PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

GENERIC DRUG NAME / COMPOUND NUMBER: Figitumumab / CP-751,871

PROTOCOL NO.: A4021010

PROTOCOL TITLE: Phase 1, Open Label, Multiple Dose Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of CP-751,871 in Patients With Advanced Solid Tumors

Study Centers: A total of 3 centers took part in the study and enrolled subjects; 2 in the United States (US) and 1 in the United Kingdom (UK).

Study Initiation, Primary Completion and Final Completion Dates:

Study Initiation Date: 01 August 2005;

Final Completion Date: 26 October 2012;

Primary Completion Date: 31 January 2011 (2 subjects were ongoing at data cut-off).

Phase of Development: Phase 1

Study Objectives:

Primary Objective:

- To define the safety, tolerability, maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of figitumumab in subjects with advanced solid tumors.

Secondary Objectives:

- To characterize the pharmacokinetics (PK) of figitumumab;
- To explore the effect of figitumumab on the number of circulating tumor cells (CTCs) and CTCs expressing insulin-like growth factor 1 receptor (IGF-IR);
- To evaluate any human anti-human antibody (HAHA) response to figitumumab.

METHODS

Study Design: This was an open-label, multiple-dose escalation, multiple-center Phase 1 study in subjects with histologically or cytopathologically confirmed advanced solid tumors,

conducted to define the MTD of figitumumab and explore its suitability as a Phase 2 dose. It was estimated that up to 36 months would be required to complete this study.

The MTD was defined as the highest dose level at which not >1 dose-limiting toxicity (DLT) was observed during Cycle 1 in 6 subjects.

DLTs were defined as any 1 of the following adverse events (AEs) that occurred in Cycle 1 following treatment with figitumumab and were considered related to the drug:

- Any National Cancer Institute Common Terminology Criteria for AEs version (v) 3.0 (CTCAE) Grade ≥4 treatment-related hematologic AEs (that lasted >7 days) and/or required therapy;
- Any CTCAE Grade ≥3 treatment-related non-hematologic AEs despite optimal supportive care;
- Grade 2 or greater allergic reaction or infusion reaction (required therapy but responded promptly to symptomatic treatment) that affected vital organs;
- Mitral valve regurgitation more than mild.

The RP2D was based on the review of the safety and tolerability observed at Cycle 1 and any Late Onset Drug Related Toxicity (LODRETs) identified. LODRETs were defined as treatment-related toxicities similar to those described under the DLT (Cycle 1) definition that occurred in subjects dosed at Cycle 2 and beyond.

In order to characterize the safety and tolerability of the RP2D in the adrenocortical carcinoma (ACC) and sarcoma (Ewing's sarcoma, desmoplastic small round cell tumors, synovial sarcoma, and rhabdomyosarcoma) subject populations, a Phase 1 extension cohort (ACC + Sarcoma Extension Cohort) was to enroll up to 24 subjects with these histologies. In addition, a Phase 1 extension cohort was to enroll up to 12 subjects, ≥9 years old, with Ewing's sarcoma family of tumors (ESFT Extension Cohort) histology to further characterize the safety and tolerability of the RP2D in this subject population.

The study visit schedule is shown in Table 1.

Table 1. Visit Schedule

Observation (Time Relative to Start of Study Treatment)	Screen	Day 1 (Predose)	Day 1 (Postdose)	Day 2	Day 4	Day 8	Day 15-21 (Day 14-28 for ESFT Extension Cohort)	End of Study[a]	Follow-Up[a]
Informed consent[b]	X								
Complete medical history	X								
Baseline signs and symptoms	X								
ECOG PS	X	X[c]						X	
Vital signs (temperature, blood pressure, pulse, weight, and height [only at screening])	X	X[c]						X	X
Physical examination	X	X[c]						X	X
Electrocardiogram	X								
Doppler echocardiography[d]	X						X	X	X
Anonymous genotyping	X								
Safety laboratories (Hematology, chemistry, coagulation, urinalysis), albumin[e] and IgG[e]	X[f]	X[c]						X	X
Concomitant medication	X	Assessed at each study visit							
Biomarkers[g]	X	X		X	X	X	X	X	
Safety evaluation (AE monitoring)		Assessed at each study visit, and as clinically indicated							
Study drug administration			X						
Pregnancy test	X[h]								
Pharmacokinetics		X[i]	X[j]	X[k]	X[l]	X[l]	X[l]	X	X
Tumor assessment	X[m]						X[n]		X
HAHA sample[o]		X							X

AE = adverse event; ESFT = Ewing's sarcoma family of tumors; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HAHA = human anti-human antibodies; IgG = immunoglobulin G.

a. An end-of-study visit occurred approximately 28 days following the last dose of study drug. Follow-up visits could be scheduled, as needed, to monitor AEs for up to 150 days from the last dose of study drug, unless the subject withdrew consent or received another treatment for his/her disease. At the last scheduled follow-up visit, a pharmacokinetic (PK) and HAHA blood sample was collected.
b. Parent or legal guardian consent or subject assent/parent permission was required for minors as per institutional practice.
c. Beginning in Cycle 2, predose activities (except for the collection of the biomarker and PK samples) could be done up to 72 hours predose. Physical

Table 1. Visit Schedule

examination and ECOG PS were done up to one week before dosing.

d. Doppler echocardiograms were performed at screen, Day 15 in Cycles 1 and 4, and End-of-Study Visits. Additional Doppler echocardiograms could be performed if medically warranted.
e. Albumin and IgG were done at Screening and End of study only.
f. Hematology, coagulation, chemistry, and urinalysis had to be done within 2 weeks prior to dosing.
g. Biomarkers included: 1) Circulating tumor cells (CTCs) and insulin-like growth factor 1 receptor (IGF-IR) positive CTCs. Predose samples for CTCs and IGF-IR positive CTCs were collected on Day 1, 30 minutes prior to dosing in all cycles (up to 17). In addition, samples on Days 2, 4, 8, and 15 were collected only in Cycle 1; samples for these biomarkers were also collected on Day 2 during Cycle 4 only for subjects in the dose extension cohort at MTD. CTC blood samples were collected from the adrenocortical carcinoma and sarcoma, and ESFT subject recommended Phase 2 dose extension cohorts. 2) Additional biomarkers included paraffin sections from previous diagnostic biopsy, pre-treatment and post treatment tumor biopsy. Diagnostic paraffin sections, when available, could be obtained at any time during the study. Optional tumor biopsy(ies) could be obtained providing the subject signed the appropriate consent. 3) Blood samples for tumor burden markers, ie, PSA or CA125, were collected at screen and end of study. Additional samples were collected as required.
h. Pregnancy test was done within 72 hours of dosing. Results had to be available before dosing.
i. PK samples were collected approximately 30 minutes prior to dosing for all cycles (up to 17).
j. PK samples were collected 1 hour post figitumumab infusion in Cycles 1-4.
k. PK samples were collected 24 hour post figitumumab infusion in Cycle 1 for subjects in the dose escalation part of the study and in Cycle 1 and Cycle 4 for subjects participating in the extension cohort at maximum tolerated dose (MTD).
l. Samples was collected on Days 4, 8, and 15 in Cycle 1 for subjects participating in the dose escalation part of this study, and on Cycle 1 and Cycle 4 for subjects enrolled in the extension cohort at MTD. Only Day 1 PK samples are required Ewing's subjects.
m. Tumor assessment was done within 4 weeks of dosing.
n. Beginning in Cycle 2 (prior to Cycle 3), a tumor assessment (eg, computed tomography [CT] or bone scan) had to be completed within 1-10 days prior to next cycle (and done at least every other cycle (ie, prior to Cycles 3, 5, 7, etc.). To confirm an objective response tumor measurement, CT scan was repeated no <4 weeks later. Additional scans could be performed if required.
o. HAHA samples were collected in Cycle 1 approximately 30 minutes prior to dosing and during the last scheduled follow-up visit.

Number of Subjects (Planned and Analyzed): Cohorts of 3-6 subjects were planned at each dose level. Additional subjects were to be accrued at the RP2D level to confirm safety and tolerability. It was estimated that approximately 60 subjects were needed to achieve the study objectives. A total of 71 subjects were enrolled (42 in the US and 29 in the UK) in the study. Of these, 65 subjects (38 in the United States [US] and 27 in the United Kingdom [UK]) entered the study. All 65 subjects received at least 1 dose of study treatment and were evaluable for safety. All 65 subjects were also included in the efficacy evaluations.

Diagnosis and Main Criteria for Inclusion: The study included male or female subjects (≥18 years) with histologically or cytopathologically confirmed advanced solid tumors, relapsed or refractory to standard therapy, or for whom no effective therapy existed. Subjects must have had a diagnosis of Ewing's sarcoma family tumors (ESFT), an Eastern Cooperative Oncology Group performance status 0-1 and trivial or lesser degree of mitral valve regurgitation as determined by Doppler echocardiogram.

