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

PROTOCOL NO.: A4021002

PROTOCOL TITLE: A Phase 1b Dose Escalation/Phase 2 Randomized, Non-Comparative, Multiple Center, Open-Label Study of CP-751,871 in Combination With Paclitaxel and Carboplatin and of Paclitaxel and Carboplatin Alone as First Line Treatment for Advanced Non-Small Cell-Lung Cancer

Study Centers:

Phase 1b: Nine (9) study centers took part in the study and enrolled subjects; 1 center in Canada, 3 centers in Spain and 5 centers in the United States (US).

Phase 2: Seventeen (17) study centers took part in the study and randomized subjects; 1 center in Canada, 1 center in Italy, 2 centers in Spain and 13 centers in the US.

Study Initiation Date and Final Completion Date: 01 March 2005 to 08 August 2011

Phases of Development: Phase 1b/2

Study Objectives:

Phase 1b Objectives (Dose-Escalation Phase):

Primary:

- To define the safety, tolerability, maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of figitumumab when given in combination with paclitaxel and carboplatin

Secondary:

- To characterize the Pharmacokinetic (PK) of figitumumab in combination with paclitaxel and carboplatin
- To test for the occurrence of a human anti-human antibody (HAHA) response to figitumumab
- To monitor any signs of efficacy of figitumumab when given in combination with paclitaxel and carboplatin

Phase 1b Objectives (Figitumumab and Erlotinib Extension Periods):

Primary:

- To further characterize the safety and tolerability of the RP2D of figitumumab when given in combination with paclitaxel and carboplatin
- To characterize the safety and tolerability of the combination of figitumumab, erlotinib, paclitaxel, and carboplatin

Secondary:

- To further characterize the PK of the RP2D of figitumumab in combination with paclitaxel and carboplatin
- To characterize the pharmacodynamics (insulin-like growth factor 1 [IGF-1] accumulation) of clonal and non-clonal figitumumab in combination with paclitaxel and carboplatin after multiple dosing
- To monitor any signs of efficacy of figitumumab in this setting
- To test for the occurrence of HAHA response to figitumumab

Phase 2 Objectives:

Primary:

- To assess the efficacy of multiple doses of figitumumab in combination with paclitaxel and carboplatin in subjects with non-small cell lung cancer ([NSCLC]; all NSCLC histologies)
- To assess the efficacy of figitumumab in combination with paclitaxel and carboplatin in subjects with NSCLC tumors of primary histology other than adenocarcinoma

Secondary:

- To assess the safety and tolerability of multiple doses of figitumumab in combination with paclitaxel and carboplatin
- To further characterize the PK of clonal and non-clonal figitumumab in combination with paclitaxel and carboplatin after multiple dosing
- To test for the occurrence of HAHA response to figitumumab
- To explore health-related quality of life outcomes in both treatment arms

METHODS

Study Design: This was a Phase 1b dose escalation/Phase 2 randomized, non-comparative, multiple-center, open-label study of figitumumab in combination with paclitaxel and carboplatin and of paclitaxel and carboplatin alone in advanced NSCLC.

The trial was conducted in 2 portions, Phase 1b and Phase 2. The Phase 1b portion contained 3 parts: Phase 1b dose escalation, Phase 1b extension of figitumumab at the RP2D, and Phase 1b extension with erlotinib.

The dose escalation schema is presented in Table 1.

Table 1. Dose Level

Cohort	Dose
-4	0.05 mg/kg
-3	0.1 mg/kg
-2	0.2 mg/kg[a]
-1	0.4 mg/kg[a]
1	0.8 mg/kg (starting dose)
2	1.5 mg/kg
3	3.0 mg/kg
4	6.0 mg/kg
5	10 mg/kg
6	20 mg/kg

Current Preparation and Administration Protocol (PAP) of figitumumab allows testing of doses of figitumumab up to 20 mg/kg. Doses >20 mg/kg were considered less feasible.
a. The originally planned dose levels of 0.2 mg/kg and 0.4 mg/kg were not studied in this trial.

The Phase 1 study schema for Phase 1b, Phase 1b extension and Phase 1b extension in combination with erlotinib are provided in Figure 1, Figure 2 and Figure 3 respectively.

Figure 1. Overview of Phase 1b Study Design

<table>
<tr><th colspan="3">Study Schema
(Phase 1b Portion [Escalation Cohort])</th></tr>
<tr><td colspan="3">Subjects with documented advanced non-hematological malignancy for whom paclitaxel and carboplatin was a reasonable treatment option.</td></tr>
<tr><td colspan="3">↓</td></tr>
<tr><th colspan="3">Cycle 1
(21-day cycle)</th></tr>
<tr><td rowspan="2">CYCLE</td><td>Day 1</td><td>Administer IV premedication for chemotherapy.
Administer paclitaxel, 200 mg/m^2 IV over 3 hours.
Administer carboplatin, AUC=6 IV over 15-60 minutes.
Administer figitumumab IV.</td></tr>
<tr><td>Day 22 (Cycle 2, Day 1)</td><td>Began Cycle 2 with above prescribed Day 1 Combination therapy regimen. (This and all subsequent cycles were normally of 21 days).</td></tr>
<tr><td colspan="3">↓</td></tr>
<tr><td colspan="3">Escalate figitumumab in cohorts of 3 to 6 subjects per dose level until the maximum tolerated dose was defined.</td></tr>
<tr><td colspan="3">And</td></tr>
<tr><td colspan="3">Treat each subject until progression or intolerable toxicity occurs. If subject's disease was stable or responding, continue chemotherapy for 6 cycles and continue figitumumab for up to 17 cycles.</td></tr>
<tr><td colspan="3">↓</td></tr>
<tr><td colspan="3">Once the maximum tolerated dose (MTD) of figitumumab was determined begin Phase 1b extension portion. If the MTD was not identified, subjects in the Phase 1b extension were to be evaluated at the RP2D.</td></tr>
<tr><td colspan="3">All subjects enrolled in the Phase 1b portion of the study were followed for disease outcome.</td></tr>
</table>

