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

PROTOCOL NO.: A4021032

PROTOCOL TITLE: A Phase 2, Randomized, Open-Label Study of Figitumumab (CP-751,871) Plus Cisplatin (or Carboplatin) and Etoposide, Versus Cisplatin (or Carboplatin) and Etoposide Alone, as First-Line Treatment in Patients With Extensive-Stage Disease Small Cell Lung Cancer

Study Centers: Eight centers took part in the study and enrolled subjects; 3 in the United States (US), 2 each in Spain and Canada, and 1 in Hungary.

Study Initiation Date and Final Completion Date: 20 April 2010 and 11 October 2011. The study was terminated prematurely.

Phase of Development: Phase 2

Study Objective: The objective of the study was to describe the safety and tolerability of etoposide and cisplatin (or carboplatin) ± figitumumab.

METHODS

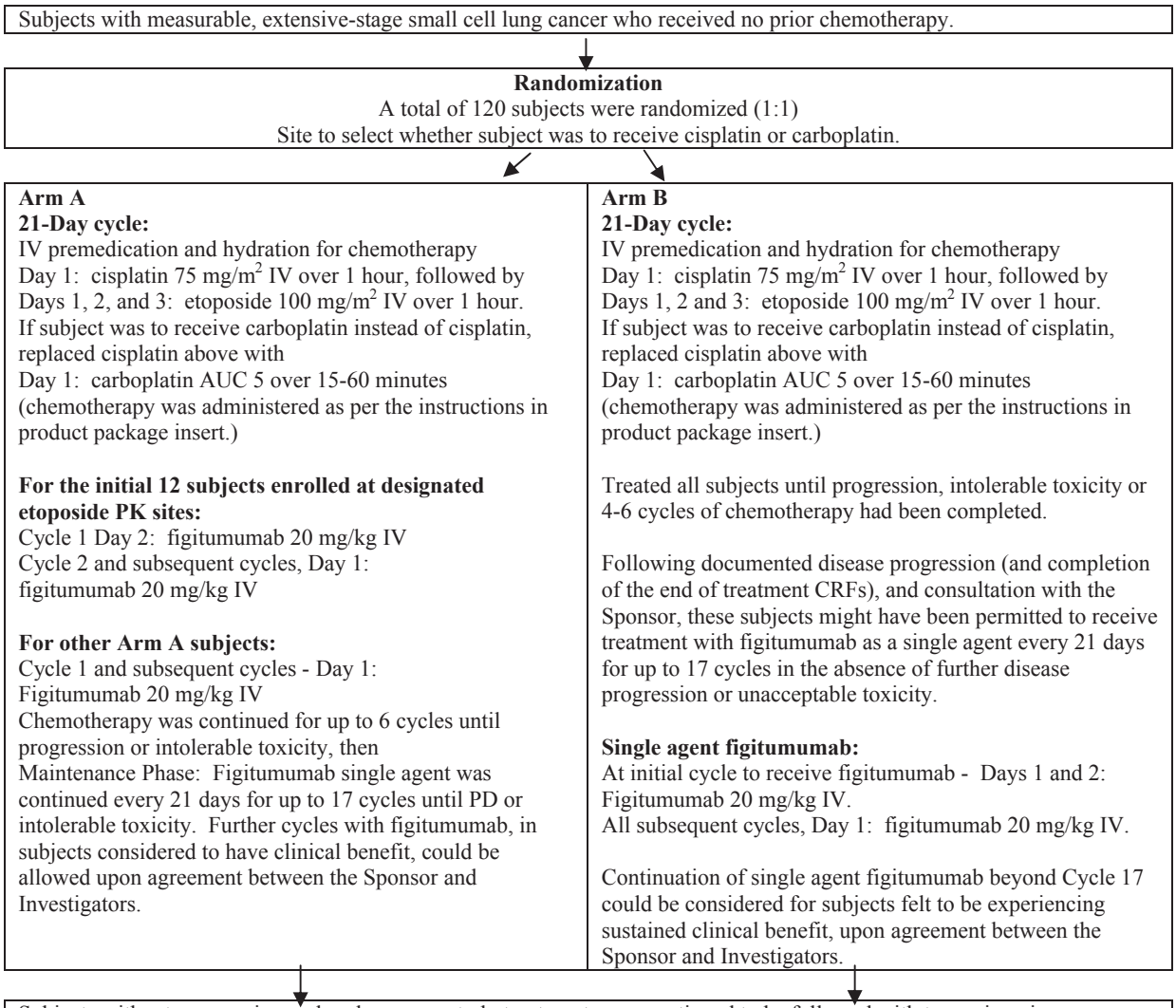
Study Design: This was a randomized, open-label, 2-arm, Phase 2 study that evaluated the safety and efficacy of figitumumab combined with cisplatin (or carboplatin) and etoposide as first-line treatment in subjects with late-stage small cell lung carcinoma (SCLC) by assessment of progression-free survival.