Study Treatment: Figitumumab was supplied as a liquid solution administered as an intravenous (IV) infusion over 2.5 hours (±15 minutes) on Day 1 of each cycle. Each cycle was 21 days (dose administered every 3 weeks [q3w]) in duration for all cohorts except the ESFT Extension Cohort. Because the ESFT Extension Cohort could enroll pediatric subjects (9 years of age or older), the cycle duration for that cohort was 4 weeks to ensure that pediatric subjects did not receive a higher cumulative dose of figitumumab than adult subjects. The starting dose of figitumumab was 3 mg/kg. A lower starting dose (1.5 mg/kg) could have been employed if late toxicities were observed in the 3 mg/kg cohort of the previous (an open label Phase 1 study of CP-751,871 in patients with multiple myeloma [NCT01536145]) trial, the first in human study of figitumumab conducted in multiple myeloma subjects.

The dose of figitumumab was reduced and/or delayed in subjects experiencing DLTs or related recurrent toxicity that was subjectively intolerable (except alopecia). Dosing resumed once signs and symptoms of toxicity returned to Baseline or to ≤Grade 1 or deemed irreversible by the Investigator.

Within each dose level (cohort), there was no required waiting period between subjects. Dose escalation (opening of a new cohort of subjects) occurred only after all the subjects in the previous cohort completed at least 3 weeks of monitoring following the first dose of figitumumab. The assessment of safety and tolerability data of all subjects within a cohort guided the dose escalation. The dose escalation followed a dose-doubling schema with 3 to 6 subjects per dose level cohort. The dose escalation was to change to 40% dose step increments when 2 or more subjects with similar moderate (CTCAE Grade 2) drug-related toxicities or 1 out of 6 subjects with DLTs were observed after the first infusion of figitumumab (Cycle 1). Intra-subject dose escalation was not permitted. The dose escalation schema is outlined the 3 subject cohorts with decision to dose escalate or expand in Table 2.

Table 2. Dose Escalation Scheme

Three Subject Cohorts With Decision to Dose Escalate or Expand	
Drug-related Toxicity	**Dose Escalation**
No DLT and <2 similar CTCAE Grade 2	Dose escalate 100% of previous dose
No DLT and 2 or more similar CTCAE Grade ≥2	Dose escalate 40% of previous dose
DLT in 1/3	Expand cohort up to 6 subjects
DLT in 1/6	Dose escalate 40% of previous dose
DLT in ≥2/3-6	Stop dose escalation Define MTD at a lower dose (either the previous dose level was expanded with 3 additional subjects or a new dose level was to be evaluated between the previous and current dose levels).
MTD Cohort Extension	
• Up to 12 subjects evaluable for safety. • If the MTD was not identified, up to 12 subjects were evaluated at the highest dose administered without DLT toxicity.	
ACC and Sarcoma Extension	
• Up to 24 subjects evaluable for safety. • If the MTD was not identified, subjects were evaluated at the highest dose administered without DLT toxicity.	
ESFT Extension	
• Up to 12 subjects evaluable for safety. • If the MTD was not identified, subjects were evaluated at the highest dose administered without DLT toxicity using an every 4 weeks (q4w) dosing regimens.	

ACC = adrenocortical carcinoma; CTCAE = Common Terminology Criteria for Adverse Events; DLT = dose-limiting toxicity; ESFT = Ewing's sarcoma family of tumors; MTD = maximum tolerated dose.

Subjects were treated for a minimum of 1 cycle and could continue therapy with figitumumab for up to 17 cycles unless disease progression or unacceptable toxicity developed. Provisions could have been be made for the continuation of dosing beyond 17 cycles if there was continued safety and toleration.

Efficacy, Safety and Pharmacokinetic Endpoints:

Primary Endpoint:

- Safety, tolerability and MTD

Secondary Endpoints:

- PK parameters
- CTC number
- IGF-IR-positive CTC number
- HAHA

Safety Evaluations: Safety evaluations included AEs, clinical examination (including blood pressure and pulse rate), laboratory tests (hematology, chemistry, coagulation function, and

urinalysis), 12-lead electrocardiograms (ECGs) and Doppler echocardiogram. The Sponsor was to be notified by the Investigator within 24 hours of awareness of any serious adverse event (SAE). The reporting period for SAEs began from the time that the subject provided informed consent through and including 150 calendar days after the last administration of the study drug. All subjects who received at least 1 dose of study medication were considered evaluable for safety analyses. The analysis of safety was extended through 150 days after the last administration of study drug.

Statistical Methods:

Analysis Populations: Subjects not enrolled to the study (ie, screen only subjects) was not included in any analysis. Three populations were analyzed for this study:

- Full analysis population was defined as all enrolled subjects.
- Per Protocol population referred to all subjects enrolled in the dose finding phase of the study (ie, not including the RP2D extension cohorts) who did not have a major treatment deviation in the first cycle of treatment.
- Safety analysis population was defined as all enrolled subjects who started treatment.

Efficacy Evaluations: Measurable disease was not a required inclusion criterion in this study. Disease and response assessment were investigated in an exploratory fashion and defined using the Response Evaluation Criteria in Solid Tumors. Changes in tumor size were categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease, the latter incorporating the appearance of new lesions. For subjects with either complete or partial response, additional assessments were required for confirmation of response. Confirmatory assessments were done no less than 4 weeks after the response was initially documented.

Pharmacokinetic Evaluations: All PK concentration data were included in concentration-time summaries unless actual time postdose was missing, or deviated by >20% from the planned time. Where actual time postdose was missing or anomalous, available data for the sample were reviewed in context with other samples for the same subject. Samples were included in PK parameter calculations using nominal time if review of the available data suggested this would be a reasonable assumption. Otherwise, samples with missing or anomalous actual time were excluded from all analyses. All subjects with sufficient concentration-time data to support PK parameter calculations were included in the analysis of PK parameters. Figitumumab PK parameters were obtained from analysis of the plasma concentration time data using non-compartmental methods.

If a subject's predose figitumumab concentration was above the lower limit of quantification (LLOQ), this Baseline concentration value was subtracted from all concentrations prior to analysis and reporting. A value of 0 was used for any samples where the result of the Baseline correction was negative. Unless otherwise specified, all PK results presented are for Baseline-corrected data.

The figitumumab PK parameters defined included maximum observed plasma concentration (C_{max}), time to first occurrence of C_{max} (T_{max}), area under the plasma concentration-time curve from time 0 to the time for the last quantifiable concentration (AUC_{last}), area under the plasma concentration-time curve from time 0 extrapolated to infinity (AUC_{inf}), area under the plasma concentration-time profile within the dosing interval (AUC_{tau}), terminal plasma elimination half-life ($t_{½}$), renal clearance (CL_R), and the volume of distribution estimated from terminal phase (V_z).

The PK parameters were calculated for each subject for Cycle 1 and/or Cycle 4, as applicable, using non-compartmental analysis of Baseline-corrected plasma concentration-time data. Samples below the LLOQ were set to 0 for analysis. Actual sample collection times relative to the end of infusion were used for PK parameter calculations. Infusion time (2.5 hours) was considered negligible in comparison with the sample collection period (3 or 4 weeks), and was not included in the parameter calculations. Cycle 2 and Cycle 5 predose samples were included in PK parameter calculations for Cycle 1 and Cycle 4, respectively. In addition, AUC_{last}, and/or AUC_{inf} (as applicable) were not reported if the predose sample for the next cycle was missing.

Safety Evaluations: Safety data were summarized by dose levels for all treated subjects using appropriate tabulations and descriptive statistics. All subjects who received at least 1 dose of study medication were evaluable for safety analyses. The analysis of safety extended through 150 days after the last administration of study drug and included AEs and laboratory test results.

RESULTS

Subject Disposition and Demography: Seventy-one subjects were screened for this study and 65 received treatment. Three centers enrolled subjects with the following overall percentages: 2 centers in the US each enrolled 41.5% of subjects, and 1 center in the UK enrolled 16.9% of subjects. Two subjects, both in the ESFT extension cohort, remained on treatment as of the data cutoff for the clinical study report. A summary of subject evaluation groups is provided in Table 3.

The largest proportion of subjects in each cohort discontinued the study due to disease progression (45 [69.2%] subjects overall; Table 4). Death due to disease progression was the reason for study discontinuation for 2 subjects, both in the 20 mg/kg RP2D Extension Cohort, and an additional 2 subjects, both in the 20 mg/kg ACC + Sarcoma Extension Cohort, discontinued from the study due to treatment-related AEs (Grade 4 proteinuria in 1 subject, AE not specified in the other subject).

A summary of demographic characteristics for subjects in this study is presented in Table 5. The demographic and baseline characteristics were similar among the treatment cohorts, except for gender in the 20 mg/kg RP2D Extension Cohort (males n=12 [92.3%], females n=1 [7.7%]) and the ESFT Extension Cohort (males n=8 [72.7%], females n=3 [27.3%]). Of note, the ESFT Extension Cohort could enroll pediatric subjects who were at least 9 years old and 5 subjects <18 years old were enrolled in this cohort.