AUC = area under curve; IV = intravenous; RP2D = recommended phase 2 dose.

Figure 2. Overview of Phase 1b Extension Study Design

Study Schema (Phase 1b Extension [RP2D Cohort])		
Subjects with Stage IIIB disease included those with a pleural effusion or Stage IV or recurrent (after surgery/radiation), non-small cell lung cancer following complete resection who had received no prior chemotherapy.		
Enroll 6-12 subjects.		
↓		
CYCLE	Day 1	Administer IV premedication for chemotherapy. Administer paclitaxel, 200 mg/m^2 IV over 3 hours. Administer carboplatin, AUC=6 IV over 15-60 minutes. Administer figitumumab IV.
	Day 22	Begin Cycle 2 with above prescribed Day 1 combination therapy regimen. (This (Cycle 2, Day 1) and all subsequent cycles will normally be 21 day cycles).
↓		
If subject's disease was stable or responding, continued chemotherapy as per Cycle 2 for up to 6 cycles total and continued figitumumab for up to 17 cycles.		
Once at least 6 subjects of the Phase 1b extension had completed Cycle 1, the protocol continued to the Phase 2 portion.		

AUC = area under curve; IV = intravenous; RP2D = recommended phase 2 dose.

Figure 3. Overview of Phase 1b Extension in Combination with Erlotinib Study Design

Study Schema (Phase 1b Extension in Combination with Erlotinib)		
Subjects with Stage IIIB disease including those with a pleural effusion or Stage IV or recurrent (after surgery/radiation), non-small-cell lung cancer (NSCLC) of primary squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma histology who have received no prior chemotherapy.		
Enroll at least 6 subjects with NSCLC of primary adenocarcinoma histology and could have been extended up to 24 subjects to further characterize safety and tolerability.		
↓		
CYCLE	Day 1	Administer IV premedication for chemotherapy. Administer paclitaxel, 200 mg/m^2 IV over 3 hours. Administer carboplatin, AUC=6 IV over 15-60 minutes. Administer figitumumab IV 20 mg/Kg. Start administration of oral erlotinib 150 mg/day continuous.
	Day 22	Begin Cycle 2 with above prescribed Day 1 combination therapy regimen.
↓		
Treat each subject until intolerable toxicity develops. If subject's disease was stable or responding, continue chemotherapy as per Cycle 2 for up to 6 cycles total and continue figitumumab alone or with erlotinib for up to 1 year.		

AUC = area under curve; IV = intravenous.

The Phase 2 portion of the study assessed the efficacy of the RP2D of figitumumab in combination with paclitaxel and carboplatin in chemotherapy naive subjects with advanced NSCLC. The Phase 2 portion of the study included 2 parts: a randomized Simon 2-Stage design and a nonrandomized expansion cohort. The Phase 2 portion of the study was initiated once at least 6 subjects of the Phase 1b expansion had completed Cycle 1. Phase 2 was a 2-arm, randomized, noncomparative study of figitumumab in combination with paclitaxel and carboplatin (Arm A), and of paclitaxel and carboplatin alone (Arm B). Subjects were randomized 2:1 (Arm A: Arm B). In total, 156 evaluable subjects were to be enrolled in the Phase 2 portion of the study. In order to minimize the expected number of subjects treated if the treatment was not efficacious; the Simon Optimum 2-Stage design was used in Arm A.

The Phase 2 study schema is provided in Figure 4.

