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

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A B S T R A C T

Purpose
A phase I first-in-human study was conducted to characterize the safety, tolerability, pharmacokinetic, and pharmacodynamic properties of the anti–insulinlike growth factor 1 receptor (IGF-IR) monoclonal antibody CP-751,871.

Patients and Methods
After informed consent and screening, 47 patients with multiple myeloma in relapse or refractory phase were enrolled into 11 dose-escalation cohorts of CP-751,871 at doses from 0.025 to 20 mg/kg for 4 weeks. Patients with less than a partial response to CP-751,871 treatment were eligible to receive CP-751,871 in combination with oral dexamethasone at the discretion of the investigator. Treatment with CP-751,871 and rapamycin with or without dexamethasone was also offered to patients enrolled in the 10 and 20 mg/kg cohorts with less than a partial response to initial therapy with single-agent CP-751,871.

Results
No CP-751,871-related dose-limiting toxicities were identified. Plasma CP-751,871 concentrations increased with dose and concentration-time profiles were consistent with those of antibodies with target-mediated disposition. Importantly, CP-751,871 administration led to a decrease in granulocyte IGF-IR expression and serum insulinlike growth factor 1 accumulation at high doses, suggesting systemic IGF-IR inhibition. Tumor response was assessed according to the European Group for Blood and Marrow Transplantation criteria. Nine responses were reported in 27 patients treated with CP-751,871 in combination with dexamethasone. Of interest, two of the patients with a partial response were progressing from dexamethasone treatment at study entry.

Conclusion
These data indicate that CP-751,871 is well tolerated and may constitute a novel agent in the treatment of multiple myeloma.

INTRODUCTION

Signaling through the anti–insulinlike growth factor 1 receptor (IGF-IR) has been extensively studied in multiple myeloma. Elevated insulinlike growth factor 1 (IGF-1) levels and IGF-IR expression are associated with worse disease prognosis.[1-4] IGF-IR is highly expressed in multiple myeloma cells,[5,6] where it regulates growth,[7-13] survival,[14-16] adhesion, and invasiveness.[17-21] Likewise, IGF-IR inhibition has been long proposed as a cancer treatment strategy[22] and IGF-IR inhibitors have been shown to block the growth myeloma tumor models.[6,23-25] We have previously described the characterization of CP-751,871, a fully human IgG2 monoclonal antibody with high affinity for the IGF-IR.[26] CP-751,871 blocks ligand binding (IGF-1, IGF-2) and induces IGF-IR downregulation by promoting its internalization and degradation.[26]

We conducted a first-in-human phase I, open-label, dose escalation study of CP-751,871 with a primary objective to test the safety and tolerability of CP-751,871 in patients with relapsed or refractory multiple myeloma.

PATIENTS AND METHODS

Patient Selection

Patients with multiple myeloma who had relapsed or were refractory to at least one standard therapy, including autologous stem-cell transplant or tandem transplant, were candidates for this study. Inclusion criteria were as follows: age ≥ 18 years; life expectancy ≥ 3 months; Eastern Cooperative Oncology Group performance status ≤ 2; quantifiable serum (M spike ≥ 1 g/dL) and/or serum free light chain (≥ 20 mg/L) and/or urine (≥ 200 mg/24-hour) M protein; adequate bone marrow function within 2 weeks before treatment defined as an absolute neutrophil count ≥ 1,000/mm^3 and platelets ≥ 75,000/mm^3 (patients who were transfusion- or growth factor-dependent were allowed, provided these values could be achieved with transfusion); adequate organ function within 2 weeks before treatment, defined as: serum creatinine ≤ 2 mg/dL, total bilirubin ≤ 1.5 × the upper limit of normal, AST and ALT ≤ 2.5 × the upper limit of normal, a 12-lead ECG with normal tracing, or nonclinically significant changes that do not require medical intervention, and a transthoracic echocardiography with Doppler with mitral valve thickness ≤ 4 mm, mitral valve gradient ≤ 4 mmHg, and mitral valve regurgitation ≤ mild; and signed written informed consent. Exclusion criteria included any of the following: prior allogeneic stem-cell transplant; or myelosuppressive, immune, radiation, surgical, or investigational therapy within 3 weeks before treatment with CP-751,871; history of second cancer; concurrent significant medical disease; active bleeding; cardiac disease, including valvular dysfunction; symptomatic amyloidosis, cirrhosis, active pancreatitis, active uncontrolled infection; and history of HIV, hepatitis B or C. All patients were required to practice effective birth control. This study was approved by local institutional review boards.