Subjects were randomized 1:1 according to a central computerized system. Selection of carboplatin instead of cisplatin was permitted at the time of randomization.

The 2 arms of the study are depicted in Table 1. For all subjects, each 21-day cycle included treatment with cisplatin or carboplatin on Day 1, and etoposide on Days 1, 2, and 3 for up to 6 cycles, or until progression of disease (PD) or intolerable toxicity. Subjects in Arm A received figitumumab on Day 1 of each cycle except for the 12 etoposide pharmacokinetic (PK) subjects who were to receive figitumumab on Day 2 of Cycle 1, and on Day 1 of each subsequent cycle, according to the Dosage and Administration Instructions (DAI) document. Subjects in Arm A continued figitumumab as a single agent every 21 days for up to 17 cycles until PD or intolerable toxicity. Subjects randomized to Arm B (chemotherapy alone) were permitted to receive treatment with figitumumab as a single agent every 21 days for up to 17 cycles in the absence of further PD or unacceptable toxicity. This treatment was contingent upon 1) documented objective PD by the response evaluation

criteria in solid tumors version 1.1, 2) completion of the appropriate "end of chemotherapy" case report forms, and 3) consultation with the Sponsor.

Table 1. Study Schematics



AUC = area under the curve; CRF = case report form; IV = intravenous; PD = progressive disease; PK = pharmacokinetic.

The schedule of activities for the study is presented in Table 2.

Table 2. Schedule of Activities

	One Cycle (21 Days) Arm A: Cisplatin (or Carboplatin) + Etoposide + Figitumumab (4 Subjects) Arm B: Cisplatin (or Carboplatin) + Etoposide (1 Subject)					Single Agent Figitumumab[a]	EOT Visit[b]	Follow-Up[c]
Activity	**Day 1[d]**	**Day 2**	**Day 3**	**Day 8**	**Day 15**	**Every 3 Weeks**	**Within 28 Days From Last Dose**	**As Defined[c]**
12-lead ECG[e]	X					X	X	
Physical examination (including vital signs, weight)	X					X	X	
Hematology, serum chemistry, coagulation[f]	X		Cycle 1 only	Cycle 1 & 2	Cycle 1 only	X	X	
Pregnancy test (serum or urine)	Per local standard of care							
Adverse events[g]	Continuous							
Concomitant medications								
Chemotherapy[h]	X	Etoposide	Etoposide					
Figitumumab[i]	X					X		
Tumor assessment[j]	X						X	
Anti-figitumumab antibody (ADA)/PK blood sampling[k]	As clinically indicated							

Schedules could vary ±3 days to allow flexibility with scheduling conflicts. Only safety results (eg, AE, SAE, concomitant medications and dosing information) were reported in the CRF. However, all the data collected according to this schedule were saved in the subject's chart and provided to the Sponsor upon request.