Figure 4 Overview of Study Design

<table>
<tr><td colspan="2">Study Schema
(Randomized Phase 2 Portion)</td></tr>
<tr><td colspan="2">Subjects with Stage IIIB disease including those with a pleural effusion or Stage IV or recurrent (after surgery/radiation), measurable NSCLC following complete resection who received no prior chemotherapy.</td></tr>
<tr><td colspan="2">⬇</td></tr>
<tr><td colspan="2">Randomize</td></tr>
<tr><td>↙</td><td>↘</td></tr>
<tr><td><u>Arm A</u>
21 Day cycle
IV premedication for chemotherapy
Paclitaxel 200 mg/m^2 IV Day 1
Carboplatin AUC = 6 IV Day 1
Figitumumab IV Day 1.</td><td><u>Arm B</u>
21 Day cycle:
IV premedication for chemotherapy
Paclitaxel 200 mg/m^2 IV Day 1
Carboplatin AUC = 6 IV Day 1.</td></tr>
<tr><td colspan="2">Stage I: Randomize 66 subjects evaluable for response (at least 44 in Arm A, 22 in Arm B). Subjects were to have measurable disease at Baseline, adequate Baseline assessment and received at least 1 dose of study drug to be evaluable for response.</td></tr>
<tr><td>⬇</td><td>⬇</td></tr>
<tr><td>Reject Regimen A as being effective at the end of Stage I and stop the trial if: there were <14 objective responses.</td><td>If Arm A was rejected, Arm B was to be closed.
If Arm A continued, initiated Stage II.</td></tr>
<tr><td>⬇</td><td>⬇</td></tr>
<tr><td colspan="2">Stage II: Randomized 90 additional subjects evaluable for response (at least 60 in Arm A, 30 in Arm B).</td></tr>
<tr><td>Regimen A was considered effective at the end of Stage II if:
There were at least 37 objective responses in Stages I and II.</td><td>⬇</td></tr>
<tr><td>Continued chemotherapy for up to 6 cycles and continued figitumumab for up to 17 cycles.</td><td>Treated all subjects until progression, intolerable toxicity or 6 cycles of therapy had been completed. Subjects in Arm B under some circumstances could receive figitumumab: PC subjects that were considered to be in stable disease after at least 4 cycles of treatment or in progressive disease at any time during the study could receive additional cycles of treatment with figitumumab in combination with PC or figitumumab alone.</td></tr>
<tr><td colspan="2">All subjects enrolled in the Phase 2 portion were followed for disease outcome and survival. A tumor assessment was to be completed at least every 2 cycles. Appropriate tumor assessment was to be completed 7 to 10 days prior to the planned start of the next cycle (dose) in order to determine if the subject could continue on therapy in the absence of progressive disease. To confirm an objective response, tumor measurement was to be repeated after 4 weeks.

Stage III: Approximately 30 additional subjects with tumor histology other than adenocarcinoma were to be enrolled (for a total of at least 50 subjects with non-adenocarcinoma NSCLC in Stages II and III [Arm A only]). Subjects in Stage III were not to be randomized.</td></tr>
</table>

AUC = area under curve; IV = intravenous; NSCLC = non-small-cell lung cancer; PC = paclitaxel and carboplatin.

Number of Subjects (Planned and Analyzed): One hundred fifty-six evaluable subjects were planned for enrollment in the Phase 2 portion of the study. The study randomized a total of 282 subjects: 14 in Canada, 26 in Italy, 58 in Spain, and 184 in the US.

Diagnosis and Main Criteria for Inclusion: Male or female subjects (≥18 years) with Stage IIIB NSCLC, including those with a pleural effusion, [Stage IV or recurrent (after surgery/radiation)], and measurable NSCLC following complete resection with no prior chemotherapy. The main criterion for inclusion was diagnosis of advanced/metastatic lung cancer. Exclusion criteria included previous treatment with chemotherapy, uncontrolled diabetes and history/active cardiovascular disease.

Study Treatment:

Phase 1b: In the Phase 1b portion (both dose-escalation and extension) of the study, subjects enrolled to receive figitumumab in combination with paclitaxel and carboplatin in an open-labeled manner on an outpatient basis. Upon completion of enrollment, subjects were successively assigned to the next available treatment slot at a dose level based on the previous cohort's safety evaluation and ongoing observations of earlier treated subjects. The starting dose for figitumumab in the Phase 1b portion of the study was defined by the review of the safety and tolerability of an ongoing Phase 1 first-in-human study. The dose escalation schema is presented in Table 1.

Figitumumab was a given in 3-week (21 days) cycles. Chemotherapy agents (carboplatin and paclitaxel) and figitumumab were administered on Day 1 of each cycle.

- Paclitaxel 200 mg/m^2 was administered intravenous (IV) over 3 hours on Days 1 of each cycle up to 6 cycles.

- Carboplatin area under curve (AUC) 6 was administered by IV infusion over 15-60 minutes, following completion of paclitaxel infusion. The dose of carboplatin was calculated using the Calvert formula based on the glomerular filtration rate (GFR) which was calculated based on creatinine clearance level using Cockroft-Gault formula. The treatment regimen was to be repeated every 21 days unless a delay was required.

- Figitumumab was administered by IV infusion, following completion of carboplatin infusion.

Precautions for anaphylaxis were observed during figitumumab administration and treatment of any hypersensitivity reactions (including anaphylactic reactions) were to be treated per standard of care. For the first 2 dose levels of the Phase 1b portion of the study, subjects remained under clinical observation for 2 hours post-infusion. When there was no evidence of severe adverse effects, subjects receiving figitumumab in subsequent dose levels were observed by the clinical staff for approximately 1 hour following infusion.

The study drug infusion was stopped when symptoms of fever or chills developed and acetaminophen was given. Once symptoms had resolved, re-infusion at a lower rate (50%)

could have been attempted. In the event of an unexpected anaphylactic reaction during administration, the figitumumab infusion was stopped and the subject was treated as clinically indicated; no re-infusion of figitumumab was recommended.

The subjects assigned to receive erlotinib in the extension cohort received standard dose of paclitaxel and carboplatin in combination with figitumumab at a dose of 20 mg/kg.

Oral erlotinib was administered at a starting dose of 150 mg/day on Day 1 of each cycle. The erlotinib dose was administered at approximately the same time each day.

Phase 2: Figitumumab was given in a 3-week (21 days) cycles. Chemotherapy agents (carboplatin and paclitaxel) and figitumumab were administered on Day 1 of each cycle.

