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

PROTOCOL NO.: A4021006

PROTOCOL TITLE: Phase 2, Single Arm Study of CP-751,871 in Patients With Refractory Metastatic Adenocarcinoma of the Colon or Rectum

Study Centers: A total of 10 centers enrolled subjects; 4 each in Spain and the United Kingdom (UK) and 2 in the United States (US).

Study Initiation and Final Completion Dates: 04 December 2007 to 22 September 2010

Phase of Development: Phase 2

Study Objectives:

Primary Objective: To evaluate 6-month overall survival (OS) in refractory, metastatic colorectal cancer (mCRC) subjects who receive figitumumab.

Secondary Objectives:

- To assess the safety and tolerability of multiple intravenous (IV) doses of figitumumab;
- To evaluate the efficacy of figitumumab in terms of progression free survival (PFS);
- To evaluate the efficacy of figitumumab in terms of OS;
- To evaluate the efficacy of figitumumab in terms of objective response (OR);
- To collect pharmacokinetics (PK) data of figitumumab for future population PK meta-analysis;
- To monitor the immunogenicity of figitumumab in terms of producing an anti-drug antibody (ADA) response;
- To explore the feasibility of quantification of circulating tumor cells (CTCs) and that of CTCs expressing the insulin-like growth factor-1 receptor (IGF-IR).

METHODS

Study Design: This was a single-arm, nonrandomized, open-label, Phase 2 clinical study that evaluated the efficacy and safety of multiple doses of figitumumab in subjects with

refractory, metastatic adenocarcinoma of the colon or rectum. Two cohorts with 20 mg/kg and 30 mg/kg figitumumab were investigated. The initial cohort of subjects received cycles (every 3 weeks) of figitumumab via an IV infusion at a dose of 20 mg/kg. Subjects received 20 mg/kg figitumumab on Days 1 and 2 of Cycle 1 (loading dose), and on Day 1 of each cycle thereafter.

Opening of a second cohort of subjects were to be dosed with 30 mg/kg of figitumumab. An additional 80 evaluable subjects were enrolled at the dose level of 30 mg/kg of figitumumab. All statistical and study conduct considerations employed at the 20 mg/kg cohort of subjects applied to the 30 mg/kg subject cohort. This second subject cohort began enrollment upon completion of enrollment of the initial cohort of subjects dosed with figitumumab 20 mg/kg. Testing of the 30 mg/kg of figitumumab was driven by new data from other figitumumab studies indicating the feasibility of 30 mg/kg of figitumumab. Subjects received 30 mg/kg figitumumab on Days 1 and 2 of Cycle 1 (loading dose), and on Day 1 of each cycle thereafter.

For both cohorts, subjects continued receiving cyclic figitumumab treatment for up to 17 cycles, until disease progression or an unacceptable toxicity developed, or the subject withdrew consent for further treatment. All subjects were followed up until 18 months after the last subject was enrolled in this dose cohort. The initial 12 subjects dosed with 20 mg/kg or 30 mg/kg dose of figitumumab served as safety cohorts for their dose level. The schedule of activities is presented in Table 1.

Table 1. Schedule of Activities

Protocol Activities	Screening (Pre-Treatment) Period		Each Treatment Cycle (21 Days)					
	≤28 Days Prior to Enrollment	≤14 Days Prior to Enrollment	Day 1 (Pre-Dose)	Day 1	Day 2 (Cycle 1 Only)	Day 15-21[a]	End of Treatment (EOT)[b]	Follow-Up[b]
Informed consent		X						
Medical history		X						
Concomitant medications	Assessed throughout the study							
ECOG PS		X	X[c]					
Height (only at Screening), weight and vital signs (temperature, BP, pulse)		X	X[c]				X	X
Physical examination		X	X[c]				X	X
Laboratory (hematology, serum chemistry, urinalysis, coagulation)[d]		X	X[c]				X	X
ECG[e]		X						
Figitumumab				X	X			
Tumor assessment[f]	X					X	X	X
Adverse events	Assessed throughout the study							
CTCs, IGF-IR positive CTCs, serum markers related to IGF-IR signaling[g]			X[h]					
Tumor biopsy[i]		X		X				
Anonymized genetic analysis			X					
PK[j]			X[j]	X[j]	X		X	X
ADA[k]			X[k]				X	X
Pregnancy test (blood/urine)			X					

ADA = antidrug antibody; BP = blood pressure; CTC = circulating tumor cells; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; IGF-IR = insulin-like growth factor-1 receptor; PK = pharmacokinetics.

a. Between Day 15 and 21, or as determined by standard of care or institutional guidelines.