ADA = anti-drug antibody; AE = adverse event; CRF = case report form; CT = computed tomography; DAI = dosage and administration instructions; ECG = electrocardiogram; EOT = end-of-treatment; INR = international normalized ratio; MRI = magnetic resonance imaging; PD = pharmacodynamic; PK = pharmacokinetic; SCLC = small cell lung cancer; SAE = serious adverse event.

a. Single agent figitumumab: For Arm A subjects, a 3-week interval occurred between last administration of cisplatin (or carboplatin) + etoposide + figitumumab and initiation of single agent figitumumab maintenance (Arm A). Arm B subjects with documented disease progression could cross over to receive single agent figitumumab, with figitumumab treatment starting as close as possible to 3 weeks from date of last chemotherapy administration. Cross over required 1) adequate recovery from chemotherapy-induced AEs, 2) all inclusion/exclusion criteria be met with the exception of any prior systemic therapy received for SCLC, and 3) Sponsor approval.

b. EOT visit: it was to be performed approximately 28 days from date of last dose of originally assigned study treatment to assess safety. For subjects in Arm B receiving single agent figitumumab after PD, this was to be performed before single agent figitumumab was started and again after the last dose of figitumumab. New safety and tumor assessments only needed to be performed if the prior assessment was performed >7 days previously. Final tumor assessments were not required for study purposes but were allowed per institutional standard.

c. Follow-up visits were to occur 45 and 90 days (±3 days) after the last dose of figitumumab for safety monitoring. Additional visits could be scheduled per Investigator discretion for safety monitoring.

d. Day 1: Cycle 1 Day 1 assessments prior to initiation of treatment needed to be repeated only if the assessments were not performed in the previous 7 days, unless otherwise specified. During subsequent cycles, Day 1 laboratory and tumor assessments were to be performed up to 7 days prior.

e. ECG were performed during screening (in case of cross over). Singlet ECG required pre-figitumumab dosing every 5 cycles (Cycles 5, 10, 15, etc). Only clinically significant ECG abnormalities were recorded (on the AE CRF).

f. Hematology/chemistry labs: hematology tests included: hemoglobin, neutrophil, lymphocyte, and platelet count and white blood cell count. Serum chemistry tests included: glucose- (minimum 4 hour fasting), blood urea nitrogen or urea, creatinine clearance (actual or calculated), sodium, potassium, chloride, bicarbonate, calcium,

Table 2. Schedule of Activities

magnesium, phosphorus, total bilirubin, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), alkaline phosphatase, lactate dehydrogenase, total protein/albumin, uric acid, troponin I and/or T. Coagulation tests included: activated partial thromboplastin time (APTT) and prothrombin time INR. Day 8 laboratory assessments were required for the first 2 cycles only, while those of Day 15 were required for Cycle 1 only. Additional laboratory assessments could be performed per Investigator discretion. Arm B subjects who crossed over to receive figitumumab after evidence of disease progression followed the Cycle 1 and Cycle 2 schedule during the first 2 cycles of figitumumab treatment.

g. Tumor assessments at Baseline within 28 days prior to randomization (eg, chest/liver/adrenal CT; head MRI (preferred) or CT; bone scan), then ~ every 6-8 weeks per institutional practice, continuing until disease progression or initiation of subsequent anticancer therapy. Tumor assessments could be repeated at the EOT visit if necessary for institutional practice, assuming more than 4 weeks had passed since the last evaluation.

h. Adverse events: The reporting period for non-serious AEs terminated a) 90 days after the last dose of study treatment for Arm A subjects, b) 28 days after the last dose of chemotherapy for Arm B subjects, c) or upon the initiation of a new anticancer treatment, whichever occurred first. At the end of the reporting period, the ongoing treatment related AEs were followed until resolution, returned to Baseline grade, chronicity, or initiation of subsequent anticancer treatment. The SAE reporting period ended 90 days after the last study treatment dose for Arm A/cross over subjects and 28 days after the last study treatment dose for Arm B subjects, irrespective of start of other treatment for the primary disease. Any SAE suspected to be related to figitumumab therapy were reported to Pfizer at any time, even if beyond the 90 days follow-up period.

i. Chemotherapy: Appropriate pretreatment was to be administered, including hydration while receiving chemotherapy. Cisplatin (or carboplatin) was infused on Day 1, prior to etoposide. Etoposide were infused on Days 1, 2, and 3 of each cycle. Chemotherapy was administered for up to 6 cycles. Each subject could receive either cisplatin or carboplatin. The option to select cisplatin or carboplatin was available at time of randomization and this treatment could not be changed during the study.

