

## Phase I Dose Escalation Study of the Anti-Insulin-Like Growth Factor-I Receptor Monoclonal Antibody CP-751,871 in Patients with Refractory Solid Tumors

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**Abstract Purpose:** This phase I study was undertaken to define the maximum tolerated dose, safety, and pharmacokinetic profile of CP-751,871.

**Experimental Design:** Using a rapid dose escalation design, patients with advanced nonhematologic malignancies were treated with CP-751,871 in four dose escalation cohorts. CP-751,871 was administered i.v. on day 1 of each 21-day cycle. Pharmacokinetic evaluation was done in all treatment cohorts during cycles 1 and 4.

**Results:** Twenty-four patients received 110 cycles at four dose levels. The maximum tolerated dose exceeded the maximal feasible dose of 20 mg/kg and, thus, was not identified. Treatment-related toxicities were generally mild. The most common adverse events were hyperglycemia, anorexia, nausea, elevated aspartate aminotransferase, elevated  $\gamma$ -glutamyltransferase, diarrhea, hyperuracemia, and fatigue. At 20 mg/kg, 10 of 15 patients experienced stability of disease. Two of these patients experienced long-term stability. There were no objective responses. Pharmacokinetic analysis revealed a dose-dependent increase in CP-751,871 exposure and ~2-fold accumulation on repeated dosing in 21-day cycles. Plasma concentrations of CP-751,871 attained were several log-fold greater than the biologically active concentration. Treatment with CP-751,871 increased serum insulin and human growth hormone levels, with modest increases in serum glucose levels.

**Conclusions:** CP-751,871 has a favorable safety profile and was well tolerated when given in continuous cycles. At the maximal feasible dose of 20 mg/kg, there was a moderate accumulation in plasma exposure, and most of the treated patients experienced stability of disease.

The insulin-like growth factor-I receptor (IGF-IR) is a receptor tyrosine kinase that serves as a key positive regulator of the IGF-I system (1). In response to the stimulatory ligands IGF-I and IGF-II, IGF-IR signaling results in proliferative and antiapoptotic effects (2). The IGF-I system, which is tightly regulated in nonmalignant tissues, contributes to the proliferation of several tumor types, including breast, prostate, lung, ovarian, and colon cancers (3–8). In addition to cancer cell proliferation, dysregulation of the IGF-I system and enhanced IGF-IR activation is implicated in the resistance to anticancer therapies,

including cytotoxic chemotherapy, biological therapies, hormonal agents, and radiation (9–17). By blocking the pro-survival signaling, inhibition of the IGF-IR can also enhance the activity of these agents. Thus, agents targeting the IGF-IR have the potential to deliver anticancer activity in a variety of tumor types as well as improve sensitivity and block resistance to existing cancer therapies.

Several lines of evidence support the strategy of inhibiting IGF-IR as a target of anticancer therapy. IGF-IR expression seems necessary for a transformed cellular phenotype (18) and patients with congenital deficiency of IGF-I seem to be protected from the development of malignancies (19). Furthermore, markers of enhanced activation of the IGF-I system (e.g., increased circulating IGF-I or IGF-II, decreased IGF-binding proteins, and increased IGF-IR expression) portend a worse prognosis in many malignancies, including multiple myeloma, prostate cancer, non-small cell lung cancer, and renal cell carcinoma (3, 4, 20, 21). Although there is conflicting data, the presence of elevated circulating IGF-I and decreased IGF-binding proteins seems to increase the relative risk of developing certain cancers (6, 22–24). Furthermore, inhibition of IGF-IR in a variety of tumor types, by a variety of strategies *in vitro* and *in vivo*, has antiproliferative effects and synergizes with other anticancer therapies (25–28).

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**Table 1.** Patient characteristics

Characteristics	No. patients
Age (y)	
Median	53
Range	33-68
Sex	
Male	19
Female	5
Performance status	
0	8
1	16
Tumor type	
Colorectal cancer	6
Lung cancer	4
Sarcoma	4
Prostate cancer	3
Bladder cancer	2
Cervical cancer	1
Gastrointestinal stromal tumor	1
Ovarian cancer	1
Pseudomyxoma peritonei	1
Thymoma	1
Prior therapy	
Surgery	24
Radiation therapy	13
Chemotherapy	20 (13, 3+ regimens)
Hormonal therapy	4

We have previously reported the preclinical activity of CP-751,871, which is a potent fully human IgG2 monoclonal antibody antagonist of IGF-IR. CP-751,871 antagonized the binding of IGF-I to IGF-IR and IGF-IR autophosphorylation and induces down-regulation of IGF-IR *in vitro* and *in vivo* in tumor xenograft models in a dose-dependent manner. CP-751,871 also blocks IGF-I-mediated and IGF-II-mediated phosphorylation of IGF-IR and Akt, suggesting both activating ligands are antagonized. In addition to exhibiting single-agent activity *in vivo*, CP-751,871 also enhances the activity of cytotoxic chemotherapy and tamoxifen in tumor xenografts (25).