Table 3. Subject Evaluation Groups

Number of Subjects		Figitumumab						
		3 mg/kg N=3 n (%)	6 mg/kg N=3 n (%)	10 mg/kg N=3 n (%)	20 mg/kg N=3 n (%)	20 mg/kg RP2D N=13 n (%)	20 mg/kg RP2D ACC + Sarcoma N=29[a] n (%)	20 mg/kg RP2D ESFT N=11 n (%)
Planned	60							
Screened	71							
Assigned to treatment	65							
Treated		3	3	3	3	13	29	11
Completed		0	0	0	0	1 (7.7)	0	1 (9.1)
Discontinued		3 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	12 (92.3)	29 (100.0)	8 (72.7)
Ongoing at date of cutoff		0	0	0	0	0	0	2 (18.2)
Evaluability:								
Without first cycle major deviation[b]		3 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	13 (100.0)	29 (100.0)	11 (100.0)
Analyzed for safety								
Adverse events		3 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	13 (100.0)	29 (100.0)	11 (100.0)
Laboratory data		3 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	13 (100.0)	29 (100.0)	11 (100.0)

ACC = adrenocortical carcinoma; ESFT = Ewing's sarcoma family of tumors; N = total number of subjects in each treatment group; n = number of subjects; RP2D = recommended Phase 2 dose.

a. A subject enrolled in the ESFT cohort received Cycle 2 after 21 days; data collected from this subject, because of programming issues, were summarized in the ACC+Sarcoma Cohort in the tables. The subject was 21 years old.

b. First cycle major deviations include: <75% of the planned Cycle 1 dose of figitumumab (provided the reduction is not due to toxicity); >125% of the planned Cycle 1 dose of figitumumab; or protocol mandated prophylaxis (prior to Day 1 of study start) not administered.

Table 4. Discontinuations From Study

Number of Subjects	Figitumumab						
	3 mg/kg N=3 n (%)	6 mg/kg N=3 n (%)	10 mg/kg N=3 n (%)	20 mg/kg N=3 n (%)	20 mg/kg RP2D N=13 n (%)	20 mg/kg RP2D ACC + Sarcoma N=29 n (%)	20 mg/kg RP2D ESFT N=11 n (%)
Subject died	0	0	0	0	2 (15.4)	0	0
Discontinuation related to study drug	0	0	0	0	0	2 (6.9)	0
Adverse event	0	0	0	0	0	2 (6.9)	0
Discontinuation not related to study drug	3 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	10 (76.9)	27 (93.1)	8 (72.7)
Adverse event	0	0	0	0	1 (7.7)	5 (17.2)	0
Laboratory abnormality	0	0	0	0	0	1 (3.4)	0
No longer willing to participate in study	0	0	0	1 (33.3)	0	1 (3.4)	1 (9.1)
Other	0	1 (33.3)[a]	0	0	1 (7.7)[b]	0	0
Progressive disease	3 (100.0)	2 (66.7)	3 (100.0)	2 (66.7)	8 (61.5)	20 (68.9)	7 (63.6)
Total	3 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	12 (92.3)[c]	29 (100.0)	8 (72.7)[c]

ACC = adrenocortical carcinoma; ESFT = Ewing's sarcoma family of tumors; N = total number of subjects in each treatment group; n = number of subjects; RP2D = recommended Phase 2 dose.

a. Subject taken off treatment to receive dexamethasone.
b. One subject discontinued due to right hip pain present at Baseline.
c. Subject completed all study treatment which was not collected as treatment discontinuation.

Table 5. Demographic Characteristics

Number of Subjects	Figitumumab						
	3 mg/kg N=3	6 mg/kg N=3	10 mg/kg N=3	20 mg/kg N=3	20 mg/kg RP2D N=13	20 mg/kg RP2D ACC + Sarcoma N=29	20 mg/kg RP2D ESFT N=11
Gender, n							
Males	2	1	2	3	12	16	8
Females	1	2	1	0	1	13	3
Age (years)							
0-<18	0	0	0	0	0	0	5
18-<65	3	3	3	2	12	28	6
65-<70	0	0	0	1	1	0	0
>70	0	0	0	0	0	1	0
Mean	59.0	60.7	48.0	58.3	50.2	40.3	27.1
SD	3.5	1.5	9.5	6.7	9.7	14.1	16.3
Range	55-61	59-62	37-54	54-66	33-68	18-77	12-63
Race, n							
White	3	3	3	3	13	27	11
Black	0	0	0	0	0	1	0
Other	0	0	0	0	0	1	0
Weight (kg)							
Mean	79.9	71.5	88.5	92.7	88.1	82.0	71.8
SD	22.8	20.7	10.4	18.1	17.0	26.7	20.2
Range	58.3-103.7	57.6-95.3	76.7-96.4	78.3-113.0	67.5-124.7	53.1-180.1	46.8-113.0
Height (cm)							
Mean	171.6	162.2	175.3	185.4	178.4	173.8	173.5
SD	10.1	11.8	9.5	2.6	6.4	9.4	11.9
Range	160.0-177.8	152.3-175.3	165.1-184.0	182.9-188.0	167.6-189.5	156.5-193.0	152.0-188.0

ACC = adrenocortical carcinoma; ESFT = Ewing's sarcoma family of tumors; N = total number of subjects in each treatment group; n = number of subjects; RP2D = recommended Phase 2 dose; SD = standard deviation.

Efficacy and Pharmacokinetic Results:

Efficacy Results: Two subjects achieved a response to treatment (Table 6), 1 CR and 1 PR, both occurred in subjects in the ESFT Extension Cohort who had measurable disease at Baseline. Both responses were durable as these subjects maintained response for over 2 years. No other cohorts had subjects who responded, however a best response of SD was observed in multiple histological tumor types. Two subjects each in the 20 mg/kg RP2D and ESFT Extension Cohorts had SD for approximately 1 year or longer.

Table 6. Summary of Best Overall Response

	With Measurable Disease at Baseline		Without Measurable Disease at Baseline	
	20 mg/kg RP2D ACC + Sarcoma (N=29) n (%)	20 mg/kg RP2D ESFT (N=11) n (%)	20 mg/kg RP2D ACC + Sarcoma (N=29) n (%)	20 mg/kg RP2D ESFT (N=11) n (%)
Number of subjects	26 (100)	10 (100)	3 (100)	1 (100)
Complete response	0	1 (10.0)	0	0
Partial response	0	1 (10.0)	0	0
Stable/No response	8 (30.8)	5 (50.0)	3 (100)	1 (100)
Objective progression	13 (50.0)	3 (30.0)	0	0
Symptomatic deterioration	0	0	0	0
Early death	0	0	0	0
Indeterminate	5 (19.2)	0	0	0
Objective Response Rate (CR+PR)	0	2 (20.0)	0	0
95% Exact CI*	[0.0, 13.2]	[2.5, 55.6]	[0.0, 70.8]	[0.0, 97.5]

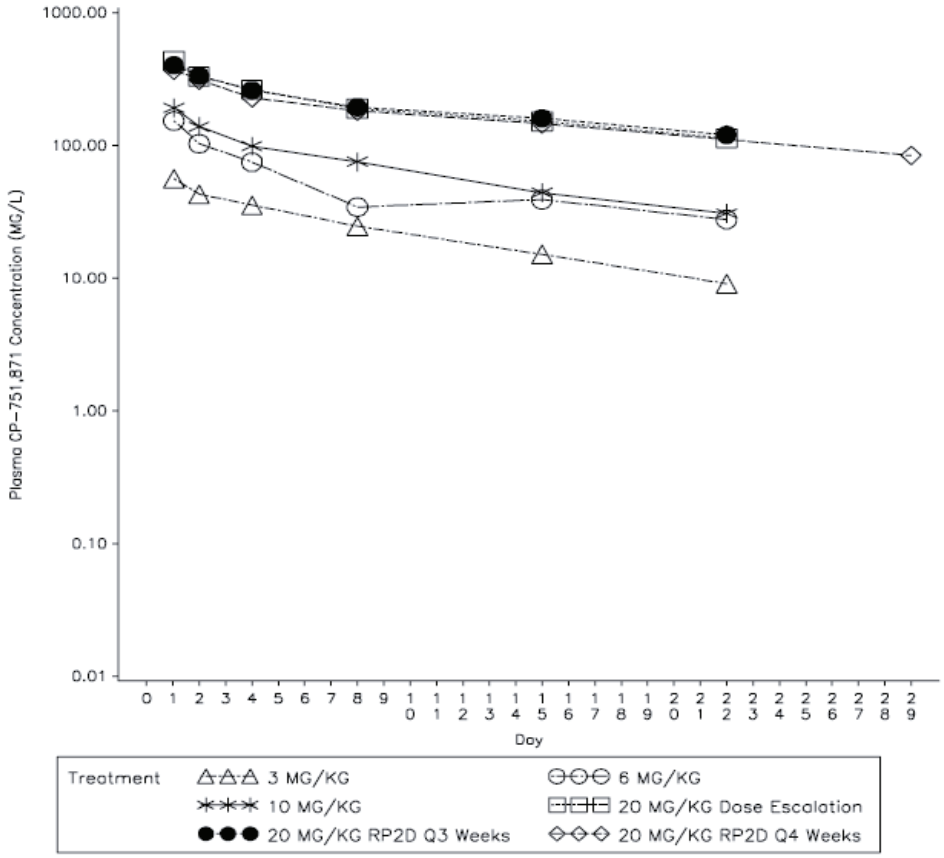
* Using exact method based on binomial distribution.
ACC = adrenocortical carcinoma; CI = confidence interval; CR = complete response; ESFT = Ewing's sarcoma family of tumors; PR = partial response; RP2D = recommended Phase 2 dose.