b. An "end of treatment" visit took place 28 days after the last dose. Follow-up visits were scheduled once a month. However, additional visits could be scheduled, as needed, to monitor either any sustained adverse event (AE) (until resolution or until deemed irreversible by the Investigator), or treatment emergent AEs (up to 150 days after the last dose of figitumumab) or efficacy (until disease progression). Protocol required last follow-up visit was scheduled approximately 150 days after the last figitumumab infusion to collect PK and ADA samples unless the subject received another treatment. Subjects were followed for survival until death or until 18 months after accrual was complete.

c. Beginning Cycle 2, certain predose activities (eg, laboratory tests) could be done up to 72 hour predose. Vital signs might be repeated postdose, if clinically indicated.

d. Hematology, coagulation, serum chemistry and urinalysis was done within 2 weeks (preferably 72 hours) prior to enrollment. Additional safety

Table 1. Schedule of Activities

assessments might have been done as per institutional standard of care. Results of these additional tests were recorded on the case report form (CRF).

e. Additional ECGs might have been performed as medically required.

f. Tumor assessment was made based on standard of care or institutional guidelines. Results was recorded in the CRF. To confirm an objective response, tumor assessment was repeated at least 4 weeks after the initial observation of a response and results were recorded on the CRF.

g. Serum samples for the measurement of markers related to IGF-IR signaling (insulin, growth hormone, insulin-like growth factor-1) were collected on Cycle 1 pre-dosing and Cycle 4 pre-dosing.

h. Blood samples for evaluation of CTCs, IGF-IR positive CTCs were collected on Cycle 1 pre-dosing and Cycle 4 pre-dosing.

i. Tumor tissue was obtained either from available diagnostic pathology specimens (diagnostic paraffin sections or slides) or from new biopsies (pre and post-treatment) of accessible disease. Paraffin sections or slides from previous diagnostic biopsies might be obtained at any time during the study, if consent was obtained. A pre-treatment tumor biopsy might have been obtained at any time from enrollment to prior to dosing after the subject has signed the appropriate informed consent. Post-treatment biopsy was collected preferably at Cycle 2 pre-dosing only from subjects that consented to provide a new (non-diagnostic) pre-treatment biopsy. Biopsy procedures were subject to Investigator and Institutional Review Board/Independent Ethics Committee approval and subject consent.

j. Blood samples for evaluation of figitumumab PK were collected during Cycle 1 up to 2 hours before Day 1 figitumumab infusion, and at 1 hour post-infusion on Day 2. In the subsequent cycles, blood samples for PK analyses were collected up to 2 hours prior to figitumumab infusion in Cycles 2, 3, 4, 5, and 6; and at 1 hour post-figitumumab infusion in Cycle 5. Additional blood samples for PK analyses were collected at the end of treatment and at the fourth scheduled follow-up visit (~150 days after the last figitumumab infusion).

k. Serum samples for evaluation of ADA response was collected up to 2 hours prior to figitumumab infusion in Cycles 1 and 4, at the end of treatment, and at the fourth scheduled follow-up visit (~150 days after the last figitumumab infusion).

Number of Subjects (Planned and Analyzed): Up to 80 evaluable subjects per cohort were planned to be enrolled, for a total of 160 subjects. A total of 168 subjects (78 in the US, 60 in Spain and 30 in the UK) were assigned to the study treatment. All subjects were analyzed for safety and efficacy.

Diagnosis and Main Criteria for Inclusion: Male and female subjects, aged ≥18 years, who had stage IV colorectal cancer; whose disease had worsened despite prior anti-cancer therapy and who had satisfactory bone marrow, kidney and liver function were included in the study. The subjects who were simultaneously treated with another anti-cancer therapy, who had previously received anti-cancer therapy that works like figitumumab (targets insulin-like growth factor receptor) and the pregnant or breast-feeding were excluded.

Study Treatment: Figitumumab was administered as an open-label IV solution. Subjects remained under clinical observation for 1 hour post-infusion. Precautions for anaphylaxis were required to be taken during figitumumab administration, and standard agents for the treatment of hypersensitivity/anaphylactic reactions were to be available. Subjects received Cycles (every 3 weeks) of 20 mg/kg or 30 mg/kg figitumumab via an IV infusion. Subjects received either 20 mg/kg or 30 mg/kg figitumumab on Days 1 and 2 of Cycle 1 (loading dose), and the same dose they received in Cycle 1 was administered on Day 1 of each cycle thereafter. Figitumumab treatment continued for up to 17 cycles, until disease progression, an unacceptable toxicity developed, or the subject withdrew consent. In the event of scheduling conflicts, dosing might have taken place on the designated dosing day ±3 days. Subjects might have received additional cycles of figitumumab upon disease progression if the Investigator considered that there was a possibility of providing clinical benefit. Provisions for the continuation of treatment beyond 17 cycles were to be made if there was continued safety and toleration.