We designed a phase I dose escalation study to evaluate the safety profile and determine the maximum tolerated dose of CP-751,871 when administered i.v. every 21 days. In addition, secondary end points included assessment of the pharmacokinetics, pharmacodynamics, and antitumor activity. We now report that CP-751,871 was safe and well tolerated and provided clinical benefit (disease stabilization) at the maximal feasible dose (MFD) regimen of 20 mg/kg every 3 weeks.

## Materials and Methods

**Trial design.** The study conducted was a two-center, phase I, open-label, dose escalation study of CP-751,871 administered i.v. in patients with advanced solid tumors in 21-day cycles. Patients continued treatment at the same dose level as long as CP-751,871 was well tolerated and there was no evidence of disease progression.

**Patients.** Eligible patients were required to have histologic or cytologic evidence of metastatic or advanced solid malignancies and failed standard effective therapy or have a tumor type for which no standard effective therapy exists. Patients were required to be  $\geq 18$  years of age with an Eastern Cooperative Oncology Group performance status of 0 or 1. Additional eligibility criteria included adequate bone marrow,

renal, and hepatic function (absolute neutrophil count  $\geq 1,000/\mu\text{L}$ , hemoglobin  $\geq 8$  g/dL, platelets  $>75,000/\mu\text{L}$ , creatinine clearance  $>30$  mL/min, total bilirubin  $<1.5\times$  the institution upper limit of normal, aspartate aminotransferase/alanine aminotransferase  $<2.5$  upper limit of normal); fully recovered from prior anticancer treatments; and use of adequate contraception in patients with reproductive potential. Due to evidence of nonpathologic, lymphocyte/granulocyte infiltration of unclear significance in the cardiac valves during preclinical toxicology studies with CP-751,871, all patients were required to have mitral valve regurgitation  $\leq$  trivial based on precautionary echocardiographic assessments.

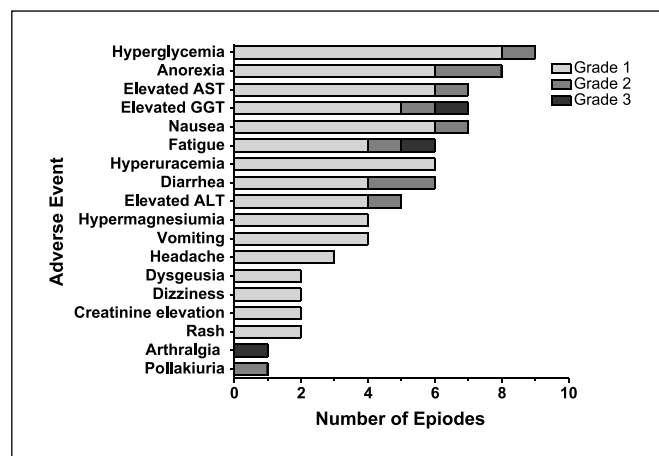
Patients were excluded if they were on approved or experimental anticancer therapy within 4 weeks of study treatment (excluding luteinizing hormone-releasing hormone analogues in prostate cancer patients). Patients were also excluded within 8 weeks of mitomycin C or nitrosoureas, 4 weeks of major surgery, 4 weeks of immunotherapy or other biological therapy, 10 days of palliative radiation therapy, or 10 days of hormonal therapy. Additional exclusion criteria were symptomatic or untreated brain metastases, women who were pregnant or breast-feeding, significant active cardiac disease, concomitant high-dose corticosteroids ( $\geq 100$  mg prednisone/day or equivalent), serious active infection, other uncontrolled significant medical illness, psychiatric illness, or social situation that would preclude study participation.

The study protocol was approved by the institutional review boards of the centers participating in this study. All patients gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki and its amendments.