j. Figitumumab infusion: Details for the figitumumab infusion were provided in the current figitumumab DAI. All subjects were weighed within 72 hours prior to dosing for every cycle to ensure they did not experience either a weight loss or gain >10% from the prior weight used to calculate the amount of figitumumab required for dose preparation. Decision to recalculate figitumumab dose based on the weight obtained at each cycle could be in accordance with institutional practice, however if the subject experienced either a weight loss or gain >10%, the amount of figitumumab required for study drug preparation and administration was recalculated using this most recent weight obtained. All subjects were observed in clinic for 1 hour following each figitumumab administration. In case an Arm B subject crossed over to receive single agent figitumumab: At the initial cycle of figitumumab administration, 2 doses of 20 mg/kg figitumumab were administered: the first on Day 1 and the second on Day 2. A single 20 mg/kg dose of figitumumab was administered on Day 1 of subsequent cycles.

k. Figitumumab Anti-Drug Antibody (ADA)/PK samples: In subjects receiving figitumumab (Arm A subjects and Arm B subjects who crossed over to figitumumab), serum samples for ADA and plasma samples for figitumumab PK were collected at Baseline (within 4 hours prior to the first figitumumab infusion) and at time points when there was an AE observation (signs or symptoms) suggesting potential ADA involvement (eg, hypersensitivity reaction).

Number of Subjects (Planned and Analyzed): The planned total sample size was 120 subjects (60 per arm). Nine subjects were enrolled (4 in the US, 2 each in Canada and Spain, and 1 in Hungary), 5 in Arm A and 4 in Arm B.

Diagnosis and Main Criteria for Inclusion: Males and females aged 18 years and older who had histologically confirmed diagnosis of extensive stage disease SCLC, (with tumor biopsy sample required) and with Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 and total insulin-like growth factor 1 (IGF-1) ≥120 ng/ml were included in this study. Subjects with any prior systemic therapy for SCLC and glycosylated hemoglobin A1c (HbA1c) ≥5.7% were excluded from the study.

Study Treatment: Commercially available formulations of etoposide and cisplatin (or carboplatin) were supplied by the study center or by the Sponsor or designee according to local regulation or agreement with the Sponsor prior to the study start. The package insert provided by the manufacturer for instructions on preparation for administration and for the most current information regarding incompatibilities and stability was consulted. In particular, intravenous (IV) set, needles or syringes containing aluminum were avoided for administering cisplatin or carboplatin. Figitumumab was supplied by the Sponsor as a liquid IV solution, and specific preparation, filtration, and dispensing instructions were provided in the DAI document. Filters were required with figitumumab IV solutions and it could be either syringe or in-line filter types.

Appropriate prophylactic measures were taken according to institutional guidelines or the instructions provided by the manufacturer in the package insert prior to administering the chemotherapy. This included appropriate hydration if subject was stratified to receive cisplatin. Subjects might receive prophylactic antibiotic while on chemotherapy. Precautions were taken and preparedness to respond to possible anaphylactic reaction when administering any of the study treatments. For each chemotherapeutic agent, the most current product package insert was referred for guidance on duration of infusion, appropriate side-effect management, dose modifications for toxicity, etc.

Despite having activated over 60 global study sites to enroll subjects, only 9 subjects from 8 sites were enrolled over a period of 9 months. The study demonstrated that it was not feasible to complete enrollment within a reasonable time frame and was closed to further accrual with approval of Protocol Amendment 2 (Amendment 2: to terminate further enrollment into this study for feasibility reasons and consequently the study objectives, end of trial definition, and schedule of activities were revised). The decision to halt enrollment was prompted by lack of feasibility, not by the identification of safety signals or concerns with figitumumab in this study or other active studies. The strict eligibility criteria introduced by Protocol Amendment 1 (Amendment 1: to implement closer safety surveillance throughout the study and to better identify the subpopulation) for baseline HbA1c and total IGF-1 levels resulted in a very high screen failure rate, which significantly contributed to the poor accrual rate.

The study was terminated prematurely; consequently, efficacy and PK evaluations were not performed in this study. Safety and tolerability remained the only objective of the study to be completed.

Safety Endpoints: Assessment of overall safety and toxicity profile characterized by type, frequency and severity, as graded using the National Cancer Institute (NCI)/Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE, v4.0), and its relationship to study therapy.