Efficacy, Pharmacokinetic, and Safety Endpoints:

Primary Endpoint: Six-month OS

Secondary Endpoints:

- PFS
- OS
- OR
- Peak and trough concentrations of figitumumab
- ADA response
- CTCs, IGF-IR positive CTCs
- Safety and tolerability

Safety Evaluations: Safety was assessed by clinical examination (including blood pressure and pulse rate), laboratory tests (hematology, serum chemistry, coagulation function, and urinalysis), and 12-lead electrocardiograms (ECGs). National Cancer Institute Common Terminology Criteria for Adverse Events (AEs), version 3.0 was used to classify the severity of AEs.

Statistical Methods:

Safety population: All enrolled subjects who started treatment.

This study was conducted in subjects with advanced, mCRC who had exhausted all available treatment options. Based on literature, median survival in this subject population was estimated to be approximately 5.4 months (range, 4.6 to 6 months; n=649). The primary objective of the study was to assess the 6-month OS. A true probability of ≥0.60 would have been of interest, while further testing should not be pursued if the true probability was 0.45 or lower. Therefore, the hypotheses to be tested were H_0: p=0.45 versus (vs) H_1: p=0.60.

Eighty evaluable subjects per cohort were anticipated to be accrued to the study, with approximately 30 subjects anticipated to be accrued in the first 4 months and 50 in the next 3 months. For each cohort, a test of the cumulative hazard function at 6 months, as described in Case and Morgan, was used for the interim analysis, which was anticipated to take place approximately 6.5 months after the start of accrual. Further accrual and treatment with figitumumab would have been stopped if the test statistic was -0.33 or less. This corresponded to a 6-month survival estimate of approximately 40%. To reject the null hypothesis at the final analysis, at least 44 of 80 subjects (55%) must have been observed to survive ≥6 months. This procedure had a level of approximately 0.047 and power of approximately 0.81. The final test was done at the nominal 0.06 level.

PFS was defined as the time from the date of enrollment to the date of first documentation of disease progression, or to the death from any case.

OS was defined as the time from the date of enrollment to date of death.

Tumor response in subjects with measurable disease was defined according to the Response Evaluation Criteria in Solid Tumors guidelines.

RESULTS

Subject Disposition and Demography: All 168 subjects who were screened for this study received treatment. Eighty-five subjects were enrolled to receive figitumumab at 20 mg/kg and 83 subjects were enrolled to receive figitumumab at 30 mg/kg. All subjects in both treatment cohorts discontinued treatment. A summary of subject evaluation groups is provided in Table 2. The largest proportion of subjects in both the treatment cohorts discontinued the treatment phase of the study due to objective progression or relapse (55 [64.7%] subjects and 58 [69.9%] subjects, respectively). There were 4 (4.7%) and 6 (7.2%) subjects in the figitumumab 20 mg/kg and figitumumab 30 mg/kg treatment cohorts, respectively, who discontinued from the study due to treatment-related AEs (Table 2).

Table 2. Subject Evaluation Groups

Subject Evaluation Groups	Figitumumab 20 mg/kg n (%)	Figitumumab 30 mg/kg n (%)
Screened: N=168		
Assigned to study treatment: N=168		
Treated	85	83
Completed	0	0
Discontinued	85 (100.0)	83 (100.0)
Subject died	5 (5.9)	1 (1.2)
Related to study drug	4 (4.7)	6 (7.2)
Adverse event	4 (4.7)	6 (7.2)
Not related to study drug	76 (89.4)	76 (91.6)
Adverse event	1 (1.2)	2 (2.4)
Global deterioration of health status	19 (22.4)	9 (10.8)
Objective progression or relapse	55 (64.7)	58 (69.9)
Other	0	2 (2.4)
Protocol violation	0	1 (1.2)
Subject refused continued treatment for reason other than adverse event	1 (1.2)	4 (4.8)
Evaluability:		
With the disease under study	85 (100.0)	83 (100.0)
Without first cycle major deviation[a]	85 (100.0)	83 (100.0)
Analyzed for safety:		
Adverse events	85 (100.0)	83 (100.0)
Laboratory data	79 (92.9)	76 (91.6)

N = number of subjects; n = number of subjects with specified criteria.

a. First cycle major deviations included: <50% of the planned Cycle 1 dose of figitumumab (provided the reduction was not due to toxicity) or >150% of the planned Cycle 1 dose of figitumumab or non-protocol anti-cancer agents given in Cycle 1 (provided the change was not due to toxicity or worsening disease).

A summary of demographic characteristics for subjects in this study is presented in Table 3. The demographic and baseline characteristics were similar between the treatment cohorts. The majority of subjects in each treatment cohort were <65 years of age (56 [65.9%] subjects in the figitumumab 20 mg/kg cohort; 59 [71.1%] subjects in the figitumumab 30 mg/kg cohort), male (46 [54.1%] subjects in the figitumumab 20 mg/kg cohort; 48 [57.8%] subjects in the figitumumab 30 mg/kg cohort), and white (80 [94.1%] subjects in the figitumumab 20 mg/kg cohort; 73 [88.0%] subjects in the figitumumab 30 mg/kg cohort).