**Dose escalation.** The starting dose of CP-751,871 was 3 mg/kg. This starting dose was chosen after review of the safety and tolerability of an ongoing first-in-human study of CP-751,871 in patients with multiple myeloma (29). No dose-limiting toxicity was observed in myeloma patients dosed with 3 mg/kg of CP-751,871. In addition, the proposed dose range (3-20 mg/kg) of CP-751,871 was expected to provide clinical benefit based on data extrapolated from xenograft models (25). Patients were enrolled in cohorts of three to six patients, with at least 3 weeks elapsing between dose escalations to allow adequate patient monitoring. Provisions were delineated in the protocol for changing the dose escalation to 40% increments if two or more patients experienced National Cancer Institute Common Terminology Criteria of Adverse Events version 3.0 grade 2 toxicities or one of six patient experiences a dose-limiting toxicity in cycle 1. The dose of CP-751,871 was escalated using a modified dose doubling design (30). Following the 3 mg/kg cohort, the dose was doubled to 6 mg/kg. As it was initially thought, due to formulation constraints, that 10 mg/kg would be the MFD, the next cohort enrolled was at this dose. Because the 10 mg/kg cohort was well tolerated, it was felt that CP-751,871 could be feasibly administered at 20 mg/kg when given as a prolonged infusion as described below. Thus, patients were treated in cohorts dosed at 3, 6, 10, and 20 mg/kg. At the MFD (20 mg/kg), the cohort was expanded to 15 patients to confirm safety and tolerability. Doses  $<6$  mg/kg were infused in 100 mL of 0.9% sodium chloride over 1 h. Doses of 6 and 10 mg/kg were administered in 250 mL of 0.9% sodium chloride and infused at 100 mL/h over 2.5 h, whereas doses of 20 mg/kg were

**Table 2.** Dose escalation scheme

CP-751,871 (mg/kg)	No. patients	No. cycles	
		Average	Range
3	3	3.3	2-4
6	3	1.6	1-2
10	3	2	—
20	15	5.9	1-24
All	24	4.6	—



**Fig. 1.** Treatment-related toxicities. Adverse events were graded as per National Cancer Institute Common Terminology Criteria of Adverse Events (version 3.0). Single-episode, grade 1 toxicities: abdominal pain, abnormal activated partial thromboplastin time, adjustment disorder, alopecia, anemia, anxiety, dry eye, dry skin, fever, flatulence, hot flush, hyperbilirubinemia, hypokalemia, increased alkaline phosphatase, muscle spasms, neutropenia, neutrophilia, paresthesia, sore throat, and stomatitis. ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT,  $\gamma$ -glutamyltransferase.

administered in 500 mL of 0.9% sodium chloride at the same rate over 5 h.

**Patient evaluation.** Safety assessments were done during each treatment cycle. All patients receiving at least one dose of CP-751,871 were assessed for safety. Treatment-related adverse events were defined as those that were possibly, probably, or definitely related to CP-751,871 administration and occurred during the period from the time of the first dose until 150 days after the last dose. Dose-limiting toxicity was defined as a treatment-related adverse event that occurred in cycle 1, which resulted in (a) National Cancer Institute Common Terminology Criteria of Adverse Events hematologic toxicity grade  $\geq 4$  lasting  $>7$  days or required therapy, (b) nonhematologic toxicity grade  $\geq 3$  despite optimal supportive care, (c) infusion reaction grade  $\geq 2$  affecting vital organs, and (d) mitral valve regurgitation  $>$  mild. Patients were assessed for subacute and late toxicities up to 150 days following the last dose. Tumor response was assessed every two cycles radiographically using Response Evaluation Criteria in Solid Tumors criteria.

**Pharmacokinetic analysis.** Blood samples were collected in sodium heparin-containing tubes at the following times during cycle 1: 30 min before and 1 h, 24 h, 3 days, 7 days, and 14 days after end of the CP-751,871 infusion. During cycles 2 to 4, samples were collected 30 min before and 1 h after end of the CP-751,871 infusion. Samples were collected 30 min before CP-751,871 infusion during cycles 5 and beyond. Patients in the maximum tolerated dose/dose expansion cohort had blood samples drawn as above with additional 24 h, 3 days, 7 days, and 14 days after end of CP-751,871 infusion samples drawn during cycle 4.