Safety Evaluations: All subjects who received at least 1 dose of any study drug were considered evaluable for safety. Safety was assessed according to NCI/CTEP CTCAE v4.0 using occurrence of adverse events (AEs), serious AEs (SAEs), clinical examination (including blood pressure and pulse rate), laboratory tests (hematology, serum chemistry, coagulation function, and urinalysis), and 12-lead electrocardiograms (ECGs). A complete physical examination included the assessment of all body systems, the measurement of body weight, height, ECG, pulse and other pertinent vital signs, and assessment of ECOG performance status at Baseline. Target examinations aimed to investigate signs and symptoms were acceptable after the Baseline complete physical examination. ECG recordings were performed in triplicate and singlet, with subject in a supine position, at specified times during the study (Table 2).

Statistical Methods: No statistical analyses were performed.

RESULTS

Subject Disposition and Demography: Table 3 presents a summary of subject disposition.

Table 3. Subject Disposition

	Arm A: Figitumumab, Cisplatin (or Carboplatin) and Etoposide (N=5)	Arm B: Cisplatin (or Carboplatin) and Etoposide (N=4)
Enrolled	5	4
Discontinued from study	5	4
Reason for discontinuation from study		
Death	3	2
Study terminated	0	2
Other	2	0
Analyzed for safety	5	4

N = number of subjects.

A summary of demographic characteristics is presented in Table 4.

Table 4. Demographic Characteristics

	Arm A			Arm B			Total		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Number of subjects	0	5	5	3	1	4	3	6	9
Age (years):									
<18	0	0	0	0	0	0	0	0	0
18-44	0	0	0	1	0	1	1	0	1
45-64	0	4	4	1	1	2	1	5	6
≥65	0	1	1	1	0	1	1	1	2
Mean	0	60.4	60.4	51.3	61	53.8	51.3	60.5	57.4
SD	0	4.4	4.4	12.1	0	11	12.1	3.9	8.2
Range	0	56-66	56-66	42-65	61-61	42-65	42-65	56-66	42-66
Race:									
White	0	4	4	3	1	4	3	5	8
Black	0	1	1	0	0	0	0	1	1
Weight (kg):									
Mean	0	70.7	70.7	77.3	65	74.2	77.3	69.8	72.3
SD	0	13.2	13.2	18.8	0	16.6	18.8	12	13.9
Range	0	53.0-89.9	53.0-89.9	64.0-98.9	65.0-65.0	64.0-98.9	64.0-98.9	53.0-89.9	53.0-98.9
N	0	5	5	3	1	4	3	6	9
Height (cm):									
Mean	0	157.8	157.8	173.9	161	170.7	173.9	158.3	163.5
SD	0	6.4	6.4	6.9	0	8.6	6.9	5.9	9.7
Range	0	151.0-166.0	151.0-166.0	166.0-178.0	161.0-161.0	161.0-178.0	166.0-178.0	151.0-166.0	151.0-178.0
N	0	5	5	3	1	4	3	6	9

Arm A: Investigational treatment with cisplatin (or carboplatin), etoposide, and figitumumab.
Arm B: Control treatment with cisplatin (or carboplatin) and etoposide.
N = number of subjects with specified criteria; SD = standard deviation.

Efficacy Results: Efficacy evaluations were not performed in this study. The study was terminated prematurely due to poor feasibility and the programmatic decisions to discontinue further development of figitumumab.

Safety Results: All subjects enrolled reported AEs during the study. When considering treatment-related AEs that occurred in >1 subject, fatigue, elevated gamma-glutamyltransferase, hemoglobin decreased, leukopenia, decreased appetite, and weight decreased were unique to Arm A. Otherwise, the safety profiles between Arm A and Arm B were similar. Treatment-emergent AEs (TEAEs) by all-causality are summarized in Table 5.