Study Design

Primary end points included safety and tolerability. Secondary end points included pharmacokinetic (PK) parameters of CP-751,871, IGF-IR expression on granulocytes using fluorescence activated cell sorting, serum IGF-1 levels, and antitumor activity as defined by the European Group for Blood and Marrow Transplantation (EBMT) criteria.[27] Toxicities were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Dose-limiting toxicities (DLTs) included any of the following cycle 1 events: grade ≥ 3 treatment-related hematologic adverse events (AEs) that lasted longer than 7 days and/or required therapy; grade ≥ 3 treatment-related nonhematologic, noncardiac AEs despite optimal supportive care; grade ≥ 2 clinical symptoms of hypersensitivity; grade ≥ 2 treatment-related cardiovascular toxicity including arrhythmia, ischemia/infarction, decrease in left ventricular function, cardiac troponin I and T elevation, hypertension or hypotension despite optimal supportive care, myocarditis, pericardial effusion or pericarditis; and any structural and/or functional threshold nonsymptomatic changes in transthoracic Doppler echocardiography parameters, including mitral valve thickness greater than 5 mm, mitral valve gradient larger than 5 mmHg, and/or mitral valve regurgitation more than mild.

Treatment

CP-751,871 was administered intravenously on day 1 of 4-week treatment cycles at doses of 0.025 to 20 mg/kg in dose-doubling dose escalation cohorts of three to six patients.[28] For cohorts one to nine, the dose of CP-751,871 administered on cycle 2 and beyond was reduced by 50% from the dose administered in cycle 1. Cohorts 10 and 11 tested multiple dosing of 10 and 20 mg/kg of CP-751,871, respectively. For each dose escalation, at least three patients had to complete cycle 1 without a DLT. The 10- and 20-mg/kg cohorts were extended to obtain further safety information. At the investigator's discretion, patients could receive salvage therapy with CP-751,871 in combination with dexamethasone in two circumstances: patients at cycle 2 and beyond who would be otherwise discontinued from the study due to disease progression; and patients at cycle 4 or beyond who had experienced less than a partial response to CP-751,871 alone.[29] The dose of dexamethasone administered in combination with CP-751,871 was 40 mg every day orally on days 1 to 4, 9 to 12, and 17 to 20 of the 4-week CP-751,871 cycle for up to three cycles, and 40 mg twice daily orally on days 1 to 4 in all subsequent cycles. Rapamycin alone or with dexamethasone in combination with CP-751,871 was offered to patients enrolled in the 10th and 11th cohorts (10-20 mg/kg CP-751,871) who experienced less than a partial response to single agent CP-751,871 as described earlier. The recommended rapamycin regimen was 2 mg/d orally continuous. Patients could receive CP-751,871 (alone or in combination) therapy until disease progression or intolerable toxicity was observed.

Safety Parameters

Before enrollment, at each treatment visit, and at treatment discontinuation, patients underwent clinical safety laboratory testing (blood chemistry, hematology, urinalysis) and were queried for AEs and concomitant medication use. Transthoracic Doppler echocardiograms were recorded at baseline and within 72 hours before dosing at each treatment cycle. Mitral valve thickness, pressure gradient, and regurgitation were determined. All Doppler echocardiograms were centrally read at the Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic (Rochester, MN). Plasma samples for detection of anti-drug antibodies were also collected before infusion at each cycle and at the end of the study.