- Paclitaxel 200 mg/m^2 was administered IV over 3 hours on Days 1 of each cycle up to 6 cycles.

- Carboplatin AUC 6 was administered by IV infusion over 15-60 minutes, following completion of paclitaxel infusion. The dose of carboplatin was calculated using the Calvert formula based on the GFR which was calculated based on creatinine clearance level using Cockroft-Gault formula. The treatment regimen was to be repeated every 21 days unless a delay was required.

- Figitumumab was administered by IV infusion, following completion of carboplatin infusion. The initial dose used in the Phase 2 was 10 mg/kg, as this was the maximum feasible dose at the time. In the second stage of the trial, after 20 mg/kg became feasible, subjects were treated with 20 mg/kg.

The study drug infusion was stopped when symptoms of fever or chills developed and acetaminophen was given. Once symptoms resolved, re-infusion at a lower rate (50%) could have been attempted. In the event of an unexpected anaphylactic reaction during administration, the figitumumab infusion was stopped and the subject was treated as clinically indicated; no re-infusion of figitumumab was recommended. Specific information about the formulation and packaging of figitumumab was given in the Dosage and Administration Instruction, which was provided separately.

Efficacy, Pharmacokinetic and Pharmacodynamic Endpoints:

Phase 1b:

Primary:

- Safety, tolerability, maximum tolerated dose and RP2D

Secondary:

- PK parameters of figitumumab
- HAHA
- Response Rate

- Number of circulating tumor-related cells (CTCs), CTC IGF-IR expression and circulating endothelial cells

Phase 2:

Primary:

- Objective response rate

Secondary:

- Safety and tolerability
- PK parameters of figitumumab at steady state
- HAHA
- Time to progression, progression free survival rate and duration of response
- Health-related quality of life as measured by the EORTC-QLQ-C30/-LC13
- Symptom severity and interference as measured by the M.D.F Anderson Symptom Inventory (MDASI)

Safety Evaluations: All subjects who started treatment in any cohort were considered evaluable for safety. Safety was assessed by collection of adverse events (AEs), clinical examination (including blood pressure and pulse rate), laboratory tests (hematology, serum chemistry, and coagulation function), and 12-lead electrocardiograms. AEs were reported according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Events that were continuations of baseline abnormalities were considered treatment-emergent adverse events (TEAEs) only if there was an increase in grade over Baseline. Initially, the active collection of all serious adverse events (SAEs) continued until 28 days after the last dose of study therapy or initiation of subsequent anticancer therapy, whichever occurred first. During the conduct of the Phase 2 portion of the study and the erlotinib extension cohort, secondary to the prolonged half-life of figitumumab, the safety reporting period was extended to 150 days from last dose of study medication due to the prolonged half-life of the drug (21 days). Deaths and other SAEs were reported through 150 days following the last dose of study drug, irrespective of any intervening treatment. Sites who did not participate in Phase 2 portion were not notified of an extension to the safety reporting period through 150 days following the last dose of study drug, but used the originally-defined 28-day safety reporting period.

Additional samples or procedures may have been undertaken, as medically required, at the discretion of the Investigator. These data were recorded on the case report forms (CRF).

Statistical Methods:
Full Analysis Set: All registered and treated subjects (Phase 1b) or all enrolled subjects (Phase 2).

Response-Evaluable Analysis Set: All registered subjects (Phase 1b) or enrolled and had disease under study (Phase 2) who received treatment; had measurable disease, and an adequate Baseline tumor assessment were be evaluated for response.

Safety Analysis Set: All subjects who received at least 1 dose of any agent were evaluated for safety analysis.

Phase 1b:

Efficacy Evaluations and Analysis: Disease and response assessments were defined using the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.0). The best overall response (BOR) was the best response recorded since the start of treatment until disease progression or recurrence (taking as reference for progressive disease (PD) the smallest measurement since treatment started). For complete response (CR) and partial response (PR) the best response assignment depended on the achievement of both the initial establishment and confirmation of CR or PR no less than 28 days after criteria for response were first met. BOR was determined programmatically.

Subjects that developed brain metastasis during the study could have been interrupted to the treatment to receive a course of cranial radiation and restarted study treatment after a recovery period of 1 week. In cases where radiologic assessment of the brain was not performed during screening, a new baseline evaluation (prior to retreatment) was used to determine subsequent response assessments.

Objective response rate was defined as the percentage of evaluable subjects with objective (CR and PR) response and based on the total number of response evaluable subjects.

Phase 1b:

Analysis of Pharmacokinetic, Pharmacodynamic and Other Parameters:

PK concentrations and parameters for Cycle 1 and Cycle 4 were summarized descriptively by treatment cohort. All PK concentration data were provided as listings.

HAHA concentration data were provided as listings.

Phase 2:

Efficacy Evaluations and Analysis: Disease and response assessments were defined using the RECIST; version 1.0. The BOR was the best response recorded since the start of treatment until disease progression or recurrence (taking as reference for PD the smallest measurement since treatment started). For CR) and PR the best response assignment depended on the achievement of both the initial establishment and confirmation of CR or PR no less than 28 days after criteria for response were first met. BOR was determined programmatically.

Objective response rate was defined as the percentage of evaluable subjects with objective (CR and PR) response based on the total number of response evaluable subjects. An exact 90% confidence interval (CI) for the objective response rate was determined as well as the corresponding p-value.