Pharmacokinetic Results: The plasma concentration-time profiles of figitumumab were evaluated in Cycle 1 for all subjects and in Cycle 4 for subjects of the RP2D extension cohorts.

Following an IV infusion, plasma figitumumab concentrations decreased slowly in a multi-exponential manner. There was a dose-dependent increase in plasma figitumumab concentrations during the dose range evaluated (Figure 1 and Figure 2). As the dose increased from 3 to 20 mg/kg for the dose escalation cohorts, the mean values of C_{max} and area under the plasma concentration-time profile from time 0 to 504 hours (21 days) (AUC_{504}) in Cycle 1 both increased approximately 8-fold (Table 7). The limited number of subjects enrolled in the dose escalation cohorts did not permit definitive comparison of CL, V_z, and $t_{½}$ across the tested doses.

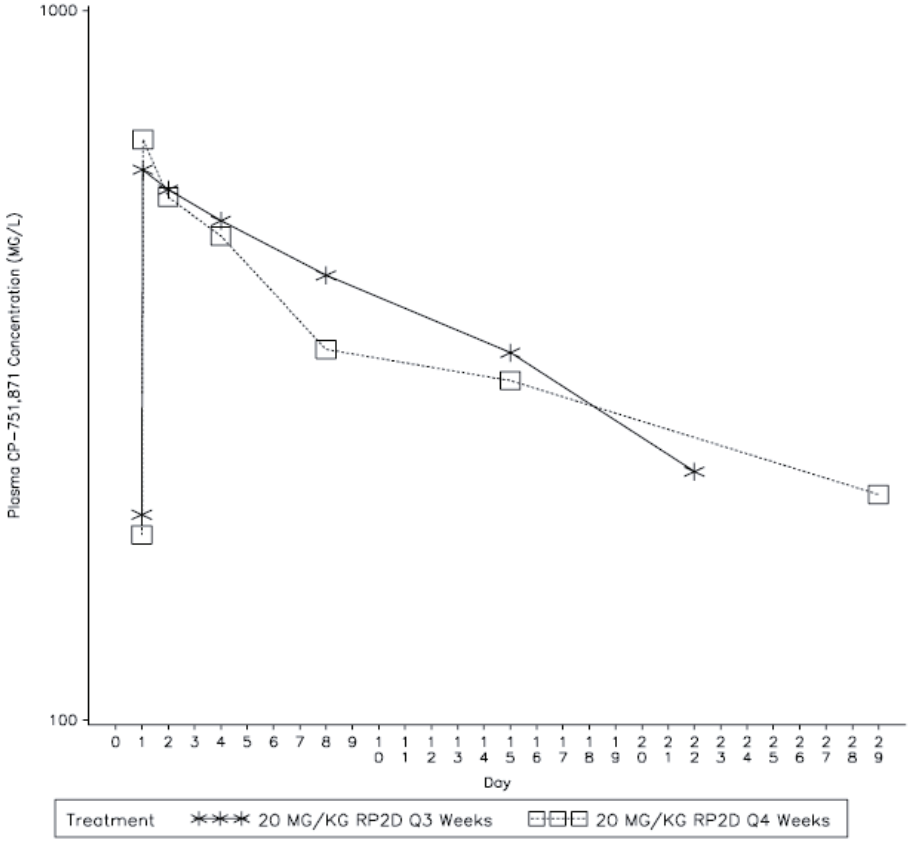
After repeated administration every 3 or 4 weeks, there was a moderate accumulation in plasma figitumumab exposure (Table 8). The accumulation ratio, estimated as the Cycle 4 to Cycle 1 AUC_{tau} ratio, was approximately 2-fold for both the q3w and q4w regimens. For subjects enrolled in dose extension cohorts, mean values of C_{max} and the average concentration (C_{avg}; estimated by AUC_{tau} / dose interval) in Cycle 4 were 6.6% and 20%, respectively, lower for the q4w regimen in comparison to the q3w regimen. There did not appear to be substantial difference in figitumumab PK between the subject populations of the 3 dose extension cohorts.

Figure 1. Median Cycle 1 Plasma Figitumumab Concentration-Time Plot by Dose Level (Semi-Log)



The LLOQ is 0.120 mg/L.
Summary statistics was calculated by setting concentration values below the LLQO to 0.
LLOQ = lower limit of quantification.

Figure 2 Median Cycle 4 Plasma Figitumumab Concentration-Time Plot for Dose Extension Cohorts by Dose Interval (Semi-Log)



The LLOQ is 0.120 mg/L.
Summary statistics was calculated by setting concentration values below the LLQO to 0.
LLOQ = lower limit of quantification.

Table 7. Cycle 1 Figitumumab Pharmacokinetic Parameters in Dose Escalation Cohorts

Parameter (Unit)	3 mg/kg		6 mg/kg		10 mg/kg		20 mg/kg	
	N	Arithmetic Mean (CV%)	N	Arithmetic Mean (CV%)	N	Arithmetic Mean (CV%)	N	Arithmetic Mean (CV%)
C_{max} (mg/L)	3	57.8 (5)	3	135 (24)	3	211 (28)	3	463 (21)
AUC_{504} (mg·h/L)	3	10900 (28)	2	23500, 31500*	3	43170 (47)	3	89430 (13)
AUC_{last} (mg·h/L)	3	10900 (28)	2	23500, 31500*	3	43900 (45)	3	89430 (13)
AUC_{inf} (mg·h/L)	2	9010, 14800*	1	40000*	3	57770 (49)	1	96300*
CL (mL/day/kg)	2	4.88, 7.99*	1	3.60*	3	4.81 (43)	1	4.99*
V_z (mL/kg)	2	60.9, 95.1*	1	49.0*	3	70.5 (37)	1	68.1*
$t_{½}$ (h)	2	198, 208*	1	226*	3	252 (22)	1	227*

*Individual values or range were listed.
AUC_{504} = area under the plasma concentration-time profile from time 0 to 504 hours (21 days), for subjects with every 3 weeks dosing; AUC_{inf} = area under the plasma concentration-time profile from time 0 extrapolated to infinite time; AUC_{last} = area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration; CL = clearance; C_{max} = maximum observed concentration; CV = coefficient of variation; N = total number of subjects per treatment group; $t_{½}$ = terminal half-life; V_z = volume of distribution estimated from terminal phase.

Table 8. Figitumumab Pharmacokinetic Parameters in Cycle 1 and Cycle 4 Following Repeated Dosing at 20 mg/kg to Subjects in Dose Extension Cohorts

Parameter (Unit)	q3w Regimen				q4w Regimen			
	Cycle 1		Cycle 4		Cycle 1		Cycle 4	
	N	Mean (CV%)	N	Mean (CV%)	N	Mean (CV%)	N	Mean (CV%)
C_{max} (mg/L)	34	458 (30)	16	697 (24)	9	392 (23)	6	651 (26)
AUC_{tau} (mg·h/L)*	31	104000 (31)	9	193100 (21)	9	102400 (25)	6	207200 (35)
AUC_{last} (mg·h/L)	31	107900 (34)	16	166500 (46)	9	102700 (25)	6	214500 (32)
AUC_{inf} (mg·h/L)	7	136000 (35)		NA	2	135000, 174000†		NA
CL (mL/day/kg)	7	3.85 (29)	9	2.58 (19)	2	2.76, 3.55†	6	2.61 (43)
V_z (mL/kg)	7	59.3 (24)	5	62.0 (33)	2	53.9, 66.8†	3	89.2 (53)
$t_{½}$ (h)	8	260 (31)	5	386 (45)	2	313, 325†	3	480 (34)

*AUC_{tau} was AUC_{504} for q3w and AUC_{672} for q4w.
†Individual values were listed.
AUC_{inf} = area under the plasma concentration-time profile from time 0 extrapolated to infinite time; AUC_{last} = area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration; AUC_{tau} = area under the plasma concentration-time profile within the dosing interval; CL = clearance; C_{max} = maximum observed concentration; CV = coefficient of variation; N = number of subjects; NA = not applicable; q3w = every 3 weeks; q4w = every 4 weeks; $t_{½}$ = terminal half-life; V_z = volume of distribution estimated from terminal phase.