PK

All patients had PK blood samples taken at 30 minutes before infusion and at 1 hour and 1, 2, 3, 7, 14, and 21 days after the end of infusion during cycle 1. For subsequent cycles, PK samples were collected at 30 minutes before infusion and 1 hour after the end of infusion. Plasma concentrations of CP-751,871 were analyzed as described previously.[30]

Table 1. Dosing Summary

Dose Cohort (mg/kg)	No. of Patients	No. of Cycles of CP-751,871 Alone	No. of Patients Receiving		No. of Cycles per Cohort	No. of Cycles per Patient
			Dexamethasone	Rapamycin		
0.025	3	4	—	—	5	1-3
0.05	4	5	3	—	14	1-9
0.1	3	17	2	—	21	3-14
0.2	3	21	1	—	29	1-17
0.4	4	12	3	—	29	2-12
0.8	3	16	1	—	18	2-11
1.5	3	6	3	—	24	4-14
3	4	8	3	—	11	2-3
6	3	10	—	—	10	2-5
10*	7	25	6	1	59	2-17
20*	10	14	5	3	32	1-6

*Denotes ongoing dosing cohort.

Pharmacodynamics

Blood samples for the measurement of IGF-1, IGFBP-3, and the acid labile subunit were collected 30 minutes before CP-751,871 infusion and 48 and 72 hours postinfusion on cycle 1, and 30 minutes before infusion on subsequent cycles. Blood samples for the measurement of IGF-IR on circulating granulocytes were collected 30 minutes before infusion and on days 2, 3, 4, 8, 15, and 22 on cycle 1. On subsequent cycles, additional samples were collected 30 minutes before infusion. IGF-IR assays were conducted as previously described.[37] Responses were assessed using the EBMT criteria.[27]

RESULTS

Patient Characteristics

A total of 47 patients were enrolled. Patients received a total of 252 treatment cycles of CP-751,871 with a median of four cycles per patient (range, one to 17). Treatment is ongoing at the 10 and 20 mg/kg cohorts. Table 1 provides a dosing summary for these patients. Demographic characteristics, performance status, disease stage at diagnosis, and prior therapies are detailed in Table 2.

Table 2. Demographic Characteristics

Characteristic	No.	%
Total No. of patients	47	
Age, years		
Mean	61.3	
Range	42-81	
Sex		
Female	17	
Male	30	
Eastern Cooperative Oncology Group performance status		
0	19	
1	16	
2	1	
Clinical stage at diagnosis (Durie-Salmon)		
IA	5	10.6
IIA	10	21.3
IIB	1	2.1
IIIA	27	57.4
IIIB	4	8.5
Prior radiotherapy	15	
Prior chemotherapy/targeted therapy	46	
No. of regimens		
0	1*	
1	9	
2	7	
3	5	
4	3	
> 5	22	
Median	4	
Range	0-8	
Prior transplant	36	
M-spike		
Heavy chain		
Immunoglobin G	38	
Immunoglobin A	3	
Light chain		
λ	4	
κ	2	

*Patient was refractory to autologous stem-cell transplant.

Safety Profile

No CP-751,871-related events of severity higher than grade 3 by National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 were reported. All cases of grade 3 toxicity, and grade 1 and 2 toxicities with a frequency higher than 4% attributed by investigators to CP-751,871 or to the combination of CP-751,871 and dexamethasone are listed in Table 3. No AEs were attributed to the combination of CP-751,871 and rapamycin. A grade 3 event of hyperglycemia was reported at cycle 1 in a patient treated with 20 mg/kg of CP-751,871. This patient discontinued treatment and received one dose of fast acting insulin and oral hypoglycemic agents. Normoglycemia was observed 60 days after CP-751,871 discontinuation. No cycle 1 DLTs were then identified. Grade 3 events of accidental fall and muscle weakness were reported at cycle 3 in a patient who received 20 mg/kg of CP-751,871 in combination with rapamycin and dexamethasone. Study treatment was discontinued in this patient. Anemia was the most common grade 2 AE (five instances), while asthenia was the most common grade 1 toxicity (four instances).

Due to the potential cardiovascular effects of an anti–IGF-IR inhibitor, all patients were monitored using Doppler echocardiogram at the completion of each treatment cycle. Echocardiograms (n = 223) were centrally reviewed at the Mayo Clinic Foundation (Rochester, MN). No medically significant findings were reported. No statistically significant dose-related changes in the echocardiogram parameters investigated were identified. No quantifiable anti-drug antibodies was detected.