Plasma concentrations of CP-751,871 were analyzed by a validated ELISA method as described previously (25). The lower limit of quantitation was 120 ng/mL. Plasma concentration-time data of CP-751,871 were analyzed by noncompartmental methods (31) using WinNonlin version 3.2 (Pharsight). For treatment cycles with sufficient data, area under the plasma concentration-time curve (AUC) from time 0 to the last sampling time point with quantifiable concentration within a cycle ( $AUC_{last}$ ) and from time 0 to the end of a cycle ( $AUC_{0-Day 22}$ ) was determined using the linear/log trapezoidal approximation. The accumulation ratio was calculated as the ratio of cycle 4  $AUC_{0-Day 22}$  to cycle 1  $AUC_{0-Day 22}$ . The apparent elimination half-life in this patient population was not determined, as sampling within the 21-day cycle did not sufficiently capture the terminal disposition phase in  $>60\%$  of the patients in the study.

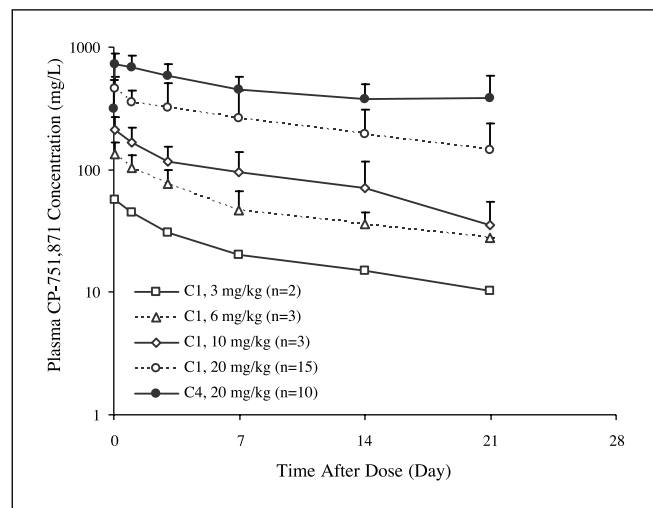
**Pharmacodynamics.** Circulating tumor cells (CTC) were isolated and enumerated using the CellTracks system (Immunicon) as described previously (32). Blood samples were collected from all patients enrolled in the study. Samples were drawn immediately before the first dose of CP-751,871 on study day 1 and 1, 3, 7, 14, and 21 days after CP-751,871 administration. Phycoerythrin-labeled antibodies were used for detecting IGF-IR (1H7, BD Pharmingen). Results of cell enumeration were expressed as the number of cells per 7.5 mL of blood. All assays were done by trained operators who were blinded to patient outcomes.

**Endocrine laboratory studies.** When feasible, fasting serum was collected from patients receiving CP-751,871 at the 20 mg/kg cohort for determinations of glucose, insulin, and human growth hormone (hGH) by the clinical laboratory tests available at the Mayo Clinic and Royal Marsden facilities. For the purposes of this study, the "prestudy" and "cycle 4" samples were collected within 7 days of receiving CP-751,871 on cycles 1 and 4, respectively. The "end of study" samples were collected 21 days ( $\pm 4$  days) after the last dose of CP-751,871 received. Cycle 4 samples were not collected on patients who did not receive cycle 4 treatment.

## Results

**Patients.** Twenty-four patients (Table 1) received 110 cycles of treatment at four different dose levels (Table 2). The median age was 53 years (range, 33-68), with 19 of the 24 patients being male. The most common tumor type treated was colorectal ( $n = 6$ ) followed by lung and sarcoma. All patients had previously undergone cancer-related surgery. Twenty patients had previously received chemotherapy, with 13 of these being heavily pretreated. The overall median number of treatment cycles delivered was 4.6. The range of treatment cycles was 1 to 24, with one patient continuing at 24 cycles. At the 20 mg/kg dose level, which included patients from the expanded cohort, 10 of the 15 (67%) patients received at least four cycles of CP-751,871 and 4 of 15 (27%) received at least six cycles.