Safety Results: Table 9 displays a summary of safety by cohort regardless of causality. No subjects experienced DLTs. All subjects in all cohorts experienced treatment-emergent AEs (TEAEs) (all causalities). No Grade 3 or 4 AEs occurred in the 3 mg/kg or 10 mg/kg Cohorts, and the following percentages of subjects in the remaining cohorts experienced Grade 3 or 4 AEs (all causalities): 6 mg/kg and 20 mg/kg (each n=1/3, 33.3%), 20 mg/kg RP2D (n=6/13, 46.2%), ACC + Sarcoma Extension Cohort (n=16/29, 55.2%), and ESFT Extension Cohort (n=5/11, 45.5%). Each cohort had ≥1 Grade 5 AE, all of which were disease progression and not related to figitumumab treatment.

Table 9. Treatment-Emergent Adverse Events – All Causalities

Number of Subjects	Figitumumab						
	3 mg/kg N=3 n (%)	6 mg/kg N=3 n (%)	10 mg/kg N=3 n (%)	20 mg/kg N=3 n (%)	20 mg/kg RP2D N=13 n (%)	20 mg/kg RP2D ACC + Sarcoma N=29 n (%)	20 mg/kg RP2D ESFT N=11 n (%)
Subjects evaluable for AEs	3	3	3	3	13	29	11
Number of AEs	29	26	27	31	152	328	254
Subjects with AEs	3 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	13 (100.0)	29 (100.0)	11 (100.0)
Subjects with serious AEs	2 (66.7)	1 (33.3)	3 (100.0)	1 (33.3)	5 (38.5)	17 (58.6)	5 (45.5)
Subjects with Grade 3 or 4 AEs	0	1 (33.3)	0	1 (33.3)	6 (46.2)	16 (55.2)	5 (45.5)
Subjects with Grade 5 AEs	1 (33.3)	1 (33.3)	3 (100.0)	1 (33.3)	3 (23.1)	8 (27.6)	3 (27.3)
Subjects discontinued due to AEs	0	0	0	0	3 (23.1)	7 (24.1)	2 (18.2)
Subjects with dose reduced due to AEs	0	0	0	0	0	0	1 (9.1)
Subjects with temporary discontinuations due to AEs	0	0	0	0	1 (7.7)	1 (3.4)	1 (9.1)

MedDRA (version 13.1) coding dictionary applied.
The AE/SAE results are not separated out.
ACC = adrenocortical carcinoma; AEs = adverse events; ESFT = Ewing's sarcoma family of tumors; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in each treatment group; n = number of subjects; RP2D = recommended Phase 2 dose; SAE = serious AE.

Table 10 presents a summary of TEAEs (all causalities) by treatment cohort, preferred term, and maximum CTCAE grade, for >1 subject for cohorts of 3 subjects, and ≥3 subjects for the RP2D cohorts. The most frequently experienced AEs across most cohorts were decreased appetite, fatigue, diarrhea, vomiting, nausea, and hyperglycemia. Hyperglycemia, a known drug class related side effect, was reported in the 20 mg/kg RP2D, ACC + Sarcoma Extension, and ESFT Extension cohorts at 38.5%, 27.6%, and 18.2%, respectively. The majority of AEs in all cohorts were Grades 1-2.

Table 10. Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade Occurring in >1 Subject (Cohorts of 3) or ≥3 Subjects (RP2D Cohorts) Treated With Figitumumab (All Causalities, All Cycles)

Preferred Term[a]	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Figitumumab 3 mg/kg (N=3)						
Any AE	1 (33.3)	1 (33.3)	0	0	1 (33.3)	3 (100.0)
Decreased appetite	2 (66.7)	0	0	0	0	2 (66.7)
Hyperglycaemia	1 (33.3)	1 (33.3)	0	0	0	2 (66.7)
Figitumumab 6 mg/kg (N=3)						
Any AE	0	2 (66.7)	0	0	1 (33.3)	3 (100.0)
Diarrhea	2 (66.7)	0	0	0	0	2 (66.7)
Nausea	0	2 (66.7)	0	0	0	2 (66.7)
Figitumumab 10 mg/kg (N=3)						
Any AE	0	0	0	0	3 (100.0)	3 (100.0)
Disease progression	0	0	0	0	3 (100.0)	3 (100.0)
Aspartate aminotransferase increased	2 (66.7)	0	0	0	0	2 (66.7)
Decreased appetite	2 (66.7)	0	0	0	0	2 (66.7)
Diarrhea	2 (66.7)	0	0	0	0	2 (66.7)
Gamma-glutamyl transferase increased	1 (33.3)	1 (33.3)	0	0	0	2 (66.7)
Nausea	2 (66.7)	0	0	0	0	2 (66.7)
Vomiting	2 (66.7)	0	0	0	0	2 (66.7)
Figitumumab 20 mg/kg (N=3)						
Any AE	1 (33.3)	0	1 (33.3)	0	1 (33.3)	3 (100.0)
Fatigue	2 (66.7)	0	1 (33.3)	0	0	3 (100.0)
Hyperglycaemia	2 (66.7)	1 (33.3)	0	0	0	3 (100.0)
Decreased appetite	2 (66.7)	0	0	0	0	2 (66.7)
Pollakiuria	1 (33.3)	1 (33.3)	0	0	0	2 (66.7)
Rash	1 (33.3)	1 (33.3)	0	0	0	2 (66.7)
Figitumumab 20 mg/kg RP2D (N=13)						
Any AE	1 (7.7)	6 (46.2)	3 (23.1)	0	3 (23.1)	13 (100.0)
Nausea	4 (30.8)	3 (23.1)	1 (7.7)	0	0	8 (61.5)
Aspartate aminotransferase increased	6 (46.2)	1 (7.7)	0	0	0	7 (53.8)
Diarrhea	4 (30.8)	2 (15.4)	0	0	0	6 (46.2)
Fatigue	3 (23.1)	3 (23.1)	0	0	0	6 (46.2)
Vomiting	3 (23.1)	2 (15.4)	1 (7.7)	0	0	6 (46.2)
Alanine aminotransferase increased	4 (30.8)	1 (7.7)	0	0	0	5 (38.5)

Table 10. Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade Occurring in >1 Subject (Cohorts of 3) or ≥3 Subjects (RP2D Cohorts) Treated With Figitumumab (All Causalities, All Cycles)

Preferred Term[a]	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Decreased appetite	3 (23.1)	2 (15.4)	0	0	0	5 (38.5)
Gamma-glutamyl transferase increased	5 (38.5)	0	0	0	0	5 (38.5)
Hyperglycaemia	2 (15.4)	2 (15.4)	1 (7.7)	0	0	5 (38.5)
Anaemia	1 (7.7)	2 (15.4)	0	0	0	3 (23.1)
Blood uric acid increased	3 (23.1)	0	0	0	0	3 (23.1)
Constipation	3 (23.1)	0	0	0	0	3 (23.1)
Dry mouth	3 (23.1)	0	0	0	0	3 (23.1)
Dyspnoea	2 (15.4)	1 (7.7)	0	0	0	3 (23.1)
Muscle spasms	3 (23.1)	0	0	0	0	3 (23.1)
Figitumumab 20 mg/kg RP2D ACC + Sarcoma (N=29)						
Any AE	2 (6.9)	9 (31.0)	8 (27.6)	2 (6.9)	8 (27.6)	29 (100.0)
Decreased appetite	8 (27.6)	6 (20.7)	0	0	0	14 (48.3)
Nausea	9 (31.0)	3 (10.3)	1 (3.4)	0	0	13 (44.8)
Fatigue	4 (13.8)	6 (20.7)	2 (6.9)	0	0	12 (41.4)
Constipation	8 (27.6)	1 (3.4)	0	0	0	9 (31.0)
Back pain	4 (13.8)	3 (10.3)	1 (3.4)	0	0	8 (27.6)
Hyperglycaemia	6 (20.7)	1 (3.4)	1 (3.4)	0	0	8 (27.6)
Aspartate aminotransferase increased	6 (20.7)	1 (3.4)	0	0	0	7 (24.1)
Disease progression	0	0	0	0	7 (24.1)	7 (24.1)
Gamma-glutamyl transferase increased	2 (6.9)	3 (10.3)	1 (3.4)	1 (3.4)	0	7 (24.1)
Headache	6 (20.7)	1 (3.4)	0	0	0	7 (24.1)
Alanine aminotransferase increased	3 (10.3)	2 (6.9)	1 (3.4)	0	0	6 (20.7)
Hypermagnesaemia	6 (20.7)	0	0	0	0	6 (20.7)
Pain in extremity	4 (13.8)	2 (6.9)	0	0	0	6 (20.7)
Vomiting	4 (13.8)	1 (3.4)	1 (3.4)	0	0	6 (20.7)
Blood uric acid increased	3 (10.3)	0	0	2 (6.9)	0	5 (17.2)
Diarrhea	4 (13.8)	1 (3.4)	0	0	0	5 (17.2)
Hyponatraemia	4 (13.8)	0	1 (3.4)	0	0	5 (17.2)
Muscle spasms	5 (17.2)	0	0	0	0	5 (17.2)
Blood alkaline phosphatase increased	1 (3.4)	1 (3.4)	2 (6.9)	0	0	4 (13.8)
Blood creatinine increased	1 (3.4)	3 (10.3)	0	0	0	4 (13.8)
Chest pain	2 (6.9)	1 (3.4)	1 (3.4)	0	0	4 (13.8)