Table 5. Treatment-Emergent Adverse Events (All-Causalities)

System Organ Class MedDRA (v14.1) Preferred Term	Arm A n (%)	Arm B n (%)
Number of subjects evaluable for adverse events:	5	4
Number (%) of subjects with adverse events	5 (100.0)	4 (100.0)
Blood and lymphatic system disorders	5 (100.0)	4 (100.0)
Anaemia	0	2 (50.0)
Granulocytopenia	1 (20.0)	0
Leukopenia	2 (40.0)	0
Neutropenia	4 (80.0)	4 (100.0)
Thrombocytopenia	1 (20.0)	1 (25.0)
Ear and labyrinth disorders	1 (20.0)	1 (25.0)
Deafness	1 (20.0)	0
Tinnitus	0	1 (25.0)
Endocrine disorders	1 (20.0)	0
Hypothyroidism	1 (20.0)	0
Eye disorders	2 (40.0)	0
Ocular hyperaemia	1 (20.0)	0
Visual acuity reduced	1 (20.0)	0
Gastrointestinal disorders	4 (80.0)	4 (100.0)
Abdominal discomfort	1 (20.0)	0
Constipation	1 (20.0)	2 (50.0)
Diarrhoea	1 (20.0)	1 (25.0)
Dry mouth	0	1 (25.0)
Gastrooesophageal reflux disease	0	1 (25.0)
Gingival bleeding	1 (20.0)	0
Gingivitis	1 (20.0)	0
Nausea	3 (60.0)	4 (100.0)
Stomatitis	2 (40.0)	0
Vomiting	1 (20.0)	2 (50.0)
General disorders and administration site conditions	4 (80.0)	3 (75.0)
Asthenia	1 (20.0)	2 (50.0)
Fatigue	2 (40.0)	0
Feeling cold	1 (20.0)	0
Influenza like illness	0	1 (25.0)
Infusion site extravasation	1 (20.0)	0
Mucosal inflammation	0	1 (25.0)
Non-cardiac chest pain	0	1 (25.0)
Oedema peripheral	1 (20.0)	0
Pyrexia	1 (20.0)	0
Infections and infestations	2 (40.0)	2 (50.0)
Candidiasis	0	2 (50.0)
Otitis media	0	1 (25.0)
Urinary tract infection	2 (40.0)	0
Investigations	4 (80.0)	1 (25.0)
Alanine aminotransferase increased	1 (20.0)	0
Aspartate aminotransferase increased	1 (20.0)	0
Blood alkaline phosphatase increased	1 (20.0)	0
Blood creatinine increased	1 (20.0)	0
Creatinine renal clearance decreased	1 (20.0)	0
Gamma-glutamyltransferase increased	2 (40.0)	0
Haemoglobin decreased	2 (40.0)	0
Weight decreased	2 (40.0)	1 (25.0)
Metabolism and nutrition disorders	3 (60.0)	3 (75.0)
Cachexia	0	1 (25.0)
Decreased appetite	2 (40.0)	1 (25.0)
Dehydration	0	2 (50.0)
Hyperglycaemia	1 (20.0)	0
Hyperuricaemia	1 (20.0)	0
Hypocalcaemia	1 (20.0)	0

Table 5. Treatment-Emergent Adverse Events (All-Causalities)