**Safety.** Figure 1 lists the treatment-related toxicities for all cycles. There were no treatment-related toxicities greater than National Cancer Institute Common Terminology Criteria of Adverse Events grade 3 observed. There were no dose-limiting toxicities identified. Grade 3 toxicities observed were one



**Fig. 2.** Mean ( $\pm$ SD) plasma concentration-time profiles of CP-751,871 in treatment cycles 1 and 4.

**Table 3.** CP-751,871 plasma exposure variables (mean  $\pm$  SD) during treatment cycles 1 and 4

Dose (mg/kg)	Cycle 1			Cycle 4				Accumulation ratio
	n	C <sub>1 h</sub> * (mg/L)	AUC <sub>last</sub> (mg·h/L)	n	C <sub>1 h</sub> * (mg/L)	C <sub>min</sub> (mg/L)	AUC <sub>last</sub> (mg·h/L)	
3	2	54.2, 60.3	13,222, 7,674	2	82.0, 71.7	—	—	—
6	3	135 $\pm$ 32	23,436 $\pm$ 8,771	—	—	—	—	—
10	3	211 $\pm$ 60	43,583 $\pm$ 20,207	—	—	—	—	—
20	15	509 $\pm$ 173	115,878 $\pm$ 47,457	10	784 $\pm$ 138	229 $\pm$ 48	193,037 $\pm$ 42,028 <sup>†</sup>	2.1 $\pm$ 0.7 <sup>†</sup>

\*C<sub>1 h</sub>: plasma concentration at 1 h after infusion.  
<sup>†</sup>n = 8.

episode of fatigue and one episode of arthralgia. All grade 3 toxicities occurred at the 20 mg/kg dose. Overall, the most common adverse events were hyperglycemia, anorexia, nausea, elevated aspartate aminotransferase, elevated  $\gamma$ -glutamyltransferase, diarrhea, hyperuracemia, and fatigue. The maximum tolerated dose was not identified as it exceeded the MFD of 20 mg/kg. Thus, the expansion cohort was treated at the MFD of 20 mg/kg of CP-751,871.

**Pharmacokinetics.** Figure 2 shows the mean plasma concentration-time profiles of CP-751,871 during treatment cycles 1 and 4. Following i.v. infusion, CP-751,871 plasma concentrations decreased multiexponentially. As shown in Table 3, the plasma concentration at the end of infusion (C<sub>1 h</sub>) and AUC<sub>last</sub> increased in a dose-dependent manner. A moderate accumulation in plasma exposure was observed in most patients following repeated CP-751,871 dosing every 3 weeks, with the mean accumulation ratio being 2.1-fold at 20 mg/kg (Table 3; Fig. 3).

**Endocrine laboratory findings.** Hepatic IGF-I production is stimulated by hGH, and hGH production is in turn regulated by IGF-I through negative feedback (33). To explore whether CP-751,871 alters the endocrine feedback mechanisms regulating hGH, blood samples were collected in some patients dosed in the 20 mg/kg cohort. Insulin and fasting glucose levels were also determined because both hGH and IGF-I are known to affect glucose homeostasis (Fig. 4; ref. 34). In patients receiving CP-751,871, there seemed to be a small increase in the blood glucose before cycle 4 and at the end of study (Fig. 4A). However, only one patient had a glucose measurement >125 mg/dL. Despite a wide range prestudy, serum insulin levels increased at cycle 4 in the majority of patients evaluated (Fig. 4B). The range of hGH values in the patients evaluated ranged from <0.1 to 2 ng/mL before treatment with CP-751,871 (Fig. 4C). Serum hGH values increased in all patients evaluated for endocrine studies while receiving CP-751,871. Chronic endocrine laboratory investigations were also done on a patient (#1011) who received CP-751,871 for >1 year (Fig. 4D). Although there was fasting glucose fluctuations, these values remained <135 mg/dL until cycle 24. On day 485 (cycle 24, day 1), the fasting glucose was 175 mg/dL. Before this date, the hGH levels fluctuated with the fasting glucose levels. In this patient, the serum insulin levels increased over the course of treatment until day 505. Similar to the fasting glucose results, day 485 also represented the highest serum insulin measurement (195  $\mu$ IU/mL) for this patient.

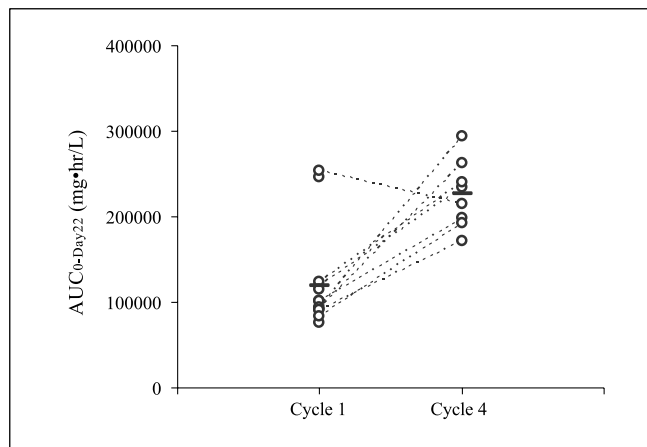
**Pharmacodynamics.** The enumeration of CTCs and IGF-IR-positive CTCs was incorporated as a pharmacodynamic end