Another secondary endpoint for efficacy was progression-free survival (PFS). PFS was defined as the time from date of enrollment (randomization) to date of first documentation of progression or symptomatic deterioration, or death due to any cause. Subjects last known to be alive and progression-free were censored at the date of the last objective disease assessment that verified lack of disease progression, with the following exception: subjects who went off treatment prior to progression were continued to be followed for progression (or death) until a new treatment was initiated. If the subject had clearly not progressed by the time of new treatment, censorship was to be at the date of new treatment. Otherwise the date of new treatment was to be used as the progression date. Treatment with figitumumab in Arm B subjects was considered as subsequent anti-cancer therapy. Other subsequent anti-cancer therapies were not collected. Since there were some subjects who had questionable failure dates (such as progression or death not documented until after multiple missing assessments), a sensitivity analysis was done to censor subjects at the last assessment if there was more than 14 weeks between the last tumor assessment and death. The sensitivity definition of PFS is reported herein.
PFS was estimated using the method of Kaplan and Meier, and hazard ratio (HR) was estimated using Cox regression.

Analysis of PK/Pharmacodynamics

Figitumumab plasma PK parameters for Cycle 4 were not determined as specified in the protocol or statistical analysis plan for Phase 2. The decision not to perform this analysis was based on the status of the figitumumab development program and an assessment of the limited value that such an analysis would provide. Plasma figitumumab concentration data were listed but not summarized.

HAHA data were provided as listings.

RESULTS

Subject Disposition and Demography:

Phase 1b: Subject disposition is summarized in Table 2.

Table 2. Summary of Subject Disposition and Subjects Analyzed

Number (%) of Subjects	Figitumumab 0.05 mg/kg	Figitumumab 0.1 mg/kg	Figitumumab 0.8 mg/kg	Figitumumab 1.5 mg/kg	Figitumumab 3 mg/kg	Figitumumab 6 mg/kg	Figitumumab 10 mg/kg[a]	Figitumumab 20 mg/kg	Erlotinib Cohort
Screened:68									
Assigned to study treatment: 61									
Treated	3	2	4	3	3	3	17	7	17
Completed	1	0	0	1	0	0	0	0	1
Discontinued	2	2	4	2	3	3	17	7	16
Evaluability:									
Without 1st cycle major deviation[b]	3	2	4	3	3	3	17	6	17
Measurable disease at baseline	3	2	3	1	3	2	15	7	16
Adequate Baseline assessment	3	2	4	1	3	2	15	7	16
Analyzed for safety:									
Adverse events	3	2	4	3	3	3	17	7	17
Laboratory data	3	2	4	3	3	3	17	7	17

Discontinuations occurred outside the lag period has been attributed to the last study treatment received.
Assigned to study treatment refer to the number of subjects assigned to a treatment and also included in test drug data set.
Two (2) subjects were assigned to the 10 mg/kg and erlotinib cohort treatment group, respectively but were not treated.
RP2D = recommended Phase 2 dose.

a. Included dose escalation and extension subjects treated at 10 mg/kg as 10 mg/kg was initially established as RP2D before 20 mg/kg was tested.

b. First cycle major deviations include: <75% of the planned Cycle 1 dose of figitumumab (provided the reduction was not due to toxicity); >125% of the planned Cycle 1 dose of figitumumab; other agents of the combination not given in Cycle 1 (provided omission was not due to toxicity); or 1 of the following drugs: dexamethasone, diphenhydramine or cimetidine, not administered in Cycle 1.

Overall, 56 subjects discontinued the study: 40 subjects in the figitumumab dose escalation and extension cohort and 16 subjects in the erlotinib cohort. The most common reason for discontinuation in the treatment phase of the study was due to objective progression.

There were no meaningful differences between the treatment cohorts for any of the measured demographic characteristics. The majority of subjects in each treatment cohort were male (24/42 subjects in the figitumumab dose escalation and extension cohort and 9/17 subjects in the erlotinib cohort). The details of subject demographics are presented in Table 3.

Table 3. Demographic Characteristics

	Phase 1 Figitumumab Dose Escalation and Extension Cohort			Erlotinib Cohort		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
Number (%) of subjects	24	18	42	9	8	17
Age (years)						
18-44	0	2	2	1	0	1
45-64	15	9	24	6	6	12
≥65	9	7	16	2	2	4
Mean	61.3	58.7	60.2	58.6	58.4	58.5
SD	10.6	12.5	11.4	10.0	10.8	10.0
Range	45-80	26-77	26-80	44-76	45-79	44-79
Race						
White	22	16	38	9	7	16
Black	0	1	1	0	0	0
Asian	2	1	3	0	1	1
Weight (kg)						
Mean	86	65.5	77.2	80.9	65.4	73.6
SD	21.5	12.8	20.8	19.1	12.1	17.6
Range	62.0-152.0	46.7-95.0	46.7-152.0	59.0-122.0	51.2-89.0	51.2-122.0
Height (cm)						
Mean	176.9	161.7	170.4	173.4	163.3	168.7
SD	8.1	6.1	10.5	5.5	5.4	7.4
Range	161.4-193.0	152.0-172.7	152.0-193.0	167.0-182.0	154.2-170.2	154.2-182.0

SD = standard deviation.