Table 3. Demographic Characteristics

Demographic Characteristic	Figitumumab 20 mg/kg			Figitumumab 30 mg/kg		
Number of Subjects	Male N=46 n (%)	Female N=39 n (%)	Total N=85 n (%)	Male N=48 n (%)	Female N=35 n (%)	Total N=83 n (%)
Age (years)						
<65	28 (60.9)	28 (71.8)	56 (65.9)	32 (66.7)	27 (77.1)	59 (71.1)
≥65	18 (39.1)	11 (28.2)	29 (34.1)	16 (33.3)	8 (22.9)	24 (28.9)
Median	61.5	57.0	60.0	61.0	58.0	60.0
Mean	60.4	57.7	59.2	59.6	57.5	58.7
SD	11.6	8.3	10.2	10.9	8.9	10.1
Range	33–86	41–71	33–86	23-82	37–74	23–82
Race						
White	43 (93.5)	37 (94.9)	80 (94.1)	41 (85.4)	32 (91.4)	73 (88.0)
Black	2 (4.3)	2 (5.1)	4 (4.7)	1 (2.1)	0	1 (1.2)
Asian	0	0	0	3 (6.3)	1 (2.9)	4 (4.8)
Other	1 (2.2)	0	1 (1.2)	3 (6.3)	2 (5.7)	5 (6.0)
Weight (kg)						
Median	83.4	65.8	73.4	84.0	70.0	76.4
Mean	85.9	68.2	77.8	83.4	72.6	78.9
SD	19.0	14.4	19.1	15.6	15.9	16.5
Range	54.0–143.2	41.0–111.0	41.0–143.2	48.4–116.0	50.0–112.0	48.4–116.0
Height (cm)						
Median	173.0	163.0	166.4	172.7	160.0	167.6
Mean	172.6	161.8	167.6	172.3	160.9	167.5
SD	9.2	6.3	9.6	8.6	7.7	9.9
Range	152.0–192.0	144.0–180.0	144.0–192.0	146.0–190.5	131.0–172.7	131.0–190.5

N = number of subjects; n = number of subjects with specified criteria; SD = standard deviation.

Efficacy and Pharmacokinetic Results:

The survival probability at 6 months in the figitumumab 20 mg/kg and 30 mg/kg cohorts were 49.4% (95% confidence interval [CI] [38.8%, 60.0%]) and 44.1% ([33.4%, 54.9%]) respectively. The probabilities were tested with a binomial test at level 0.06. Neither the figitumumab 20 mg/kg dose cohort nor the figitumumab 30 mg/kg dose cohort showed a significant improvement of 6-month survival probability from the null (0.45) (Table 4). The median OS was 5.8 months (95% CI [4.3, 7.1]) and 5.6 months (95% CI [4.1, 6.9]) in the figitumumab 20 mg/kg and 30 mg/kg cohorts, respectively (Table 4).

Table 4. Overall Survival

Overall Survival	Figitumumab 20 mg/kg N=85 n (%)	Figitumumab 30 mg/kg N=83 n (%)
Number of deaths	82 (96.5)	73 (88.0)
Cause of death		
Disease under study	78 (91.8)	68 (81.9)
Study treatment toxicity	0	0
Unknown	4 (4.7)	4 (4.8)
Other	0	1 (1.2)
Number censored	3 (3.5)	10 (12.0)
Reason for censorship		
Alive	3 (3.5)	6 (7.2)
Subject no longer willing to participate	0	2 (2.4)
Lost to follow-up	0	2 (2.4)
Number of subjects with last contact date >1 year prior to data cutoff date	0	2 (2.4)
Survival probability at Month 6[a] (95% CI)[b]	49.4 (38.8, 60.0)	44.1 (33.4, 54.9)
Kaplan-Meier estimates of time to event (month); quartiles (95% CI)[c]		
25%	2.7 (1.9, 4.1)	2.9 (2.1, 3.6)
50%	5.8 (4.3, 7.1)	5.6 (4.1, 6.9)
75%	12.2 (7.9, 17.0)	11.4 (8.0, 16.2)

CI = confidence interval, N = number of subjects; n = number of subjects with specified criteria.
a. Estimated from the Kaplan-Meier curve.
b. Calculated from the product-limit method.
c. Based on the Brookmeyer and Crowley method.

In the figitumumab 20 mg/kg cohort, 61 (71.8%) subjects had a PFS event (ie, objective disease progression or death); the median PFS was 1.4 months (95% CI [1.3, 1.8]). In the figitumumab 30 mg/kg cohort, 62 (74.7%) subjects had a PFS event; the median PFS was 1.4 months (95% CI [1.3, 1.7]) (Table 5).