Figure 1A depicts the mean plasma concentration-time profiles of CP-751,871 in cycle 1. Plasma CP-751,871 concentrations were mostly below the lower limit of quantification for the two lowest dose levels (0.025 and 0.05 mg/kg). At 0.1 and 0.2 mg/kg, the plasma concentrations declined very rapidly after the end of infusion and were not quantifiable within 7 days. At 1.5 mg/kg and higher dose levels, the decline in plasma concentrations was slower. Plasma CP-751,871 concentration at the end of infusion ($C_{1\ hour}$) and $AUC_{0\text{-}day29}$ increased with dose (Table 4). The increase in $AUC_{0\text{-}day29}$ was approximately dose proportional at dose levels higher than 1.5 mg/kg. Furthermore, dose increases led to decreases in mean plasma clearance and increases in the apparent disposition half-life ($t_{1/2}$) of CP-751,871, likely reflecting an involvement of the IGF-IR in CP-751,871 disposition with saturation of accessible IGF-IR at high CP-751,871 doses. At 20 mg/kg, the plasma clearance and $t_{1/2}$ were not determined since PK sampling within the 28-day cycle did not allow for full characterization of the terminal disposition phase.

Pharmacodynamic Analysis

Figure 1B shows the relative expression of IGF-IR on granulocytes after infusions of CP-751,871 at doses from 0.025 to 20 mg/kg. At doses equal or greater than 0.8 mg/kg, a complete downregulation of granulocyte IGF-IR expression was achieved for the entire dosing period. Similarly, serum IGF-1 concentrations appeared to increase with CP-751,871 dose (Fig 1C), although, in this case, sustained serum IGF-1 elevation was only apparent at doses equal or greater than 6 mg/kg. Similar dose-dependent increases were also observed in circulating acid labile subunit and IGFBP3 (not shown).

Efficacy

No objective responses according to EMBT criteria were seen when CP-751,871 was given as a single agent. However, 28 patients

Table 3. Adverse Events Attributed to CP-751,871

CP-751,871 Group	Adverse Event Grade					
	1		2		3	
	No.	%	No.	%	No.	%
Alone (n = 47)						
Diarrhea	2	4.3				
Anemia			3	6.4	1	2.1
Thrombocytopenia	2	4.3				
Increased AST	3	6.4				
Hyperglycemia					1	2.1
Nausea	2	4.3				
Rash	2	4.3				
In combination with dexamethasone (n = 27)						
Diarrhea	1	3.7	1	3.7		
Asthenia	3	11	2	7.4		
Leg cramps	2	7.4				
Accidental fall					1	3.7
Muscle weakness					1	3.7
Nausea	2	7.4				
Anemia	2	7.4	1	3.7		
Thrombocytopenia	1	3.7	1	3.7		
Increased ALT	3	11				
Increased AST	1	3.7			1	3.7
Increased creatinine	2	7.4				
Hyperglycemia	2	7.4				

experienced disease stabilization with this agent, despite progression at study entry. Median number of treatment cycles with CP-751,871 alone was three. Median duration of stable disease was 2 months (range, 1 to 11). Six patients were stable for at least 6 months with single-agent CP-751,871.

Dexamethasone was added to the treatment regimen of 27 study patients, including two patients who received CP-751,871 with dexamethasone and rapamycin. Nineteen patients experienced disease progression on treatment with CP-751,871 alone. Two patients received only rapamycin and CP-751,871. Eighteen patients opted to discontinue study participation on progression on CP-751,871 alone, were not eligible or not willing to receive dexamethasone or rapamycin. Six partial responses and three minimal responses were observed in patients receiving CP-751,871 in combination with dexamethasone. The characteristics of the responses are summarized in Table 5. Interestingly, two patients with a partial response appeared to be refractory to dexamethasone treatment at study entry. Most of the responses took place at the first cycle of combination regimen and were observed in patients with one to two previous treatments. Median duration of response was 8 months (range, 2 to 14). In addition, 13 patients receiving CP-751,871 and dexamethasone had stable disease (range 2 to 6 months). No objective responses were observed in patients receiving rapamycin.