Phase 2: Subject disposition is summarized in Table 4. A total of 221 subjects were assigned to study drug. One hundred and sixty three subjects were enrolled on the randomized part of the Phase 2 study, 107 to Arm A and 56 to Arm B1. Fifty-eight (58) subjects were treated with 10 mg/kg figitumumab and 49 subjects were treated with 20 mg/kg figitumumab.

Out of 163 subjects, 101 were evaluable for response in Arm A and 52 subjects were evaluable for response in Arm B1. Additionally, 57 subjects were enrolled on the non-randomized part of the Phase 2 study, all of whom were treated, but 1 subject was not treated with figitumumab. Fifty-three (53) subjects were evaluable for response; however 1 subject had NSCLC with adenocarcinoma histology.

Table 4. Summary of Subject Disposition and Subjects Analyzed

Number (%) of Subjects	Arm A 10 mg/kg	Arm A 20 mg/kg	Arm B1	Arm B2	Arm A Non-Randomized[a]
Screened: 241					
Assigned to Study Treatment: 221					
Treated	58	49	56	22	56
Completed	0	2 (4.1)	2 (3.6)	1 (4.5)	3 (5.4)
Discontinued from the study	58 (100.0)	47 (95.9)	32 (57.1)	21 (95.5)	53 (94.6)
Crossover	0	0	22 (39.3)	0	0
Evaluability:					
Measurable disease at baseline	53 (91.4)	48 (98.0)	52 (92.9)	22 (100.0)	53 (94.6)
Adequate baseline assessment	53 (91.4)	48 (98.0)	53 (94.6)	22 (100.0)	53 (94.6)
Analyzed for safety:					
Adverse events	58 (100.0)	49 (100.0)	56 (100.0)	22 (100.0)	56 (100.0)
Laboratory data	58 (100.0)	48 (98.0)	54 (96.4)	22 (100.0)	56 (100.0)

Discontinuations occurred outside the lag period has been attributed to the last study treatment received.
Assigned to study treatment refer to the number of subjects randomized or assigned to a treatment and also included in test drug data set.
Lag = 150 days (Included data up to 150 days after last dose of study drug).
Arm B1 included all Arm B2 subjects without regard to treatment status.
Arm B2 consisted of a subset of subjects who crossed over from Arm B1 to receive treatment with figitumumab as described in the study design.
a. Non-randomized extension cohort treated with 20 mg/kg.

The largest proportion of subjects in each treatment arm discontinued the treatment phase of the study due to objective progression.

Demography is summarized for all randomized/enrolled subjects. There were no meaningful differences between the treatment arms for any of the measured demographic characteristics. The majority of subjects in each treatment arm were male (75 [68.81%] Arm A, 34 [61.82%] Arm B, and 42 [73.68%] Arm A non-randomized). The details of subject demographics are presented in Table 5.

Table 5. Demographic Characteristics

	Arm A Figitumumab + Paclitaxel and Carboplatin			Arm B Paclitaxel and Carboplatin			Arm A Non-Randomized[a] Figitumumab + Paclitaxel and Carboplatin		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Number (%) of subjects	75	34	109	34	21	55	42	15	57
Age (years)									
18-44	7 (9.3)	2 (5.9)	9 (8.3)	0	2 (9.5)	2 (3.6)	0	2 (13.3)	2 (3.5)
45-64	33 (44.0)	19 (55.9)	52 (47.7)	18 (52.9)	13 (61.9)	31 (56.4)	15 (35.7)	4 (26.7)	19 (33.3)
≥65	35 (46.7)	13 (38.2)	48 (44.0)	16 (47.1)	6 (28.6)	22 (40.0)	27 (64.3)	9 (60.0)	36 (63.2)
Mean	61.7	59.7	61.1	62.8	61.0	62.1	65.2	62.9	64.6
SD	11.3	10.0	10.9	8.7	9.6	9.0	8.3	11.3	9.1
Range	35-80	41-76	35-80	46-78	38-77	38-78	48-85	38-76	38-85
Race									
White	65 (86.7)	31 (91.2)	96 (88.1)	34 (100.0)	16 (76.2)	50 (90.9)	38 (90.5)	14 (93.3)	52 (91.2)
Black	4 (5.3)	1 (2.9)	5 (4.6)	0	3 (14.3)	3 (5.5)	4 (9.5)	0	4 (7.0)
Asian	1 (1.3)	0	1 (0.9)	0	0	0	0	0	0
Other	5 (6.7)	2 (5.9)	7 (6.4)	0	2 (9.5)	2 (3.6)	0	1 (6.7)	1 (1.8)
Weight (kg)									
Mean	80.2	71.9	77.6	79.9	72.8	77.2	78.8	74.1	77.6
SD	13.4	18.4	15.5	18.4	19.0	18.8	14.9	16.0	15.2
Range	55.0-120.0	44.1-119.1	44.1-120.0	48.0-126.0	45.8-129.0	45.8-129.0	54.4-120.8	42.0-106.0	42.0-120.8
N	73 (97.3)	34 (100.0)	107 (98.2)	34 (100.0)	21 (100.0)	55 (100.0)	42 (100.0)	15 (100.0)	57 (100.0)
Height (cm)									
Mean	174.5	162.3	170.6	171.7	161.4	167.7	175.3	163.0	171.9
SD	8.4	6.2	9.6	7.7	5.6	8.6	7.7	4.1	8.8
Range	154.0-193.0	143.0-172.7	143.0-193.0	153.0-188.0	149.9-172.0	149.9-188.0	158.0-188.0	155.0-170.1	155.0-188.0
N	73 (97.3)	34 (100.0)	107 (98.2)	34 (100.0)	21 (100.0)	55 (100.0)	40 (95.2)	15 (100.0)	55 (96.5)

Demography characteristics were tabulated for all randomized/enrolled subjects.
N = number of subjects; SD = standard deviation.
a. Non-randomized extension cohort treated with 20 mg/kg.