point. Four patients had detectable CTCs at baseline: one patient with colorectal cancer, two patients with hormone-refractory prostate cancer, and one patient with ovarian cancer. The ovarian patient had the largest number of CTCs (n = 14/7.5 mL) and IGF-IR-expressing CTCs (n = 5/7.5 mL). On CP-751,871 dosing (6 mg/kg) in cycle 1, CTCs and IGF-IR-positive CTCs decreased in number, reaching a nadir by day 15, with some recovery in CTC and IGF-IR-positive CTCs by the next dosing on cycle 2, day 1. These data have been reported elsewhere (35).

**Antitumor activity.** All patients presented with stage IV metastatic disease. No confirmed responses were seen by Response Evaluation Criteria in Solid Tumors criteria among the 24 patients treated with CP-751,871. However, 7 of 12 patients with measurable disease by Response Evaluation Criteria in Solid Tumors criteria at the 20 mg/kg cohort showed minor decreases in tumor size (Fig. 5). These patients remained on study for a higher number of cycles (range, 4-24). For example, a patient with metastatic thymoma who experienced an ~10% reduction in tumor size by Response Evaluation Criteria in Solid Tumors criteria has had prolonged stability of disease for >1 year (24 cycles, subject still on study).

## Discussion

The IGF system represents a novel and attractive target for the development of anticancer therapies. It represents a key



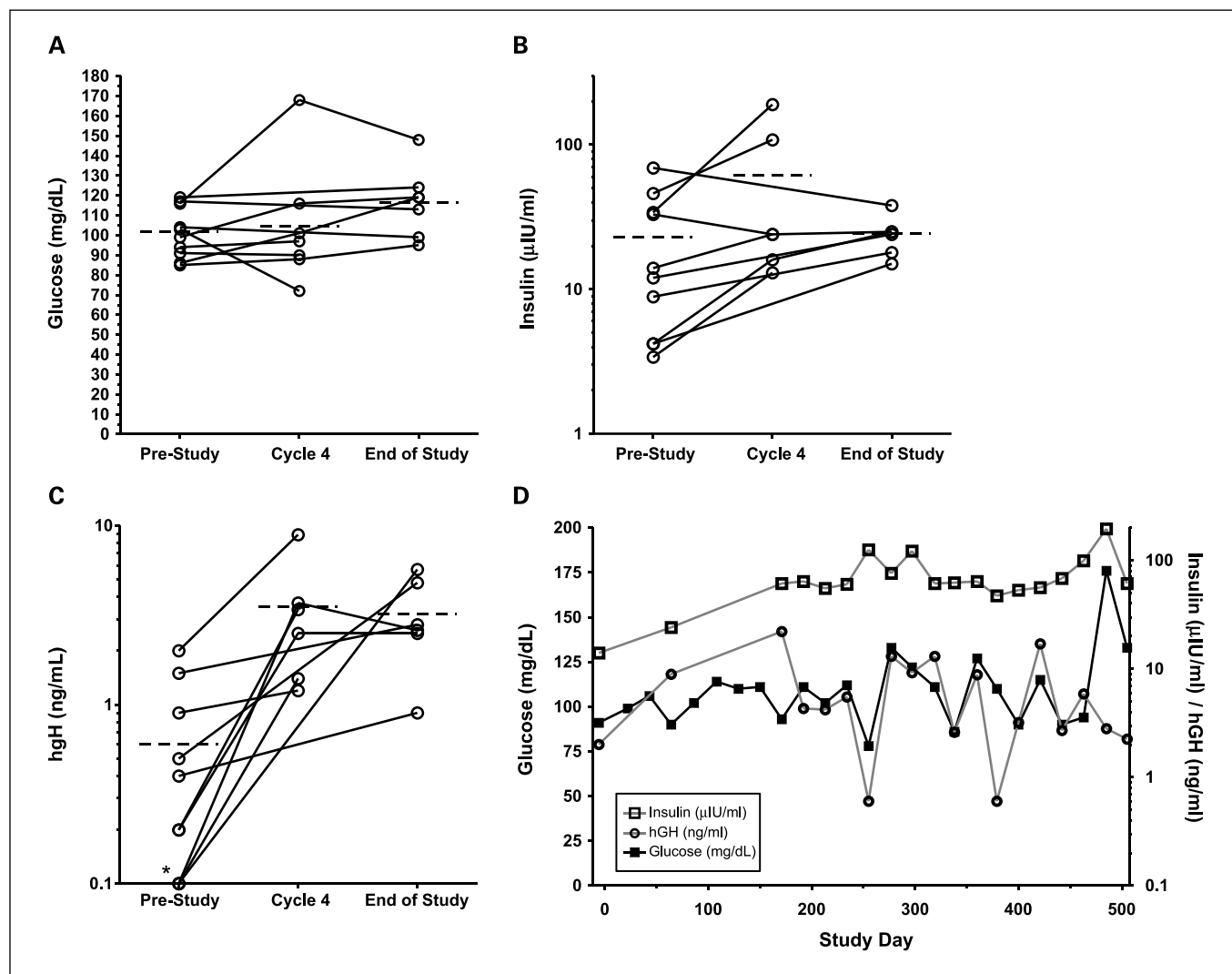
**Fig. 3.** Comparison of plasma CP-751,871 AUC during cycles 1 and 4 in individual patients treated with 20 mg/kg CP-751,871 on 3-wk cycles. Symbols, individual measurements; short solid lines, mean values.