Table 10. Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade Occurring in >1 Subject (Cohorts of 3) or ≥3 Subjects (RP2D Cohorts) Treated With Figitumumab (All Causalities, All Cycles)

Preferred Term[a]	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Dizziness	3 (10.3)	1 (3.4)	0	0	0	4 (13.8)
Dry mouth	4 (13.8)	0	0	0	0	4 (13.8)
Dyspnoea	2 (6.9)	2 (6.9)	0	0	0	4 (13.8)
Hypertension	0	3 (10.3)	1 (3.4)	0	0	4 (13.8)
Muscular weakness	3 (10.3)	1 (3.4)	0	0	0	4 (13.8)
Musculoskeletal pain	0	4 (13.8)	0	0	0	4 (13.8)
Abdominal distension	0	3 (10.3)	0	0	0	3 (10.3)
Alopecia	3 (10.3)	0	0	0	0	3 (10.3)
Anaemia	1 (3.4)	1 (3.4)	1 (3.4)	0	0	3 (10.3)
Cough	2 (6.9)	1 (3.4)	0	0	0	3 (10.3)
Flatulence	3 (10.3)	0	0	0	0	3 (10.3)
Haemoglobin decreased	0	3 (10.3)	0	0	0	3 (10.3)
Influenza-like illness	2 (6.9)	1 (3.4)	0	0	0	3 (10.3)
Oedema peripheral	1 (3.4)	1 (3.4)	1 (3.4)	0	0	3 (10.3)
Pallor	3 (10.3)	0	0	0	0	3 (10.3)
Proteinuria	2 (6.9)	0	0	1 (3.4)	0	3 (10.3)
Stomatitis	3 (10.3)	0	0	0	0	3 (10.3)
Weight decreased	1 (3.4)	2 (6.9)	0	0	0	3 (10.3)
Figitumumab 20 mg/kg RP2D ESFT (N=11)						
Any AE	2 (18.2)	4 (36.4)	1 (9.1)	1 (9.1)	3 (27.3)	11 (100.0)
Diarrhoea	4 (36.4)	3 (27.3)	0	0	0	7 (63.6)
Fatigue	5 (45.5)	2 (18.2)	0	0	0	7 (63.6)
Vomiting	3 (27.3)	3 (27.3)	1 (9.1)	0	0	7 (63.6)
Decreased appetite	4 (36.4)	2 (18.2)	0	0	0	6 (54.5)
Muscle spasms	4 (36.4)	2 (18.2)	0	0	0	6 (54.5)
Arthralgia	2 (18.2)	2 (18.2)	1 (9.1)	0	0	5 (45.5)
Cough	5 (45.5)	0	0	0	0	5 (45.5)
Dyspnoea	4 (36.4)	1 (9.1)	0	0	0	5 (45.5)
Constipation	3 (27.3)	1 (9.1)	0	0	0	4 (36.4)
Disease progression	0	0	0	1 (9.1)	3 (27.3)	4 (36.4)
Epistaxis	4 (36.4)	0	0	0	0	4 (36.4)
Headache	1 (9.1)	2 (18.2)	1 (9.1)	0	0	4 (36.4)

Table 10. Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade Occurring in >1 Subject (Cohorts of 3) or ≥3 Subjects (RP2D Cohorts) Treated With Figitumumab (All Causalities, All Cycles)

Preferred Term[a]	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Nausea	3 (27.3)	1 (9.1)	0	0	0	4 (36.4)
Pyrexia	3 (27.3)	0	1 (9.1)	0	0	4 (36.4)
Back pain	1 (9.1)	1 (9.1)	1 (9.1)	0	0	3 (27.3)
Dyspepsia	2 (18.2)	1 (9.1)	0	0	0	3 (27.3)
Lethargy	3 (27.3)	0	0	0	0	3 (27.3)
Musculoskeletal pain	1 (9.1)	1 (9.1)	1 (9.1)	0	0	3 (27.3)
Nasopharyngitis	2 (18.2)	1 (9.1)	0	0	0	3 (27.3)
Oropharyngeal pain	2 (18.2)	1 (9.1)	0	0	0	3 (27.3)
Pain	3 (27.3)	0	0	0	0	3 (27.3)

The AE/SAE results are not separated out
ACC = adrenocortical carcinoma; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ESFT = Ewing's sarcoma family of tumors; MedDRA = Medical Dictionary for Regulatory Activities, N = total number of subjects in each treatment group; n = number of subjects; RP2D = recommended Phase 2 dose.
a. MedDRA (version 13.1) coding dictionary applied.

Most subjects in each cohort experienced treatment-related AEs but most were Grade 1-2. The treatment-related treatment-emergent AEs included in Table 11 are those reported for ≥1 subject for cohorts of 3 subjects, and ≥3 subjects for the RP2D cohorts. No Grade 3 or 4 treatment-related AEs occurred in the 3 mg/kg, 6 mg/kg, or 10 mg/kg cohorts, and the following percentages of subjects in the remaining cohorts experienced treatment-related Grade 3 AEs: 20 mg/kg (n=1/3, 33.3%), 20 mg/kg RP2D (n=1/13, 7.7%), ACC + Sarcoma Extension Cohort (n=2/29, 6.9%), and ESFT Extension Cohort (n=1/11, 9.1%). Grade 4 AEs occurred in 2 cohorts, the ACC + Sarcoma Extension Cohort (n=3/29, 10.3%) and the ESFT Extension Cohort (n=1/11, 9.1%).

Table 11. Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade Occurring in ≥1 Subject (Cohorts of 3) or ≥3 Subjects (RP2D Cohorts) Treated With Figitumumab (All Cycles)

Preferred Term[a]	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Figitumumab 3 mg/kg (N=3)						
Any AE	1 (33.3)	1 (33.3)	0	0	0	2 (66.7)
Hyperglycaemia	0	1 (33.3)	0	0	0	1 (33.3)
Blood magnesium increased	1 (33.3)	0	0	0	0	1 (33.3)
Blood potassium decreased	1 (33.3)	0	0	0	0	1 (33.3)
Blood uric acid increased	1 (33.3)	0	0	0	0	1 (33.3)
Decreased appetite	1 (33.3)	0	0	0	0	1 (33.3)
Hyperbilirubinaemia	1 (33.3)	0	0	0	0	1 (33.3)
Vomiting	1 (33.3)	0	0	0	0	1 (33.3)
Figitumumab 6 mg/kg (N=3)						
Any AE	2 (66.7)	0	0	0	0	2 (66.7)
Aspartate aminotransferase increased	1 (33.3)	0	0	0	0	1 (33.3)
Blood uric acid increased	1 (33.3)	0	0	0	0	1 (33.3)
Decreased appetite	1 (33.3)	0	0	0	0	1 (33.3)
Diarrhea	1 (33.3)	0	0	0	0	1 (33.3)
Dizziness	1 (33.3)	0	0	0	0	1 (33.3)
Gamma-glutamyl transferase increased	1 (33.3)	0	0	0	0	1 (33.3)
Hyperglycaemia	1 (33.3)	0	0	0	0	1 (33.3)
Muscle spasms	1 (33.3)	0	0	0	0	1 (33.3)
Nausea	1 (33.3)	0	0	0	0	1 (33.3)
Pyrexia	1 (33.3)	0	0	0	0	1 (33.3)
Figitumumab 10 mg/kg (N=3)						
Any AE	2 (66.7)	1 (33.3)	0	0	0	3 (100.0)
Gamma-glutamyl transferase increased	0	1 (33.3)	0	0	0	1 (33.3)
Decreased appetite	2 (66.7)	0	0	0	0	2 (66.7)
Anxiety	1 (33.3)	0	0	0	0	1 (33.3)
Blood uric acid increased	1 (33.3)	0	0	0	0	1 (33.3)
Diarrhea	1 (33.3)	0	0	0	0	1 (33.3)
Hot flush	1 (33.3)	0	0	0	0	1 (33.3)
Nausea	1 (33.3)	0	0	0	0	1 (33.3)
Rash	1 (33.3)	0	0	0	0	1 (33.3)

Table 11. Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade Occurring in ≥1 Subject (Cohorts of 3) or ≥3 Subjects (RP2D Cohorts) Treated With Figitumumab (All Cycles)