DISCUSSION

First-in-human studies for monoclonals antibodies in oncology have been historically conducted as "single-agent single-dose" trials.[31,32] Single-dose phase I studies are followed by "single-agent multiple-dose" and subsequently by multiple-dose phase Ib trials of combination with other agents. This approach weighs patient safety but extends phase I testing and is unlikely to provide benefit to patients in its initial steps. In other to expedite the development of CP-751,871 and to provide an opportunity for clinical benefit while ensuring patient safety, the following elements were incorporated in the study design: target patient population was relapsed or refractory to standard therapy; patients had to meet inclusion criteria at each treatment cycle; the dose of CP-751,871 administered on cycle 2 and beyond was reduced to 50% from the cycle 1 dose; patient must have responded to therapy on study or remain stable for readministration; patients who experienced disease progression with single-agent CP-751,871 had to add dexamethasone (dexamethasone and/or rapamycin for cohorts 10 and 11) to their CP-751,871 regimen (salvage therapy) to continue on study. Dose reduction at cycle 2 and beyond was conducted to minimize the potential for drug accumulation (ie, CP-751,871 plasma concentrations would not exceed those already tested at cycle 1, assuming a half-life close to that of a natural immunoglobulin). The addition of salvage therapy with dexamethasone provided an opportunity to extend CP-751,871 testing, including multiple dose PK, and to explore the safety of CP-751,871 with an agent commonly employed in multiple myeloma regimens that has shown synergy with anti–IGF-IR therapy in preclinical models.[6] Addition of rapamycin was considered at cohorts 10 and 11 based on a potential synergy of mammalian target of rapamycin inhibitors with dexamethasone[33,34] and IGF-IR inhibitors.[35-36]

CP-751,871 was safe and well tolerated as a single agent and in combination with dexamethasone. Addition of rapamycin also appeared safe, but further testing is necessary due to the limited number of subjects that received that agent. A grade 3 event of hyperglycemia was reported. Hyperglycemia has also been observed in other CP-751,871 studies.[30] Its mechanism is currently unknown; however, multiple evidence support a role the IGF-IR pathway in glucose