Table 5. Progression-Free Survival

Progression Free Survival	Figitumumab 20 mg/kg N=85 n (%)	Figitumumab 30 mg/kg N=83 n (%)
Number of subjects with event	61 (71.8)	62 (74.7)
Type of event		
Objective progression	51 (60.0)	58 (69.9)
Death without objective progression	10 (11.8)	4 (4.8)
Number censored	24 (28.2)	21 (25.3)
Reason for censorship		
No adequate baseline assessments	7 (8.2)	1 (1.2)
No on-study disease assessments	7 (8.2)	11 (13.3)
Given new anti-cancer treatment prior to tumor progression	2 (2.4)	3 (3.6)
Off treatment prior to progression	7 (8.2)	3 (3.6)
Withdrew consent for follow-up	0	0
Lost to follow-up	0	0
Unacceptable gap (>8 weeks) between PD or death to the most recent prior adequate assessment	1 (1.2)	3 (3.6)
In follow-up for progression	0	0
Probability of being event free at Month 6[a] (95% CI)[b]	9.9 (2.5, 17.4)	4.3 (0.0, 9.9)
Kaplan-Meier estimates of time to event (month); quartiles (95% CI)[c]		
25%	1.2 (1.1, 1.3)	1.2 (1.1, 1.3)
50%	1.4 (1.3, 1.8)	1.4 (1.3, 1.7)
75%	2.7 (1.8, 4.0)	2.7 (1.8, 3.0)

CI = confidence interval, N = number of subjects; n = number of subjects with specified criteria;
PD = progressive disease.
a. Estimated from the Kaplan-Meier curve.
b. Calculated from the product-limit method.
c. Based on the Brookmeyer and Crowley method.

There were no complete or partial responses to treatment noted during this study.

Descriptive summary of figitumumab concentration (mg/L) vs time summary is presented in Table 6.

Table 6. Descriptive Summary of Figitumumab Concentration (mg/L) Versus Time Summary

Visit	Figitumumab 20 mg/kg N=85			Figitumumab 30 mg/kg N=83		
	n	Mean	SD	n	Mean	SD
Cycle1/Day1	84			79		
Cycle1/Day2	80	647.0	288.23	77	877.7	230.22
Cycle2/Day1	7	244.0	114.00	8	221.0	119.65
Cycle3/Day1	3	255.7	60.476	2	245.0	19.799
Cycle4/Day1	2	76.30	1.2728	2	427.0	86.267
Cycle5/Day1	13	756.2	239.08	8	745.5	216.14

Summary statistics have been calculated by setting concentration values below the lower limit of quantification to 0.
N = number of subjects; n = number of observations (non-missing concentrations); SD = standard deviation.

All serum ADA samples were negative for anti-figitumumab antibodies in the screening ADA assay.

Biomarker results for CTC (IGF-1R) CTCs are presented in Table 7.

Table 7. Descriptive Statistics of Biomarker

	Figitumumab 20 mg/kg N=85			Figitumumab 30 mg/kg N=83		
	n	**Median**	**SD**	**n**	**Median**	**SD**
Circulating Tumor Cells (IGF-1R)						
Pre-treatment and/or baseline	44	2.02	8.79	71	0.54	1.29
Post-Baseline and/or follow-up	18	0.22	0.55	17	0	0
Circulating Tumor Cells						
Pre-treatment and/or baseline	44	7.25	16.59	71	4.90	9.83
Post-Baseline and/or follow-up	19	1.26	1.94	17	2.18	7.06

IGF-1R = insulin-like growth factor-1 receptor; N = number of subjects; n = number of units analyzed; SD = standard deviation.

Safety Results:

Treatment-emergent non serious AEs (all causalities) in ≥5% subjects are presented in Table 8.