proliferative and prosurvival signaling pathway in a variety of malignancies (36). The IGF system also plays a key role in the development of resistance to a variety of clinically useful cancer therapies (36). Thus, blocking the IGF pathway has the potential to provide clinical benefit in a wide range of malignancies and in a variety of clinically relevant treatment scenarios, including neoadjuvant, adjuvant, maintenance, and palliative therapy. As the first clinical step toward investigating these possibilities, we report in this study the results of a phase I clinical trial with CP-751,871, a potent, specific, humanized monoclonal antibody directed against the key positive regulator of the IGF-I system—the IGF-IR.

CP-751,871 was well tolerated in patients with advanced cancer. Most adverse events experienced by patients were mild. Indeed, the maximum tolerated dose was not exceeded and CP-751,871 was very well tolerated even at the MFD dose of 20 mg/kg. Two patients received at least 16 cycles of CP-751,871 without any evidence of cumulative toxicity. Thus, continuous repeated dosing up to 1 year was feasible.

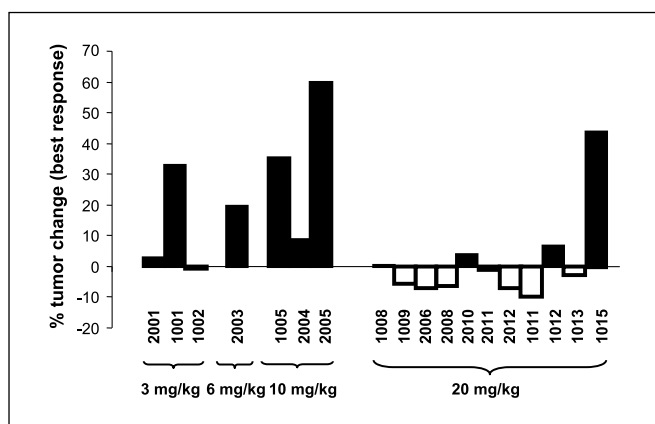
We have previously shown that CP-751,871 induced down-regulation of 50% of the IGF-IR in the peripheral blood mononuclear cells in humans at a concentration of  $\sim 50 \mu\text{g/L}$  ( $\text{IC}_{50}$ ,  $0.3 \text{ nmol/L}$ ; ref. 25). This concentration was exceeded at the lowest dose level of 3 mg/kg, where the trough concentration at the end of cycle 1 treatment was  $\sim 10 \text{ mg/L}$  (Fig. 2). At 20 mg/kg, the mean trough ( $C_{\text{min}}$ ) concentration at the end of cycle 4 treatment was  $\sim 4,580$ -fold above the  $\text{IC}_{50}$  value of  $50 \mu\text{g/L}$ . Thus, patients were able to tolerate repeated cycles of CP-751,871 several orders of magnitude above the minimal biologically efficacious concentration. These data suggest that CP-751,871 can be administered safely and repeatedly at pharmacologically relevant doses.