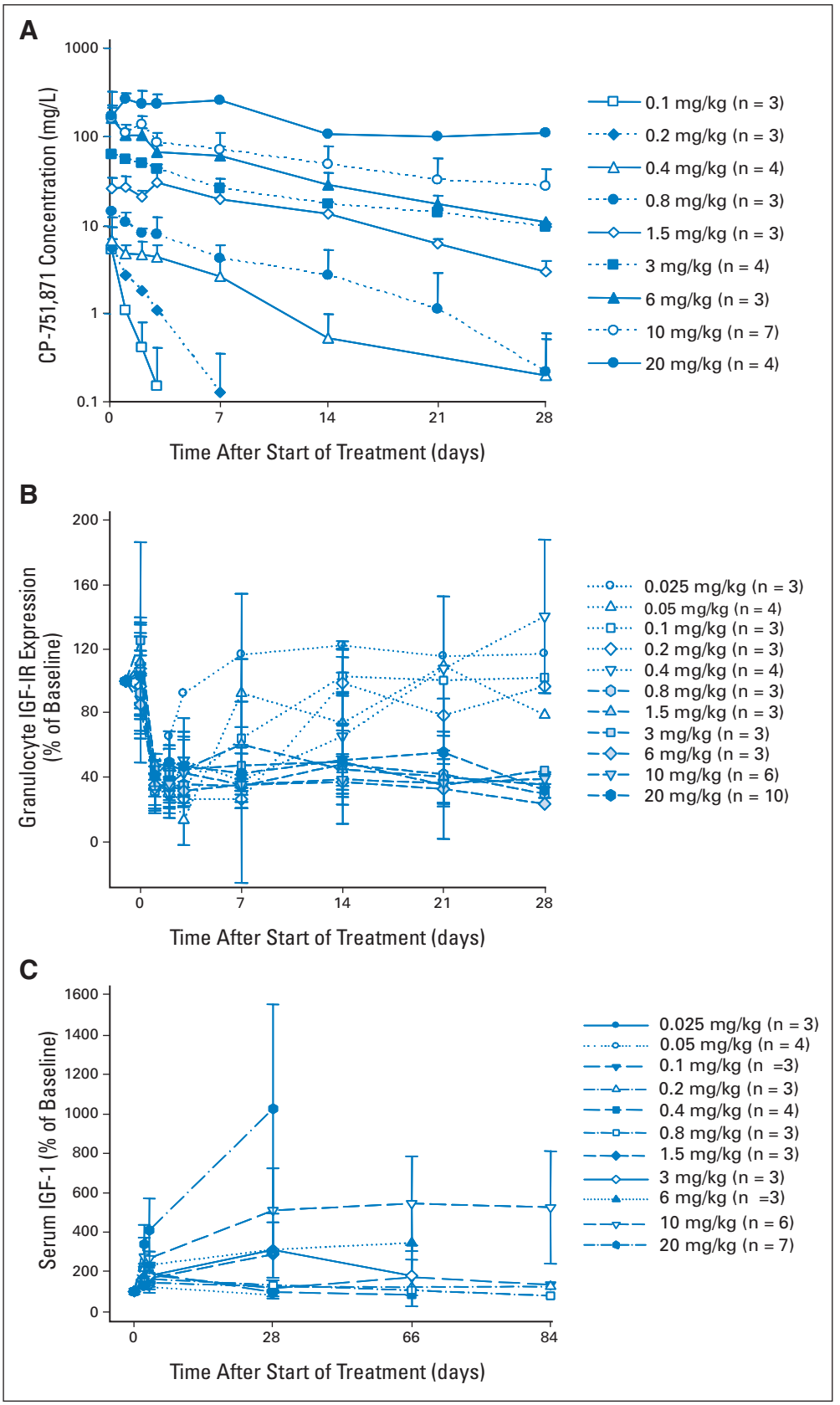

Fig 1. (A) Mean (± standard deviation) plasma concentration-time profiles of CP-751,871 in multiple myeloma patients after cycle 1 CP-751,871 treatment. (B) Anti–insulinlike growth factor 1 receptor (IGF-IR) expression on granulocytes after CP-751,871 infusion. Data are represented as percentage of baseline fluorescence intensity. (C) Serum insulinlike growth factor 1 (IGF-1) levels in patients receiving CP-751,871 alone. Data are represented as percentage of baseline levels.

Table 4. Pharmacokinetic Parameters of CP-751,871 in Patients With Multiple Myeloma During Cycle 1 Treatment

Dose (mg/kg)	No.	C_{1hr} (mg/L)		$AUC_{0\text{-}day29}$ (mg × hr/L)		CL (L/d/kg)		Vd (L/kg)		$t_{1/2}$ (day)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0.1	3	5.32	6.85	82.6	154*	0.0307†	0.0307†	0.059†	0.059†	1.3†	
0.2	3	5.36	1.52	248	26	0.020	0.003	0.046	0.011	1.7	0.6
0.4	4	6.66	2.84	1,000	477	0.012	0.008	0.065	0.027	4.6	2.8
0.8	3	12.2	16.9*	2,180	1,360	0.010	0.005	0.072	0.022	5.3	1.4
1.5	3	26.0	9.0	8,820	4,320	0.0041	0.0025*	0.073	0.022*	12.3	6.0*
3	4	62.7	13.5	15,100	6,430	0.0052	0.0009‡	0.079	0.028‡	10.3	2.2‡
6	3	159	57	26,900	4,450	0.0046	0.0008	0.078	0.025	11.6	3.5
10	7	160	66	37,200	17,300	0.0090	0.0088§	0.095	0.036§	10.1	4.0§
20	4	171	147	90,000	38,500	NE	NE	NE	NE	NE	NE

Abbreviations: $C_{1\ hour}$, plasma concentration at 1 hour after the end of infusion; $AUC_{0\text{-}day29}$, total area under the plasma concentration-time curve during cycle 1 (time 0 to day 29); CL, clearance; Vd, apparent volume of distribution; $t_{1/2}$, apparent disposition half-life; NE, not estimable.
*n = 2.
†n = 1.
‡n = 3.
§n = 5.

metabolism.[38-41] One case of grade 3 and two cases of grade 2 anemia were observed. A role for IGF-1 in erythropoiesis have been long proposed, and the IGF-IR is found on both erythrocyte precursors as well as mature erythrocytes.[42,43] However, anemia is also commonly found in patients with refractory multiple myeloma and was reported as a prestudy condition in 15 of our study patients. Mild diarrhea and other transient nonspecific gastrointestinal symptoms were reported. This is not surprising as the IGF-IR is expressed in the gastrointestinal track.[44] Gastrointestinal symptoms are frequently observed with somatostatin analogs that suppress IGF-1 production.[45] In summary, systemic inhibition of the IGF-IR in patients with myeloma did not translate to significant toxicity. CP-751,871 did not appear to affect the toxicity profile of dexamethasone or rapamycin; however, this is difficult to determine due to the absence of a control arm and the small number of patients in this study.