Preferred Term[a]	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Vomiting	1 (33.3)	0	0	0	0	1 (33.3)
Figitumumab 20 mg/kg (N=3)						
Any AE	2 (66.7)	0	1 (33.3)	0	0	3 (100.0)
Fatigue	2 (66.7)	0	1 (33.3)	0	0	3 (100.0)
Hyperglycaemia	1 (33.3)	1 (33.3)	0	0	0	2 (66.7)
Decreased appetite	2 (66.7)	0	0	0	0	2 (66.7)
Abdominal pain	1 (33.3)	0	0	0	0	1 (33.3)
Blood creatinine increased	1 (33.3)	0	0	0	0	1 (33.3)
Blood magnesium increased	1 (33.3)	0	0	0	0	1 (33.3)
Blood uric acid increased	1 (33.3)	0	0	0	0	1 (33.3)
Headache	1 (33.3)	0	0	0	0	1 (33.3)
Hypermagnesaemia	1 (33.3)	0	0	0	0	1 (33.3)
Pollakiuria	0	1 (33.3)	0	0	0	1 (33.3)
Stomatitis	1 (33.3)	0	0	0	0	1 (33.3)
Figitumumab 20 mg/kg RP2D (N=13)						
Any AE	6 (46.2)	4 (30.8)	1 (7.7)	0	0	11 (84.6)
Aspartate aminotransferase increased	5 (38.5)	1 (7.7)	0	0	0	6 (46.2)
Gamma-glutamyl transferase increased	5 (38.5)	0	0	0	0	5 (38.5)
Nausea	4 (30.8)	1 (7.7)	0	0	0	5 (38.5)
Alanine aminotransferase increased	3 (23.1)	1 (7.7)	0	0	0	4 (30.8)
Diarrhea	2 (15.4)	2 (15.4)	0	0	0	4 (30.8)
Blood uric acid increased	3 (23.1)	0	0	0	0	3 (23.1)
Hyperglycaemia	2 (15.4)	1 (7.7)	0	0	0	3 (23.1)
Figitumumab 20 mg/kg RP2D ACC + Sarcoma (N=29)						
Any AE	8 (27.6)	7 (24.1)	2 (6.9)	3 (10.3)	0	20 (69.0)
Decreased appetite	6 (20.7)	1 (3.4)	0	0	0	7 (24.1)
Fatigue	2 (6.9)	3 (10.3)	1 (3.4)	0	0	6 (20.7)
Aspartate aminotransferase increased	4 (13.8)	1 (3.4)	0	0	0	5 (17.2)
Nausea	4 (13.8)	1 (3.4)	0	0	0	5 (17.2)
Alanine aminotransferase increased	3 (10.3)	0	1 (3.4)	0	0	4 (13.8)
Gamma-glutamyl transferase increased	2 (6.9)	1 (3.4)	0	1 (3.4)	0	4 (13.8)

Table 11. Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade Occurring in ≥1 Subject (Cohorts of 3) or ≥3 Subjects (RP2D Cohorts) Treated With Figitumumab (All Cycles)

Preferred Term[a]	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Influenza-like illness	3 (10.3)	0	0	0	0	3 (10.3)
Vomiting	4 (13.8)	0	0	0	0	4 (13.8)
Diarrhoea	3 (10.3)	0	0	0	0	3 (10.3)
Hyperglycaemia	2 (6.9)	0	1 (3.4)	0	0	3 (10.3)
Hypermagnesaemia	3 (10.3)	0	0	0	0	3 (10.3)
Muscle spasms	3 (10.3)	0	0	0	0	3 (10.3)
Proteinuria	2 (6.9)	0	0	1 (3.4)	0	3 (10.3)
Figitumumab 20 mg/kg RP2D ESFT (N=11)						
Any AE	4 (36.4)	5 (45.5)	1 (9.1)	1 (9.1)	0	11 (100.0)
Arthralgia	2 (18.2)	2 (18.2)	0	0	0	4 (36.4)
Decreased appetite	2 (18.2)	2 (18.2)	0	0	0	4 (36.4)
Muscle spasms	2 (18.2)	2 (18.2)	0	0	0	4 (36.4)
Epistaxis	3 (27.3)	0	0	0	0	3 (27.3)
Fatigue	3 (27.3)	0	0	0	0	3 (27.3)
Headache	0	2 (18.2)	1 (9.1)	0	0	3 (27.3)
Lethargy	3 (27.3)	0	0	0	0	3 (27.3)

The AE/SAE results are not separated out.
AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; N = total number of subjects in each treatment group; n = number of subjects; RP2D = recommended Phase 2 dose; SAE = serious AE.
a. MedDRA (version 13.1) coding dictionary applied.

SAEs (including disease progression with an outcome of death) were reported through and including 150 calendar days after the last administration of the study drug. The incidence of SAEs by cohort is summarized in Table 12. All SAEs reported, listed by cohort and maximum grade, are presented in Table 13 At least 1 subject in each cohort experienced SAEs, however, only the 20 mg/kg ACC + Sarcoma and ESFT extension cohorts had subjects who experienced treatment-related SAEs (Table 14).

The largest proportion of subjects in all cohorts discontinued the study due to disease progression (Table 4). One subject in 20 mg/kg RP2D Extension Cohort withdrew from the study due to a Grade 4 intestinal obstruction, due to disease under study. The event worsened off-treatment and the subject eventually died. Six subjects in the 20 mg/kg ACC + Sarcoma Extension Cohort discontinued from the study due to the following AEs: Grade 4 proteinuria (treatment-related), Grade 3 edema peripheral (not treatment-related), Grade 3 peripheral motor neuropathy (not treatment-related), Grade 3 superior vena cava obstruction (not treatment-related), Grade 3 acute renal failure (not treatment-related), and Grade 2 dyspnea (not treatment-related). One additional subject in the ACC + Sarcoma Extension Cohort discontinued from the study due to AEs according to the reasons for withdrawal; however, no AEs were checked as the reason for treatment withdrawal on the AE page. The Sponsor conservatively coded the reason for withdrawal as due to a treatment-related AE. One subject, also in the ACC + Sarcoma Extension Cohort, discontinued from the study with a reason of laboratory abnormality (Grade 2 thrombocytopenia, not treatment-related).

Two subjects died while on study, which, in both subjects, was the reason for study discontinuation. These subjects both died due to disease progression and both were in the 20 mg/kg RP2D extension cohort. During the treatment period and during the safety follow-up for 150 days after the last dose of study drug, 20 subjects overall had Grade 5 AEs, all but 2 of the Grade 5 AEs were reported as disease progression; none of the Grade 5 AEs were considered treatment-related. One subject in the 20 mg/kg RP2D cohort had a Grade 5 intestinal obstruction (due to disease under study; subject withdrew from treatment when the AE was at Grade 4) and 1 subject in the ACC + Sarcoma Extension Cohort died with a preferred term reported as Death.

Table 12. Treatment-Emergent Serious Adverse Events (All Causalities and Treatment-Related)

Adverse Event Criteria	Serious Adverse Events	
	All Causality	Treatment-Related
Figitumumab 3 mg/kg (N=3)		
No. of SAEs	2	0
Subjects with SAEs	2 (66.7)	0
Subjects with Grade 3 or 4 SAEs	0	0
Subjects with Grade 5 SAEs	1 (33.3)	0
Figitumumab 6 mg/kg (N=3)		
No. of SAEs	4	0
Subjects with SAEs	1 (33.3)	0
Subjects with Grade 3 or 4 SAEs	1 (33.3)	0
Subjects with Grade 5 SAEs	1 (33.3)	0
Figitumumab 10 mg/kg (N=3)		
No. of SAEs	3	0
Subjects with SAEs	3 (100.0)	0
Subjects with Grade 3 or 4 SAEs	0	0
Subjects with Grade 5 SAEs	3 (100.0)	0
Figitumumab 20 mg/kg (N=3)		
No. of SAEs	1	0
Subjects with SAEs	1 (33.3)	0
Subjects with Grade 3 or 4 SAEs	0	0
Subjects with Grade 5 SAEs	1 (33.3)	0
Figitumumab 20 mg/kg RP2D (N=13)		
No. of SAEs	7	0
Subjects with SAEs	5 (38.5)	0
Subjects with Grade 3 or 4 SAEs	5 (38.5)	0
Subjects with Grade 5 SAEs	3 (23.1)	0
Figitumumab 20 mg/kg RP2D ACC + Sarcoma (N=29)		
No. of SAEs	29	3
Subjects with SAEs	17 (58.6)	2 (6.9)
Subjects with Grade 3 or 4 SAEs	11 (37.9)	2 (6.9)
Subjects with Grade 5 SAEs	8 (27.6)	0
Figitumumab 20 mg/kg RP2D ESFT (N=11)		
No. of SAEs	15	6
Subjects with SAEs	5 (45.5)	1 (9.1)
Subjects with Grade 3 or 4 SAEs	3 (27.3)	1 (9.1)
Subjects with Grade 5 SAEs	3 (27.3)	0

MedDRA (version 13.1) coding dictionary applied.
Except for the number of SAEs, subjects were counted only once per treatment in each row. Serious AEs were based on Investigator assessment. Includes data up to 150 days after the last dose of study drug.
ACC = adrenocortical carcinoma; CTCAE = Common Terminology Criteria for Adverse Events; ESFT = Ewing's sarcoma family of tumors; MedDRA = Medical Dictionary for Regulatory Activities, N = total number of subjects in each treatment group; n = number of subjects; RP2D = recommended Phase 2 dose; SAE = serious adverse event.

