] $n = 14$; [d] $n = 7$; [e] $n = 9$; [f] $n = 4$.

$C_{1\ h}$, plasma concentration at 1 h post the end of infusion; $C_{day\ 22}$, plasma concentration at day 22 of the cycle; $AUC_{0-day\ 22}$, area under the plasma concentration-time curve from time 0 to day 22; *n,* the number of patients included in the analysis; accumulation ratio (RAC) = (cycle 4 $AUC_{0-day\ 22}$)/(cycle 1 $AUC_{0-day\ 22}$); AUC, area under the curve; PK, pharmacokinetic.

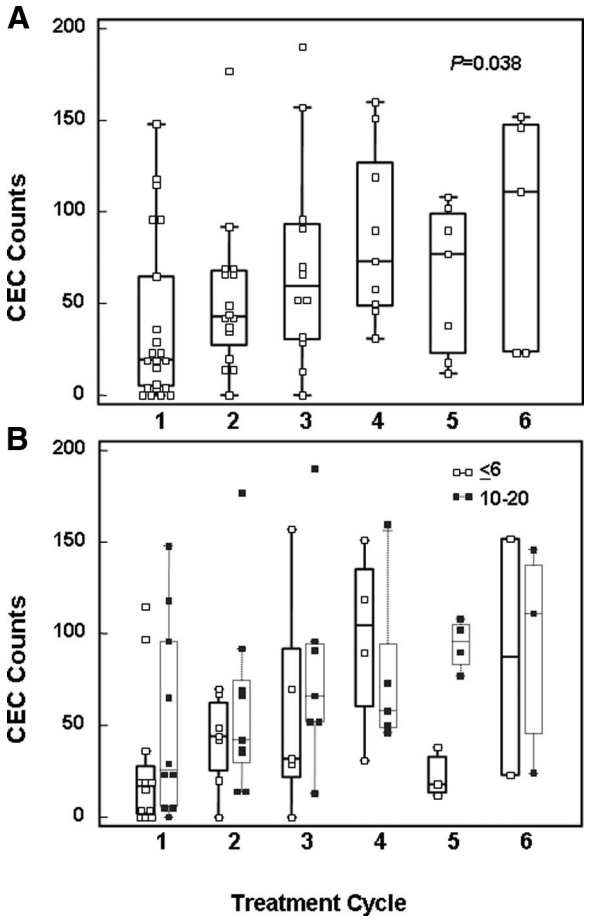

FIGURE 2. Time profiles of circulating endothelial cell (CEC) counts in (*A*) all patients with providing samples for CEC enumeration ($N = 22$) and (*B*) according to figitumumab (F) treatment doses ≤6 mg/kg ($N = 12$) or 10 to 20 mg/kg ($N = 10$). Data are represented as box plots (minimum, 25 percentile, median, 75 percentile, maximum) and individual CEC counts. Values outside the box plots are considered outliers (smaller or larger than the minimum or maximum estimates).

enumerated to evaluate any potential effect of F on this angiogenesis marker. CECs were detected in all patients, with a median of 52 cells per blood sample. Mean CEC counts increased with treatment cycle but no effect of F treatment on this pharmacodynamic parameter was observed (Figure 2).

Additional blood samples ($n = 351$) were analyzed for the determination of plasma levels of sIGF-1R, fIGF-1, and IGFBP-3. An inverse correlation (Rho = −0.426, $p = 0.03$) between baseline fIGF-1 and sIGF-1R was observed. No correlation with demographic parameters was identified. At low-F doses, transient decreases followed by rebound increases in circulating sIGF-1R levels were observed (Figure 3). In contrast, sIGF-1R levels were maximally suppressed for the entire dosing period at F doses levels of 3 mg/kg and above. Meanwhile, fIGF-1 and IGFBP-3 increased in patients in response to F treatment in a dose-dependent fashion, although the magnitude of increase in IGFBP-3 was generally more modest than that of fIGF-1 (Figure 3).

Efficacy

Fifteen objective responses (RECIST) were observed (36%), including two complete responses, one in a patient with ovarian carcinoma, and one in a patient with stage IV NSCLC. Fourteen objective responses were seen in patients with stages IIIB and IV NSCLC (40%). Median duration of response was 6.5 months (range, 2–49). In addition, 16 patients with NSCLC experienced a best response of stable disease. The median duration of disease stabilization was 2 months (range, 1–11). Six patients were stable for ≥6 months on single agent F maintenance therapy.