Efficacy, Pharmacokinetic and Pharmacodynamic Results:

Phase 1b:

Efficacy Results:

Best Overall Response:

A summary of BOR for each cohort is provided in Table 6. The objective response rate (ORR, defined as CR + PR) was 33.3% (12 subjects) in the figitumumab dose escalation and extension cohort and 25.0% (4 subjects) in the erlotinib cohort. None of the subjects had a complete response; 12 subjects (33.3%) in the figitumumab dose escalation and extension cohort and 4 subjects (25.0%) in the erlotinib cohort had a PR. All of the PRs were observed in NSCLC subjects, except for 1 PR in an ovarian cancer subject.

Table 6. Summary of Best Overall Response - Response Evaluable Population

Best Overall Response	Phase I Figitumumab Dose Escalation and Extension Cohort (N=36)	Erlotinib Cohort (N=16)
	n (%)	n (%)
Complete response	0	0
Partial response	12 (33.3)	4 (25.0)
Unconfirmed complete response	0	0
Unconfirmed partial response	0	0
Stable/no response	12 (33.3)	7 (43.8)
Objective progression	7 (19.4)	3 (18.8)
Symptomatic deterioration	0	0
Early death	0	0
Indeterminate	5 (13.9)	2 (12.5)
Objective response rate (CR+PR)	12 (33.3)	4 (25.0)

Response evaluable population referred to subjects who had measurable disease at Baseline, adequate Baseline assessment, and received at least 1 dose of study drug.
CR = complete response; N = total number of subjects in a given treatment group; n = number of subjects with data; PR = partial response.

Pharmacokinetic Results:

Plasma figitumumab concentration data for samples analyzed >1 year after collection were not considered valid since figitumumab concentrations in plasma had been shown to decrease after 1 year under the storage conditions used (-20°C). Only PK parameters determined using valid concentration results are presented and discussed here. However, there were a number of samples analyzed outside of the storage stability period (>1 year after collection).

Reportable PK parameters were obtained for all dose levels, except the lowest dose of 0.05 mg/kg. The number of observations for each PK parameter within a dose group varied based on the available data. Apparent terminal half-life ($t_{1/2;}$ Cycle 1 and Cycle 4) and AUC_{inf} (Cycle 1 only) were reported if the goodness of fit statistic for the linear regression was ≥0.9, and the percent of AUC_{inf} extrapolated was ≤30%. If the plasma figitumumab concentration at 504 hours postdose was not available (504 hour post-dose sample = predose

sample from the next Cycle), AUC_{504} was not reported unless the concentration in the prior sample was below the limit of quantitation or, in the case of Cycle 1, if AUC_{inf} was reportable.

PK parameters (excluding data outside of 1-year storage stability) are summarized in Table 7 for Cycle 1 and Table 8 for Cycle 4. Plasma concentration at the end of infusion (C_{endinf}) and AUC for the 3-week dosing cycle (AUC_{504}) increased with increasing dose for both Cycle 1 and Cycle 4. Increases in AUC_{504} generally appeared to be dose proportional at dose ≥0.8 mg/kg at both Cycle 1 and Cycle 4. Mean values for apparent $t_{1/2}$ for Cycle 1 were approximately 10 days at doses ≥3 mg/kg. For Cycle 4, only 3 subjects had reportable $t_{½}$ estimates: (2) subjects at 0.8 mg/kg (2.97 and 7.75 days) and 1 subject at 6 mg/kg (15.4 days). Moderate accumulation of approximately 2-fold was observed with repeated administration every 3 weeks at doses ≥3 mg/kg.

PK results for the subjects receiving erlotinib in addition to paclitaxel and carboplatin were similar to those seen for subjects receiving the same 20 mg/kg figitumumab dose without erlotinib (all subjects received paclitaxel and carboplatin) at both Cycle 1 and Cycle 4.

Table 7. Summary of Plasma Figitumumab Pharmacokinetic Parameters for Cycle 1 (Excluding Data Outside of 1-Year Storage Stability)

Figitumumab	C_{endinf} (mg/L)		AUC_{504} (mg.hr/L)		AUC_{inf} (mg.hr/L)		$t_{½}$ (hr)	
Dose (mg/kg)	n	Mean (%CV)[a]	n	Mean (%CV)[a]	n	Mean (%CV)[a]	n	Mean ± SD[a]
0.1	1	1.51	1	22.3	0	--	0	--
0.8	4	17.34 (59)	4	2011 (52)	3	1434 (64)	3	2.84 ± 1.82
1.5	3	37.47 (24)	1	5320	0	--	0	--
3	3	75.17 (30)	2	7820, 17800	2	11300, 22200	2	9.12, 12.5
6	3	147.3 (18)	2	27200, 33800	1	41200	1	8.35
10	1		1		4	69180 (15)	4	9.56 ± 2.02
	4	261.3 (24)	0	54650 (26)				
20	6	415.7 (25)	5	79820 (27)	1	121000	1	11.1
20 (Erlotinib	1	485.0 (27)	1	85240 (40)	7	107400 (35)	7	9.89 ± 1.81
cohort)	6		7					

The lower limit of quantification is 0.120 mg/L.
%CV = percent coefficient of variation; AUC_{504} = area under the plasma concentration-time profile (AUC) from time 0 to 504 hours, the end of the 3-week dosing cycle (Day 22); AUC_{inf} = AUC extrapolated to infinity; C_{endinf} = concentration at end of infusion; n = number of subjects with reportable data; SD = standard deviation; $t_{½}$ = apparent terminal half-life.
a. Individual value(s) for n<3.