The most common laboratory abnormality was hyperglycemia, which was grade 1 or 2 in all occurrences. Earlier studies with CP-751,871 have shown that there is no binding of the antibody to the insulin receptor at concentrations up to 3,000 mg/L (25). The  $C_{\text{max}}$  for repeated dosing with CP-751,871 at the MFD was  $<1,000 \text{ mg/L}$  (Fig. 2), suggesting that the



**Fig. 4.** Endocrine laboratory findings. Fasting serum determinations for patients at the 20 mg/kg dose levels before cycles 1 and 4 and after completion of therapy with CP-751,871. Serum levels for glucose (A), insulin (B), and hGH (C). Horizontal dashed bars, mean for the individual measurements. \*, includes two values determined to be less than the limit of detection for hGH ( $0.1 \text{ ng/mL}$ ). D, chronic endocrine laboratory measurements made on patient (#1011) during 24 cycles of CP-751,871. Day 1 represents first day of treatment.





**Fig. 5.** Best response on study. The graph represents the percentage of tumor size change between consecutive scans taken every two cycles or highest percentage of tumor decrease on study when compared with baseline. Numbers below X-axis, patient identification numbers.

occurrence of hyperglycemia is unlikely to be due to insulin receptor binding. There are data to support the importance of the IGF-I ligand and system on glucose metabolism. IGF-I administration in humans results in hypoglycemia, decreased serum levels of fatty acids, and increased lipogenesis (37, 38). Recombinant IGF-I increases insulin sensitivity in the liver and muscle in patients with type II diabetes mellitus and improved glucose control (39). In addition, IGF-I suppresses hepatic, renal, and intestinal gluconeogenesis and has "insulin-like" effects via the IGF-IR, including increased glycogen formation, increased translocation of glucose transporters, and increased glucose uptake (40, 41). IGF-IR inhibition was accompanied by an increase in hGH production (Fig. 4C). This is not surprising as genetic alterations that cause IGF-I or IGF-IR inactivation result in hGH accumulation (36). Interestingly, hGH may have hyperglycemic effects by promoting liver gluconeogenesis (42). CP-751,871 also induced an increased level of insulin in some patients, whereas the level of glucose (fasting) did not show similar changes (Fig. 4A and B).

In the one patient who received >1 year of CP-751,871 (on cycle 24 at the time of this article), glucose levels >115 mg/dL

were only observed after insulin levels increased to >120  $\mu$ U/mL (Fig. 4D). Indeed, on day 485, the patient experienced a fasting glucose level of 176 mg/dL with an insulin level of 195  $\mu$ U/mL. Although alternative hypotheses exist, one possible explanation for this finding is that the increased insulin levels acted as a compensatory mechanism to control the hyperglycemic effect produced by hGH increase and IGF-IR inactivation. It is conceivable that accumulation of CP-751,871 after 24 cycles leads to a degree of IGF-IR activation that leads to decompensation of the hyperinsulinemia effect, and thus, hyperglycemia ensues. Further endocrine studies in larger numbers of patients will be necessary to fully interpret these provocative findings.

Multiple groups have described the isolation and characterization of CTCs in the blood of patients with a wide range of malignancies (43, 44). The analysis of CTCs was particularly appealing in this trial, as the IGF-IR has been postulated to play a key role in metastasis by regulating cell adhesion, motility, migration, and angiogenesis (45). Few patients in this study, however, presented with detectable number of CTCs, and although decreases in CTC number were observed, no relationship to tumor burden or patient outcome was observed. It is possible that our analysis was limited by an insufficient number of observations. A full description of the methods of detection and analysis of CTCs and IGF-IR-expressing CTCs in all ongoing CP-751,871 trials has been reported elsewhere (35).

Although determining efficacy of CP-751,871 was not the primary objective of this phase I study, there was preliminary evidence of clinical benefit at the MFD of 20 mg/kg. Of the 15 patients treated at this dose level, 10 (67%) derived benefit through stability of disease. Two of these patients had prolonged disease stabilization for at least 48 weeks. These encouraging results suggest that CP-751,871 may have clinical benefit as a single agent. Importantly, stabilization of disease was observed despite diverse tumor histology, suggesting a key role of IGF-IR in tumor progression. In addition, preclinical studies of CP-751,871 in combination with chemotherapy and targeted agents indicate that CP-751,871 significantly improves the activity of these anticancer agents. Several phase II studies combining CP-751,871 with chemotherapy and other therapies are under way.

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