Table 8. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) for ≥5 Subjects

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA Preferred Term	Figitumumab 20 mg/kg N=85 n (%)	Figitumumab 30 mg/kg N=83 n (%)
Number of subjects with adverse events	82 (96.5)	79 (95.2)
Blood and lymphatic system disorders	8 (9.4)	8 (9.6)
Anaemia	6 (7.1)	5 (6.0)
Gastrointestinal disorders	55 (64.7)	60 (72.3)
Abdominal pain	13 (15.3)	11 (13.3)
Abdominal pain upper	8 (9.4)	6 (7.2)
Constipation	16 (18.8)	13 (15.7)
Diarrhoea	12 (14.1)	22 (26.5)
Dyspepsia	2 (2.4)	6 (7.2)
Nausea	21 (24.7)	27 (32.5)
Vomiting	19 (22.4)	16 (19.3)
General disorders and administration site conditions	55 (64.7)	61 (73.5)
Asthenia	27 (31.8)	22 (26.5)
Fatigue	22 (25.9)	29 (34.9)
Mucosal inflammation	4 (4.7)	5 (6.0)
Pain	2 (2.4)	6 (7.2)
Pyrexia	5 (5.9)	3 (3.6)
Infections and infestations	20 (23.5)	11 (13.3)
Urinary tract infection	9 (10.6)	6 (7.2)
Investigations	25 (29.4)	37 (44.6)
Blood alkaline phosphatase increased	5 (5.9)	5 (6.0)
Blood creatinine increased	4 (4.7)	5 (6.0)
Gamma-glutamyltransferase increased	9 (10.6)	11 (13.3)
Weight decreased	10 (11.8)	17 (20.5)
Metabolism and nutrition disorders	50 (58.8)	55 (66.3)
Decreased appetite	34 (40.0)	37 (44.6)
Dehydration	3 (3.5)	9 (10.8)
Hyperglycaemia	22 (25.9)	25 (30.1)
Musculoskeletal and connective tissue disorders	33 (38.8)	30 (36.1)
Back pain	15 (17.6)	11 (13.3)
Muscle spasms	5 (5.9)	7 (8.4)
Musculoskeletal pain	7 (8.2)	3 (3.6)
Pain in extremity	5 (5.9)	1 (1.2)
Nervous system disorders	24 (28.2)	22 (26.5)
Headache	6 (7.1)	8 (9.6)
Lethargy	10 (11.8)	6 (7.2)
Psychiatric disorders	11 (12.9)	12 (14.5)
Insomnia	5 (5.9)	4 (4.8)
Renal and urinary disorders	17 (20.0)	12 (14.5)
Haematuria	5 (5.9)	3 (3.6)
Respiratory, thoracic and mediastinal disorders	22 (25.9)	19 (22.9)
Cough	7 (8.2)	7 (8.4)
Dyspnoea	8 (9.4)	5 (6.0)
Skin and subcutaneous tissue disorders	22 (25.9)	20 (24.1)
Pruritus	9 (10.6)	5 (6.0)
Rash	4 (4.7)	6 (7.2)
Vascular disorders	3 (3.5)	11 (13.3)
Hypertension	2 (2.4)	6 (7.2)

Table 8. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) for ≥5 Subjects

Subjects are only counted once per treatment for each row.
Includes data up to 150 days after last dose of study drug.
MedDRA (version 13.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects evaluable for adverse events; n = number of subjects with adverse events.

A summary of treatment-emergent treatment-related AEs reported for ≥5% of subjects is presented in Table 9. The 2 most frequently experienced treatment-related AEs in the figitumumab 20 mg/kg cohort were hyperglycemia (20 [23.5%] subjects) and decreased appetite and fatigue (each in 19 [22.4%] subjects) and in the figitumumab 30 mg/kg cohort were hyperglycemia (27 [32.5%] subjects) and fatigue (26 [31.3%] subjects).

Table 9. Summary of Treatment-Emergent Adverse Events (Treatment-Related) in ≥5% of Subjects

Preferred Term	Total n (%)
Figitumumab 20 mg/kg	
Any AE	75 (88.2)
Hyperglycemia	20 (23.5)
Decreased appetite	19 (22.4)
Fatigue	19 (22.4)
Asthenia	18 (21.2)
Nausea	14 (16.5)
Diarrhea	12 (14.1)
Lethargy	12 (14.1)
Vomiting	10 (11.8)
Abdominal pain	7 (8.2)
Constipation	7 (8.2)
Weight decreased	6 (7.1)
Figitumumab 30 mg/kg	
Any AE	70 (84.3)
Hyperglycemia	27 (32.5)
Fatigue	26 (31.3)
Decreased appetite	23 (27.7)
Asthenia	19 (22.9)
Nausea	17 (20.5)
Diarrhea	15 (18.1)
Gamma-glutamyl transferase increased	9 (10.8)
Vomiting	7 (8.4)
Lethargy	6 (7.2)
Mucosal inflammation	5 (6.0)
Muscle spasms	5 (6.0)
Rash	5 (6.0)

Medical Dictionary for Regulatory Activities (Version 13.1) coding dictionary applied.
AE = adverse event, n = number of subjects.

Treatment-emergent serious AEs (all causalities) are presented in Table 10.