No apparent relationships between efficacy and PK, CTC, or CEC parameters were identified. Baseline blood samples for the analysis of plasma markers were available from 40 patients, including 13 patients with objective responses. Patients responding to treatment at F doses ≤6 mg/kg seemed to have high baseline IGFBP-3 and low fIGF-1 levels (Figure 4). As both parameters are likely interrelated, we analyzed the ratio of fIGF-1 to IGFBP3 according to F dose (≤6 mg/kg versus 10–20 mg/kg) and objective response. Of interest, patients responding to treat-

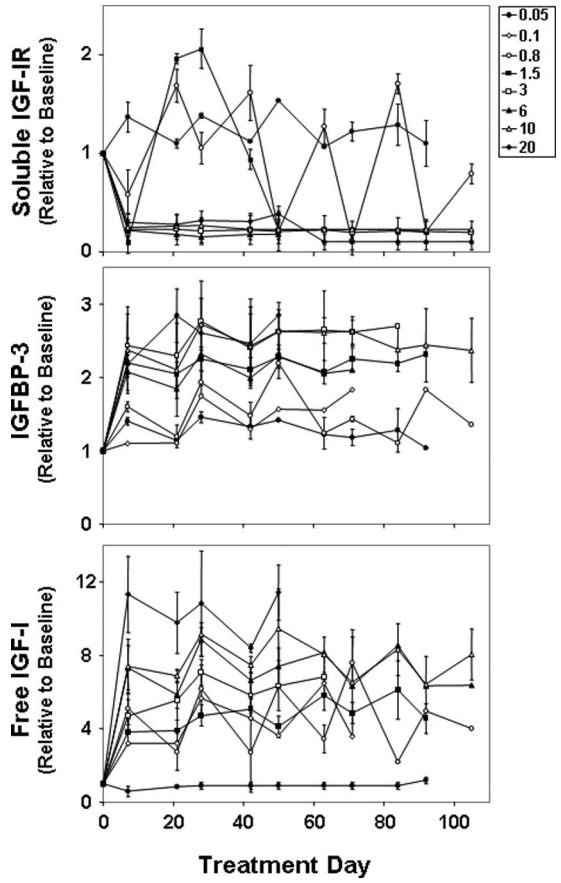

FIGURE 3. Soluble insulin-like growth factor type 1 receptor (IGF-1R) extracellular domain (sIGF-1R), IGF binding protein-3 (IGFBP-3), and free IGF-1 (fIGF-1) levels by figitumumab (F) dose. Data are represented relative to baseline levels.

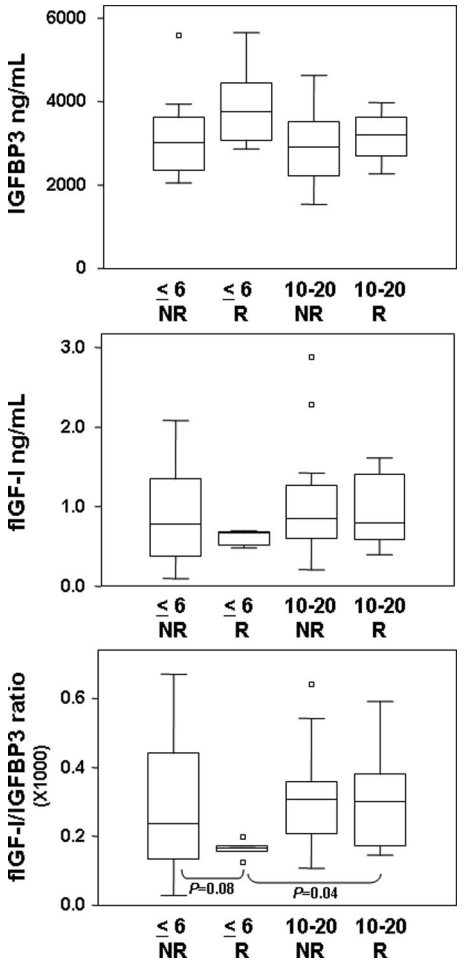

FIGURE 4. Analysis of insulin-like growth factor (IGF) binding protein-3 (IGFBP-3), free IGF-1 (fIGF-1) levels, and fIGF-1/IGFBP-3 ratio in responders (R) and nonresponders (NR) to treatment, according to RECIST, at figitumumab (F) treatment doses ≤6 mg/kg (N = 18) or 10 to 20 mg/kg (N = 22).