PK and pharmacodynamic of CP-751,871 were also characterized. Escalating doses of CP-751,871 resulted into increasing plasma exposures ($C_{1\ hour}$ and AUC_{last}) and PK profiles were consistent with target-mediated disposition.[46] Based on results from this and three other CP-751,871 phase I studies, the $t_{1/2}$ of CP-751,871 at the 20 mg/kg dose is estimated to approach that of endogenous IgG2 (approximately 20 days). At doses of 0.8 mg/kg or higher, CP-751,871 induced a sustained lack of expression of granulocyte IGF-IR receptor. IGF-IR downregulation by internalization and degradation appears to be a common effect of antibodies against this receptor.[26,47,48] Of note, a residual expression of approximately 25% to 30% of the baseline levels was observed despite excess CP-751,871. This is likely to be an artifact due to nonspecific binding of the 1H7 anti–IGF-IR analytic antibody to human leukocytes. Doses equal or greater than 1.5 mg/kg caused transient increases in serum IGF-1; however, sustained IGF-1 accumulation was only apparent at doses equal or greater than 6 mg/kg. IGF-1 accumulation has been previously reported in children born with inactivating mutations of the IGF-IR,[49] suggesting that high doses of CP-751,871 result into systemic IGF-IR inhibition. Importantly, doses of 6 mg/kg for 4 weeks resulted in end of cycle plasma concentrations of CP-751,871 similar to those needed for complete downregulation of the IGF-IR in tumor xenografts, approximately 35 μg/mL.[26]

Six patients that received only CP-751,871 had a best response of stable disease ≥ 6 months. This activity was encouraging, given that all patients were progressing at enrollment. Furthermore, nine of 27 patients experienced objective responses according to EMBT criteria

Table 5. Objective Responses

Patient ID	Initial Stage (DS)	Year	CP-751,871 Dose (mg/kg/4 wk)*	Cycle When Dexamethasone Was Added	Response in Cycle No.	No. of Prior Treatments	Last Treatment	Response Duration (months)
2005	IIA	1999	0.05	3	PR C3	1	Dexamethasone	7
2002	IIIA	1999	0.2	10*	PR C11	2	Transplant	7
1009	IIA	2002	0.4	3	PR C5	1	Transplant	8
2019	IIA	2000	1.5	3	MR C5	4	Velcade	2
2021	IIIA	2003	1.5	4	MR C4	1	Transplant	11
2025	IA	2002	10	4	PR C4	2	Dexamethasone	9
2027	IA	2000	10	3	PR C3	1	Transplant	9
3101	IIIA	2004	10	4	PR C4	1	Transplant	14
6101	IIB	2003	20	2	MR C2	1	Transplant	6

Abbreviations: DS, Durie-Salmon; PR, partial response; MR, XXX.
*Patient with disease stabilization on CP-751,871 alone at the time of the addition of dexamethasone. Other patients were on progressive disease at the time of the addition of dexamethasone.

when CP-751,871 was combined with dexamethasone. This included two patients who received also rapamycin but did not experience a response. This response rate (33%) is similar to that observed with dexamethasone alone in the refractory myeloma setting (18%).[50] Of interest, two patients with a partial response were progressing from dexamethasone regimens at study entry, suggesting that IGF-IR may act as a mechanism of resistance to dexamethasone-induced tumor cell death.[6,14,51] However, formal phase II testing will be required to support that hypothesis.

In conclusion, CP-751,871 was safe and well tolerated in patients with multiple myeloma. On the basis of its safety, PK and pharmacodynamic profiles the dose regimens of 6-20 mg/kg for 4 weeks have been selected for further investigation in phase II studies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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