Table 13. Summary of Treatment-Emergent Serious Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade Occurring All Subjects Treated With Figitumumab (All Causalities, All Cycles)

Preferred Term[a]	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Figitumumab 3 mg/kg (N=3)						
Subjects with any SAEs	0	1 (33.3)	0	0	1 (33.3)	2 (66.7)
Disease progression	0	0	0	0	1 (33.3)	1 (33.3)
Blood creatinine increased	0	1 (33.3)	0	0	0	1 (33.3)
Figitumumab 6 mg/kg (N=3)						
Subjects with any SAEs	0	0	0	0	1 (33.3)	1 (33.3)
Disease progression	0	0	0	0	1 (33.3)	1 (33.3)
Female genital tract fistula	0	0	1 (33.3)	0	0	1 (33.3)
Nausea	1 (33.3)	0	0	0	0	1 (33.3)
Vomiting	0	0	1 (33.3)	0	0	1 (33.3)
Figitumumab 10 mg/kg (N=3)						
Subjects with any SAEs	0	0	0	0	3 (100.0)	3 (100.0)
Disease progression	0	0	0	0	3 (100.0)	3 (100.0)
Figitumumab 20 mg/kg (N=3)						
Subjects with any SAEs	0	0	0	0	1 (33.3)	1 (33.3)
Disease progression	0	0	0	0	1 (33.3)	1 (33.3)
Figitumumab 20 mg/kg RP2D (N=13)						
Subjects with any SAEs	0	0	2 (15.4)	0	3 (23.1)	5 (38.5)
Disease progression	0	0	0	0	2 (15.4)	2 (15.4)
Anaemia	0	1 (7.7)	0	0	0	1 (7.7)
Back pain	0	0	1 (7.7)	0	0	1 (7.7)
Intestinal obstruction	0	0	0	0	1 (7.7)	1 (7.7)
Small intestinal obstruction	0	0	1 (7.7)	0	0	1 (7.7)
Staphylococcal infection	0	0	1 (7.7)	0	0	1 (7.7)
Figitumumab 20 mg/kg RP2D ACC + Sarcoma (N=29)						
Subjects with any SAEs	0	1 (3.4)	7 (24.1)	1 (3.4)	8 (27.6)	17 (58.6)
Disease progression	0	0	0	0	7 (24.1)	7 (24.1)
Blood uric acid increased	0	0	0	1 (3.4)	0	1 (3.4)
Ascites	0	0	1 (3.4)	0	0	1 (3.4)
Back pain	0	1 (3.4)	0	0	0	1 (3.4)
Bone pain	0	0	1 (3.4)	0	0	1 (3.4)
Death	0	0	0	0	1 (3.4)	1 (3.4)
Fatigue	0	1 (3.4)	0	0	0	1 (3.4)
Gastroenteritis	0	0	1 (3.4)	0	0	1 (3.4)
Haemoglobin decreased	0	1 (3.4)	0	0	0	1 (3.4)
Ileus	0	0	1 (3.4)	0	0	1 (3.4)
Musculoskeletal pain	0	1 (3.4)	0	0	0	1 (3.4)

Table 13. Summary of Treatment-Emergent Serious Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade Occurring All Subjects Treated With Figitumumab (All Causalities, All Cycles)

Preferred Term[a]	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Nausea	0	0	1 (3.4)	0	0	1 (3.4)
Oedema peripheral	0	0	1 (3.4)	0	0	1 (3.4)
Pain in extremity	0	1 (3.4)	0	0	0	1 (3.4)
Pleural effusion	0	1 (3.4)	0	0	0	1 (3.4)
Pneumonia	0	0	1 (3.4)	0	0	1 (3.4)
Proteinuria	0	0	0	1 (3.4)	0	1 (3.4)
Renal failure acute	0	0	1 (3.4)	0	0	1 (3.4)
Renal pain	0	0	1 (3.4)	0	0	1 (3.4)
Spinal cord compression	0	0	1 (3.4)	0	0	1 (3.4)
Superior vena caval occlusion	0	0	1 (3.4)	0	0	1 (3.4)
Thrombosis	0	0	1 (3.4)	0	0	1 (3.4)
Vomiting	0	0	1 (3.4)	0	0	1 (3.4)
Figitumumab 20 mg/kg RP2D ESFT (N=11)						
Subjects with any SAE	0	1 (9.1)	0	1 (9.1)	3 (27.3)	5 (45.5)
Disease progression	0	0	0	0	3 (27.3)	3 (27.3)
Alanine aminotransferase increased	0	0	0	1 (9.1)	0	1 (9.1)
Aspartate aminotransferase increased	0	0	0	1 (9.1)	0	1 (9.1)
Blood culture positive	0	0	1 (9.1)	0	0	1 (9.1)
Gamma-glutamyltransferase increased	0	0	1 (9.1)	0	0	1 (9.1)
Headache	0	0	1 (9.1)	0	0	1 (9.1)
Intracranial pressure increased	0	1 (9.1)	0	0	0	1 (9.1)
Lower respiratory tract infection	0	0	1 (9.1)	0	0	1 (9.1)
Lower respiratory tract infection viral	0	1 (9.1)	0	0	0	1 (9.1)
Pain in extremity	0	0	1 (9.1)	0	0	1 (9.1)
Pneumomediastinum	0	1 (9.1)	0	0	0	1 (9.1)
Pyrexia	0	0	1 (9.1)	0	0	1 (9.1)
Vomiting	0	0	1 (9.1)	0	0	1 (9.1)

ACC = adrenocortical carcinoma; CTCAE = Common Terminology Criteria for Adverse Events; ESFT = Ewing's sarcoma family of tumors; MedDRA = Medical Dictionary for Regulatory Activities, N = total number of subjects in each treatment group; n = number of subjects; RP2D = recommended Phase 2 dose; SAE = serious adverse event.
a. MedDRA (Version 13.1) coding dictionary applied.

Table 14. Summary of Treatment-Related Serious Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade Occurring in All Subjects Treated With Figitumumab (All Cycles)

Preferred Term[a]	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Figitumumab 20 mg/kg RP2D ACC + Sarcoma (N=29)						
Subjects with any treatment-related SAE	0	0	1 (3.4)	1 (3.4)	0	2 (6.9)
Blood uric acid increased	0	0	0	1 (3.4)	0	1 (3.4)
Proteinuria	0	0	0	1 (3.4)	0	1 (3.4)
Thrombosis	0	0	1 (3.4)	0	0	1 (3.4)
Figitumumab 20 mg/kg RP2D ESFT (N=11)						
Subjects with any treatment-related SAE	0	0	0	1 (9.1)	0	2 (18.2)
Alanine aminotransferase increased	0	0	0	1 (9.1)	0	1 (9.1)
Aspartate aminotransferase increased	0	0	0	1 (9.1)	0	1 (9.1)
Gamma-glutamyltransferase increased	0	0	1 (9.1)	0	0	1 (9.1)
Headache	0	0	1 (9.1)	0	0	1 (9.1)
Intracranial pressure increased	0	1 (9.1)	0	0	0	1 (9.1)
Vomiting	0	0	0	1 (9.1)	0	1 (9.1)

ACC = adrenocortical carcinoma; CTCAE = Common Terminology Criteria for Adverse Events; ESFT = Ewing's sarcoma family of tumors; MedDRA = Medical Dictionary for Regulatory Activities, N = total number of subjects in each treatment group; n = number of subjects; RP2D = recommended Phase 2 dose; SAE = serious adverse event.
a. MedDRA (Version 13.1) coding dictionary applied.

Doppler echocardiograms revealed that mitral valve regurgitation of a degree greater than mild was not observed in any subjects, either at Baseline or through the end-of-study visit. No obvious hematology or coagulation toxicities were noted. The majority of abnormal hematology and coagulation laboratory test results were Grades 1 or 2. There were no Grade 4 abnormalities and the Grade 3 abnormalities included prothrombin time, lymphocytes (absolute), neutrophils (absolute), and hemoglobin. The most common laboratory abnormality was hyperglycemia, an expected toxicity associated with treatment with IGF-IR inhibitors. The most common Grade 3 laboratory abnormality was increased gamma glutamyl transferase, and Grade 4 laboratory abnormalities were hypercalcemia, hyperglycemia, hyperkalemia, and hypermagnesemia. There were no significant abnormalities related to urine protein for subjects noted in this study.

CONCLUSIONS: Safety data resulted in the identification of figitumumab 20 mg/kg q3-4 weeks as the RP2D and this dose was well tolerated. There were no drug-related deaths in this study. Fatigue, decreased appetite, nausea, vomiting, and diarrhea were the most common non-hematologic AEs in the 20 mg/kg dosing cohorts. Abnormal hemoglobin (decreased) and absolute lymphocytes (decreased) were the most common hematological abnormalities. Additional safety data available at the time of the Supplemental Synopsis Clinical Study Report produced minor changes to the numbers of reported hyperglycemic events. Overall mild to moderate hyperglycemia was noted, while severe hyperglycemia (Grade 3) was reported in 4 subjects. Gamma glutamy-l transferase increase was the most common biochemical abnormality.