ment at F doses ≤6 mg/kg had fIGF-1 to IGFBP-3 ratios lower than patients responding in the 10 and 20 mg/kg cohorts (p = 0.04) (Figure 4), suggesting that low bioactive IGF-1 levels may be associated with response to chemotherapy in the absence of IGF-1R blockade. Indeed, nine responses were observed in 16 patients with a fIGF-1/IGFBP3 ratio ≤0.018%. On the other hand, only five of 24 patients with higher fIGF-1/IGFBP3 ratios responded (p = 0.04), and all these responders received F at 10 or 20 mg/kg. No association of sIGF-1R levels at study entry or degree of down-regulation post-treatment with patient response was identified.

DISCUSSION

An every 3-week regimen of the anti-IGF-1R monoclonal antibody F at doses up to 20 mg/kg in combination with paclitaxel and carboplatin was well tolerated. Grade 3 events of hyperglycemia, fatigue, diarrhea, GGT elevation, and thrombocytopenia (one case each) were reported as possibly related to F. Hyperglycemia seems to be characteristic of this class of compounds,[10] although contributions of comorbid conditions, such as diabetes and steroid premedication for paclitaxel cannot be excluded. Importantly, the event of hyperglycemia was generally manageable with antidiabetic medication. Mild to moderate fatigue and sporadic isolated GGT elevations have been observed in previous studies of F. In contrast, severe thrombocytopenia has been rare when F was given as single agent.[6,7] This is important because hematological toxicity has been reported to be dose limiting for other anti-IGF-1R antibodies.[11–13] It is possible that differences in IgG subtype may be responsible for some of these differences. F is a fully human IgG2 antibody[4] and, consequently, is expected to be a poor activator of antibody mediated cytotoxicity and complement fixation.

The extended effective half-life of F of approximately 3 weeks at 10 and 20 mg/kg doses compares favorably with other monoclonal antibodies in the anti-IGF-1R class.[7] Mean terminal half-lives of 4 to 11 days have been reported for other IGF-1R monoclonal antibodies.[9] These differences could be due in part to their IgG backbone.[14] PK exposure parameters of F given in combination with paclitaxel and

carboplatin were similar to those previously observed with single agent F,[9] suggesting that the combination with paclitaxel/carboplatin does not significantly alter the PK properties of F. Based on its favorable safety profile and its optimal PK and pharmacodynamic properties, the maximal feasible dose of 20 mg/kg has been selected for further investigation.

CTCs were detected in approximately 40% of the patients, but the number of circulating cells was too low for systematic analysis. CTC counts have been proposed as a novel and noninvasive approach for pharmacodynamic studies in NSCLC and in breast and prostate cancer.[5,8,15] Further research would be required to improve the sensitivity of current methodologies in NSCLC. Intriguingly, the median number of CECs increased during the study in a manner independent to F treatment. This finding may reflect a chemotherapy effect or patient selection based on prognosis, with those patients with a higher number of CECs receiving a larger number of treatment cycles. In that respect, it has been previously reported that baseline CEC counts are associated with better patient response and outcome in NSCLC.[16] No relationship between CEC counts and response was apparent in this study. Further research should be undertaken to determine the prognostic value of CECs in the treatment of NSCLC.

Finally, we found that IGF-1 bioactivity may be critical for NSCLC response to chemotherapy and that blockade of the IGF-1/IGF-1R interaction by F may translate to clinical benefit, particularly in settings of high IGF-1 bioactivity. These findings should be considered with caution due to the small data set investigated in this study. However, these results are consistent with previous reports associating high-IGFBP-3 levels with longer overall, disease-free, and event-free survival in NSCLC.[17,18] Additional research will be needed to determine the predictive value of fIGF-1 and IGFBP-3 levels and their potential use for patient selection or stratification in studies of anti-IGF-1R therapy. Pharmacodynamic measures are currently underway in ongoing studies to validate these provocative observations.[19,20]