Table 10. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA Preferred Term	Figitumumab 20 mg/kg N=85 n (%)	Figitumumab 30 mg/kg N=83 n (%)
Number of subjects with adverse events	56 (65.9)	53 (63.9)
Blood and lymphatic system disorders	5 (5.9)	3 (3.6)
Anaemia	3 (3.5)	1 (1.2)
Coagulopathy	0	1 (1.2)
Heparin-induced thrombocytopenia	0	1 (1.2)
Neutropenia	2 (2.4)	0
Ear and labyrinth disorders	0	1 (1.2)
Deafness bilateral	0	1 (1.2)
Gastrointestinal disorders	10 (11.8)	10 (12.0)
Abdominal pain	1 (1.2)	2 (2.4)
Abdominal pain upper	0	1 (1.2)
Ascites	0	1 (1.2)
Constipation	1 (1.2)	0
Diarrhoea	4 (4.7)	4 (4.8)
Gastrointestinal haemorrhage	1 (1.2)	0
Gastrointestinal perforation	0	1 (1.2)
Nausea	2 (2.4)	2 (2.4)
Proctalgia	1 (1.2)	0
Small intestinal obstruction	1 (1.2)	0
Upper gastrointestinal haemorrhage	1 (1.2)	1 (1.2)
Vomiting	2 (2.4)	4 (4.8)
General disorders and administration site conditions	50 (58.8)	44 (53.0)
Asthenia	0	2 (2.4)
Disease progression	49 (57.6)	43 (51.8)
Fatigue	1 (1.2)	0
General physical health deterioration	2 (2.4)	3 (3.6)
Malaise	1 (1.2)	0
Oedema peripheral	1 (1.2)	0
Pyrexia	0	1 (1.2)
Ulcer	1 (1.2)	0
Hepatobiliary disorders	0	2 (2.4)
Cholecystitis	0	1 (1.2)
Hepatic pain	0	1 (1.2)
Infections and infestations	7 (8.2)	6 (7.2)
Abdominal sepsis	0	1 (1.2)
Bacteraemia	0	1 (1.2)
Escherichia infection	0	1 (1.2)
Infection	1 (1.2)	2 (2.4)
Klebsiella bacteraemia	1 (1.2)	0
Lower respiratory tract infection	1 (1.2)	0
Pneumonia	1 (1.2)	1 (1.2)
Pyelonephritis	1 (1.2)	0
Urinary tract infection	3 (3.5)	1 (1.2)
Injury, poisoning and procedural complications	1 (1.2)	1 (1.2)
Fracture	0	1 (1.2)
Spinal cord injury cauda equina	1 (1.2)	0
Investigations	1 (1.2)	0
Blood creatinine increased	1 (1.2)	0
Metabolism and nutrition disorders	3 (3.5)	6 (7.2)

Table 10. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA Preferred Term	Figitumumab 20 mg/kg N=85 n (%)	Figitumumab 30 mg/kg N=83 n (%)
Dehydration	1 (1.2)	3 (3.6)
Diabetes mellitus	1 (1.2)	0
Hyperglycaemia	1 (1.2)	3 (3.6)
Musculoskeletal and connective tissue disorders	3 (3.5)	2 (2.4)
Arthralgia	1 (1.2)	0
Back pain	2 (2.4)	2 (2.4)
Pain in extremity	2 (2.4)	0
Nervous system disorders	4 (4.7)	2 (2.4)
Cerebral haemorrhage	1 (1.2)	0
Cognitive disorder	1 (1.2)	0
Dizziness	1 (1.2)	0
Headache	0	1 (1.2)
Lethargy	2 (2.4)	0
Transient ischaemic attack	0	1 (1.2)
Psychiatric disorders	1 (1.2)	3 (3.6)
Confusional state	1 (1.2)	3 (3.6)
Renal and urinary disorders	4 (4.7)	3 (3.6)
Hydronephrosis	0	1 (1.2)
Renal failure	1 (1.2)	0
Renal failure acute	3 (3.5)	2 (2.4)
Respiratory, thoracic and mediastinal disorders	2 (2.4)	3 (3.6)
Dyspnoea	1 (1.2)	1 (1.2)
Pulmonary embolism	1 (1.2)	2 (2.4)

Subjects are only counted once per treatment for each row.
Includes data up to 150 days after last dose of study drug.
MedDRA (version 13.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects evaluable for adverse events; n = number of subjects with adverse events.

Seven (8.2%) subjects in the figitumumab 20 mg/kg cohort and 11 (13.3%) subjects in the figitumumab 30 mg/kg cohort had treatment-related SAEs (Table 11).

Table 11. Summary of Treatment-Emergent Serious Adverse Events (Treatment-Related)

System Organ Class Preferred Term	Total n (%)
Figitumumab 20 mg/kg	
Any treatment-related serious AE	7 (8.2)
Gastrointestinal disorders	2 (2.4)
Constipation	1 (1.2)
Diarrhea	2 (2.4)
General disorders and administration site conditions	2 (2.4)
Fatigue	1 (1.2)
General physical health deterioration	1 (1.2)
Malaise	1 (1.2)
Edema peripheral	1 (1.2)
Metabolism and nutrition disorders	3 (3.5)
Dehydration	1 (1.2)
Diabetes mellitus	1 (1.2)
Hyperglycemia	1 (1.2)
Nervous system disorders	4 (4.7)
Cognitive disorder	1 (1.2)
Dizziness	1 (1.2)
Lethargy	2 (2.4)
Figitumumab 30 mg/kg	
Any treatment-related serious AE	11 (13.3)
Ear and labyrinth disorders	1 (1.2)
Deafness bilateral	1 (1.2)
Gastrointestinal disorders	3 (3.6)
Diarrhea	2 (2.4)
Vomiting	2 (2.4)
General disorders and administration site conditions	1 (1.2)
Asthenia	1 (1.2)
Metabolism and nutrition disorders	4 (4.8)
Dehydration	1 (1.2)
Hyperglycemia	3 (3.6)
Nervous system disorders	1 (1.2)
Transient ischemic attack	1 (1.2)
Psychiatric disorders	1 (1.2)
Confusional state	1 (1.2)
Renal and urinary disorders	1 (1.2)
Renal failure acute	1 (1.2)