System Organ Class MedDRA (v14.1) Preferred Term	Arm A n (%)	Arm B n (%)
Hypokalaemia	0	1 (25.0)
Hypomagnesaemia	1 (20.0)	1 (25.0)
Hyponatraemia	1 (20.0)	1 (25.0)
Musculoskeletal and connective tissue disorders	1 (20.0)	4 (100.0)
Arthralgia	0	1 (25.0)
Back pain	0	3 (75.0)
Bone pain	0	1 (25.0)
Mobility decreased	1 (20.0)	0
Musculoskeletal pain	0	1 (25.0)
Neck pain	0	1 (25.0)
Pain in extremity	1 (20.0)	1 (25.0)
Nervous system disorders	4 (80.0)	2 (50.0)
Balance disorder	0	1 (25.0)
Convulsion	0	1 (25.0)
Dizziness	0	1 (25.0)
Dysgeusia	0	1 (25.0)
Headache	0	1 (25.0)
Neuropathy peripheral	1 (20.0)	1 (25.0)
Peripheral sensory neuropathy	1 (20.0)	0
Somnolence	2 (40.0)	0
Psychiatric disorders	2 (40.0)	1 (25.0)
Confusional state	1 (20.0)	0
Insomnia	2 (40.0)	1 (25.0)
Renal and urinary disorders	1 (20.0)	0
Polyuria	1 (20.0)	0
Reproductive system and breast disorders	1 (20.0)	0
Breast pain	1 (20.0)	0
Respiratory, thoracic and mediastinal disorders	2 (40.0)	1 (25.0)
Cough	1 (20.0)	0
Dyspnoea	0	1 (25.0)
Epistaxis	2 (40.0)	0
Hiccups	1 (20.0)	0
Hypoxia	0	1 (25.0)
Nasal ulcer	1 (20.0)	0
Pharyngeal disorder	1 (20.0)	0
Sneezing	1 (20.0)	0
Skin and subcutaneous tissue disorders	3 (60.0)	3 (75.0)
Alopecia	3 (60.0)	2 (50.0)
Dermatitis acneiform	0	1 (25.0)
Dry skin	1 (20.0)	0
Nail disorder	1 (20.0)	0
Pruritus	1 (20.0)	0
Rash papular	1 (20.0)	0
Vascular disorders	1 (20.0)	1 (25.0)
Deep vein thrombosis	1 (20.0)	0
Hypotension	0	1 (25.0)
Pallor	1 (20.0)	1 (25.0)

Arm A: Investigational treatment with cisplatin (or carboplatin), etoposide, and figitumumab.
Arm B: Control treatment with cisplatin (or carboplatin) and etoposide.
Subjects are only counted once per treatment for each row.
Includes data up to 150 days after last dose of study drug.
MedDRA (version 14.1) coding dictionary applied.
MedDRA (v14.1) = Medical Dictionary for Regulatory Activities (version 14.1); n = number of subjects.

Table 6 presents treatment related TEAEs reported in >1 subject in decreasing order of frequency.

Table 6. Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA Preferred Term Occurring in >1 Subject (Decreasing Order of Frequency)

Preferred Term	Total n (%)
Arm A, N=5	
Any AEs	5 (100.0)
Neutropenia	4 (80.0)
Alopecia	3 (60.0)
Nausea	3 (60.0)
Decreased appetite	2 (40.0)
Fatigue	2 (40.0)
Gamma-glutamyltransferase increased	2 (40.0)
Haemoglobin decreased	2 (40.0)
Leukopenia	2 (40.0)
Vomiting	2 (40.0)
Weight decreased	2 (40.0)
Arm B, N=4	
Any AEs	4 (100.0)
Nausea	4 (100.0)
Neutropenia	4 (100.0)
Alopecia	2 (50.0)
Anaemia	2 (50.0)
Vomiting	2 (50.0)

Arm A: Investigational treatment with cisplatin (or carboplatin), etoposide, and figitumumab.
Arm B: Control treatment with cisplatin (or carboplatin) and etoposide.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with that characteristic; N = number of subjects in each arm.

Treatment-Emergent Serious Adverse Events (All-Causalities): Table 7 presents the treatment-emergent SAEs (all-causality) reported during the study.

Table 7. Treatment-Emergent Serious Adverse Events (All-Causalities)

System Organ Class MedDRA (v14.1) Preferred	Arm A n (%)	Arm B n (%)
Number of subjects evaluable for adverse events	5	4
Number (%) of subjects with adverse events	4 (80.0)	2 (50.0)
Blood and lymphatic system disorders	1 (20.0)	1 (25.0)
Anaemia	0	1 (25.0)
Febrile neutropenia	1 (20.0)	0
Cardiac disorders	1 (20.0)	0
Myocardial infarction	1 (20.0)	0
Gastrointestinal disorders	1 (20.0)	0
Diarrhoea	1 (20.0)	0
Vomiting	1 (20.0)	0
General disorders and administration site conditions	1 (20.0)	1 (25.0)
Disease progression	1 (20.0)	1 (25.0)
Metabolism and nutrition disorders	1 (20.0)	0
Dehydration	1 (20.0)	0
Psychiatric disorders	1 (20.0)	0
Psychotic disorder	1 (20.0)	0
Respiratory, thoracic and mediastinal disorders	1 (20.0)	0
Pulmonary embolism	1 (20.0)	0

Arm A: Investigational treatment with cisplatin (or carboplatin), etoposide, and figitumumab.
Arm B: Control treatment with cisplatin (or carboplatin) and etoposide.
Subjects are only counted once per treatment for each row.
Includes data up to 150 days after last dose of study drug.
MedDRA (version 14.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects.