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REFERENCES

1. Pollak M. Insulin and insulin-like growth factor signalling in neoplasia. *Nat Rev Cancer* 2008;8:915–928.
2. Favoni RE, De Cupis A, Ravera F, et al. Expression and function of the insulin like growth factor 1 system in human non small cell lung cancer and normal lung cell lines. *Int J Cancer* 1994;56:858–866.
3. Spitz MR, Barnett MJ, Goodman GE, Thornquist MD, Wu X, Pollak M. Serum Insulin like growth factor (IGF) and IGF binding protein levels and risk of lung cancer: a case control study nested in the beta carotene and retinol efficacy trial cohort. *Cancer Epidemiol Biomarkers Prev* 2002;11:1413–1418.
4. Cohen BD, Baker DA, Soderstrom C, et al. Combination therapy enhances the inhibition of tumor growth with the fully human anti-type 1 insulin-like growth factor receptor monoclonal antibody figitumumab. *Clin Cancer Res* 2005;11:2063–2073.
5. de Bono JS, Scher HI, Montgomery RB, et al. Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. *Clin Cancer Res* 2008;14:6302–6309.
6. Lacy MQ, Alsina M, Fonseca R, et al. Phase I, pharmacokinetic and pharmacodynamic study of the anti-insulinlike growth factor type 1 Receptor monoclonal antibody CP-751,871 in patients with multiple myeloma. *J Clin Oncol* 2008;26:3196–3203.
7. Haluska P, Shaw HM, Batzel GN, et al. Phase I dose escalation study of the anti-insulin-like growth factor-I receptor monoclonal antibody figitumumab in patients with refractory solid tumors. *Clin Cancer Res* 2007;13:5834–5840.
8. Maheswaran S, Sequist LV, Nagrath S, et al. Detection of mutations in EGFR in circulating lung-cancer cells. *N Engl J Med* 2008;359:366–377.
9. Punglia RS, Lu M, Hsu J, et al. Regulation of VEGF expression by IGF-1. *Diabetes* 1997;46:1619–1626.
10. Weroha SJ, Haluska PJ. IGF-1 receptor inhibitors in clinical trials–early lessons. *Mammary Gland Biol Neoplasia* 2008;13:471–483.
11. Tolcher AW, Rothenberg ML, Rodon J, et al. A phase I pharmacokinetic and pharmacodynamic study of AMG 479, a fully human monoclonal antibody against insulin-like growth factor type 1 receptor (IGF-IR), in advanced solid tumors. *J Clin Oncol ASCO Annu Meet Proc* 2007: abstract# 3002.
12. Atzori F, Tabernero J, Cervantes A, et al. Phase I, pharmacokinetic (PK) and pharmacodynamic (PD) study of weekly (qW) MK-0646, an insulin-like growth factor-1 receptor (IGF1R) monoclonal antibody (MAb) in patients (pts) with advanced solid tumors. *J Clin Oncol ASCO Annu Meet Proc* 2008:abstract# 3519.
13. Hidalgo M, Tirado Gomez N, Lewis, et al. A phase I study of MK-0646, a humanized monoclonal antibody against the insulin-like growth factor receptor type 1 (IGF1R) in advanced solid tumor patients in a q2 wk schedule. *J Clin Oncol ASCO Annu Meet Proc* 2008:abstract# 3520.
14. Goodin S. Development of monoclonal antibodies for the treatment of colorectal cancer. *Am J Health Syst Pharm* 2008;65:S3–S7.
15. Cristofanilli M, Budd GT, Ellis MJ, et al. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. *N Engl J Med* 2004;351:781–791.
16. Kawaishi M, Fujiwara Y, Fukui T, et al. Circulating endothelial cells in non-small cell lung cancer patients treated with carboplatin and paclitaxel. *J Thorac Oncol* 2009;4:208–213.
17. Chang YS, Kong G, Sun S, et al. Clinical significance of insulin-like growth factor-binding protein-3 expression in stage I non-small cell lung cancer. *Clin Cancer Res* 2002;8:3796–3802.
18. Han JY, Choi BG, Choi JY, Lee SY, Ju SY. The prognostic significance of pretreatment plasma levels of insulin-like growth factor (IGF)-1, IGF-2, and IGF binding protein-3 in patients with advanced non-small cell lung cancer. *Lung Cancer* 2006;54:227–234.
19. Karp DD, Paz-Ares LG, Novello S, et al. Phase II study of the anti-insulin-like growth factor type 1 receptor antibody CP-751,871 in combination with paclitaxel and carboplatin in previously untreated, locally advanced, or metastatic non-small-cell lung cancer. *J Clin Oncol* 2009;27:2516–2522.
20. Hixon ML, Gualberto A, Demers L, et al. Correlation of plasma levels of free insulin-like growth factor 1 and clinical benefit of the IGF-IR inhibitor figitumumab (CP-751,871). *J Clin Oncol ASCO Annu Meet Proc* 2009:abstract# 3539.