Medical Dictionary for Regulatory Activities (Version 13.1) coding dictionary applied.
AE = adverse event; n = number of subjects.

Deaths: All the 8 (9.4%) subjects in the figitumumab 20 mg/kg cohort and the 1 (1.2%) subject in the figitumumab 30 mg/kg cohort who died on treatment or within 28 days of the last dose of study drug, died of progressive disease (Table 12).

Table 12. Cause of Death Summary

Summary of Subject Deaths	Figitumumab 20 mg/kg N=85 n (%)	Figitumumab 30 mg/kg N=83 n (%)
Total number of deaths	82 (96.5)	73 (88.0)
Subjects who died on treatment or within 28 days of last dose	8 (9.4)	1 (1.2)
Cause of death		
Disease under study	8 (9.4)	1 (1.2)
Subjects who died within 150 days of last dose	49 (57.6)	45 (54.2)
Cause of death		
Disease under study	46 (54.1)	42 (50.6)
Unknown	3 (3.5)	2 (2.4)
Other	0	2 (2.4)

N = number of subjects; n = number of subjects with specified criteria.

Discontinuations: The largest proportion of subjects in the figitumumab 20 mg/kg and figitumumab 30 mg/kg treatment cohorts discontinued the treatment phase of the study due to objective progression or relapse (55 [64.7%] subjects and 58 [69.9%] subjects, respectively). There were 4 (4.7%) and 6 (7.2%) subjects in the figitumumab 20 mg/kg and figitumumab 30 mg/kg treatment cohorts, respectively, who discontinued from the study due to treatment-related AEs. None of the deaths that occurred on study or within 150 days of last dose of study drug were considered related to study treatment. The largest proportion of subjects in the figitumumab 20 mg/kg and figitumumab 30 mg/kg treatment cohorts discontinued the study phase due to death (77 [90.6%] subjects and 72 [86.7%] subjects, respectively).

Hematology and Coagulation: No obvious hematology or coagulation toxicities were noted. The majority of abnormal hematology and coagulation laboratory test results were Grades 1 or 2. The most frequently noted Grade 3 abnormalities in the figitumumab 20 mg/kg cohort were for lymphocytes (absolute) (5 subjects) and in the figitumumab 30 mg/kg cohort were for prothrombin time and prothrombin time/international normalized ratio (each in 5 subjects).

Chemistries: The most common Grade 3 and Grade 4 laboratory test abnormalities noted for the figitumumab 20 mg/kg cohort were related to gamma-glutamyl transferase (GGT) increase, with 20 (26.3%) and 10 (13.2%) subjects, respectively. The most common Grade 3 and Grade 4 laboratory abnormalities noted for the figitumumab 30 mg/kg cohort were also related to GGT increase, with 20 (27.8%) and 6 (8.3%) subjects, respectively. In both cohorts, liver enzymes (aspartate aminotransferase and alkaline phosphatase) were elevated.

Urinalysis: There were no abnormalities related to urine protein for subjects in the figitumumab 20 mg/kg and 30 mg/kg cohorts noted in this study.

Electrocardiograms: ECGs were obtained at Baseline. Of the 85 subjects in the figitumumab 20 mg/kg cohort, 58 (68.2%) had ECGs that were considered to be normal at Baseline, 26 (30.6%) were abnormal, but not clinically significant, and 1 (1.2%) was not done. Of the 83 subjects in the figitumumab 30 mg/kg cohort, 58 (69.9%) had ECGs that were considered

to be normal at Baseline, 24 (28.9%) were abnormal, but not clinically significant, and 1 (1.2%) was not done.

CONCLUSIONS:

Efficacy: The null hypothesis of 45% 6-month survival was not rejected in either cohort. Increasing the figitumumab dose from 20 mg/kg to 30 mg/kg showed no evidence of improved outcome.

Safety: Safety data suggested the figitumumab 20 mg/kg dose was more tolerable than the figitumumab 30 mg/kg dose. There were no drug-related deaths in this study. Hyperglycemia, fatigue, decreased appetite, and asthenia were the most common non-hematologic AEs in both dosing cohorts. GGT increase was the most common biochemical abnormality in both cohorts. There was no detection of ADA against figitumumab.