Treatment-Emergent Treatment-Related Serious Adverse Events: Table 8 presents the treatment-emergent treatment-related SAEs reported during the study. Treatment-related SAEs were reported for 3 subjects (60%) in Arm A (Grade 2 diarrhea and vomiting, Grade 3 dehydration and psychotic disorder, and Grade 4 febrile neutropenia, all in 1 subject each) and for 1 subject (25%) in Arm B (Grade 3 anemia).

Table 8. Treatment-Emergent Treatment-Related Serious Adverse Events Reported During the Study (By Descending Order of Frequency, All Cycles)

Preferred Term	Total n (%)
Arm A, N=5	
Any AEs	3 (60.0)
Dehydration	1 (20.0)
Diarrhoea	1 (20.0)
Febrile neutropenia	1 (20.0)
Psychotic disorder	1 (20.0)
Vomiting	1 (20.0)
Arm B, N=4	
Any AEs	1 (25.0)
Anaemia	1 (25.0)

Arm A: Investigational treatment with cisplatin (or carboplatin), etoposide, and figitumumab.
Arm B: Control treatment with cisplatin (or carboplatin) and etoposide.
AE = adverse event; N = number of subjects in each treatment arm; n = number of subjects with adverse events.

Deaths: Five subjects died during the study: 3 in Arm A and 2 in Arm B. All deaths were due to PD, with the exception of 1 subject who died of myocardial infarction. This event was not considered related to study drug.

Permanent Discontinuations due to Adverse Events: Table 9 presents permanent discontinuations from study due to AEs.

Table 9. Permanent Discontinuations From Study Due to Adverse Events

Treatment	Serial Number/ Gender/Age	Treatment Phase	Final Dose	Duration of Treatment (Days)	Cycle	Cycle Day	Day of Last Dose	Relationship to Study Drug	Reason
Arm A	1/female/66	Active	1720 mg	28	Follow-up	65	323	Not related	Other (Sponsor denied this subject continuation on study due to SUSAR attributed to figitumumab)
	2/female/59	Active	1100 mg	19	Follow-up	55	148		Subject died
	3/female/56	Active	164 mg	18	Follow-up	74	129	Not related	Other (started new chemotherapy regimen for primary disease on 13-December-2010)
	4/female/64	Active	131 mg	18	Follow-up	11	115		Subject died
	5/female/57	Active	170 mg	9	3	13	54		Subject died
Arm B	6/male/42	Active	180 mg	12	Follow-up	27	66		Subject died
	7/male/65	Active	180 mg	18	Follow-up	170	106	Not related	Study terminated by Sponsor
	8/female/61	Active	169 mg	18	Follow-up	292	129	Not related	Study terminated by Sponsor
	9/male/47	Active	177 mg	18	Follow-up	38	110		Subject died

SUSAR = serious unexpected suspected adverse reaction

Laboratory Abnormalities: Most Grade 3 or 4 laboratory abnormalities were hematologic in nature and included low absolute neutrophil count, low white blood cell count, low absolute lymphocyte count, and low platelet count. No Grade 3 or 4 hyperglycemia was reported. No subjects discontinued treatment due to laboratory abnormalities.

CONCLUSIONS: This study was terminated prematurely due to operational feasibility and figitumumab programmatic decisions. Early termination of the study was not related to any safety concern. As per Protocol Amendment 2, only the safety data were analyzed. When considering treatment-related AEs that occurred in >1 subject, fatigue, elevated gamma-glutamyltransferase, hemoglobin decreased, leukopenia, decreased appetite, and weight decreased were unique to Arm A. There were no events of Grade 3 or 4 hyperglycemia. Additionally, no treatment-related deaths were reported for this study. Due to data being available for only 9 subjects, it is difficult to draw any other meaningful conclusions.