Table 8. Summary of Plasma Figitumumab Pharmacokinetic Parameters for Cycle 4 (Excluding Data Outside of 1-Year Storage Stability)

Figitumumab Dose (mg/kg)	n	C_{endinf} (mg/L) Mean (%CV)[a]	n	AUC_{504} (mg.hr/L) Mean (%CV)[a]	n	C_{504} (mg/L) Mean (%CV)[a]	n	Rac Mean (%CV)[a]
0.1	2	1.59, 4.36	1	77.6	1	0.00	1	3.48
0.8	2	18.0, 20.3	2	1780, 3040	2	0.00, 0.926	2	0.61, 1.41
1.5	1	40.7	0	--	0	--	0	--
3	2	79.4, 122	2	14700, 31700	2	21.8, 33.6	2	1.78, 1.88
6	1	327	1	52500	1	21.2	1	1.55
10	8	331.1 (38)	7	94360 (12)	7	125.3 (13)	7	1.98 (15)
20	3	440.3 (48)	1	214000	1	357	1	2.26
20 (Erlotinib cohort)	9	447.3 (47)	6	133200 (16)	7	158.6 (17)	6	1.96 (22)

The lower limit of quantification is 0.120 mg/L.
%CV = percent coefficient of variation; AUC_{504} = area under the plasma concentration-time profile (AUC) from time 0 to 504 hours, the end of the 3-week dosing cycle (Day 22); C_{504} = concentration at 504 hours; C_{endinf} = concentration at end of infusion; hr = hour(s); n = number of patients with reportable data;
Rac = accumulation ratio (Cycle 4 AUC_{504} / Cycle 1 AUC_{504}).
a. Individual value(s) for n <3.

HAHA Result

Among available results, with the exception of 3 samples from 1 subject, no serum samples were positive for HAHA. The positive HAHA results for 2 subjects were not associated with any hypersensitivity reactions.

Phase 2:

Efficacy Results:

Best Overall Response:

The primary efficacy endpoint of this study was the objective response (CR or PR). A summary of BOR for each arm is provided in Table 9.

The estimate of probability of confirmed response on Arm A was 37.4%, with 90% CI from 29.2 to 46.1. The primary test of H0: p=0.28 was rejected at level 0.05, p=0.027. The estimate of probability of response (confirmed plus unconfirmed) was 53.5%.

The estimate of probability of confirmed response on reference Arm B1 was 27.5%, consistent with the null hypothesis specified for the trial. The estimate of probability of response (confirmed plus unconfirmed) was 41.2%.

The estimate of probability of confirmed response in Arm A from Stage 1, treated with 10 mg/kg was 40.0% (55.6% confirmed plus unconfirmed response), which met the Stage 1 requirements.

Table 9. Summary of Best Overall Response - Response Evaluable Population

Number (%) of Subjects Best Overall Response	Arm A All Randomized (N=99)	Arm B1 (N=51)	Arm A Non-Randomized[a] (Non-Adenocarcinoma) (N=52)
Objective response rate (CR+PR)	37 (37.4%)	14 (27.5%)	20 (38.5%)
90 % Exact CI[b]	[29.2, 46.1]	[17.4, 39.5]	[27.1, 50.8]
Confirmed + Unconfirmed	53 (53.5%)	21 (41.2%)	28 (53.8%)
Adenocarcinoma[c]	16/50 (32.0%)	2/20 (10.0%)	
Non-adenocarcinoma[c]	21/49 (42.9%)	12/31 (38.7%)	
Stage 1	N=45	N=22	
Objective response rate (CR+PR)	18 (40.0%)	7 (31.8%)	
90 % Exact CI[b]	[27.7, 53.3]	[16.0, 51.5]	
Confirmed + unconfirmed response	25 (55.6%)	9 (40.9%)	
Stage 1 adenocarcinoma[c]	6/20 (30.0%)	2/10 (20.0%)	
Stage 1 non-adenocarcinoma[c]	12/25 (48.0%)	5/12 (41.7%)	

Response evaluable population refers to subjects who had measurable disease at Baseline, adequate Baseline assessment, and have received at least 1 dose of study drug.
CI = confidence interval; CR = complete response; N = total number of subjects in a given treatment group; PR = partial response.

a. Non-randomized extension cohort treated with 20 mg/kg; 1 non-randomized subject with Non-small cell lung cancer of adenocarcinoma histology is not included in this tabulation.
b. Used exact method based on binomial distribution.
c. Objective response rate (CR+PR).

Non-adenocarcinoma NSCLC Verification Cohort Results:

Subjects with non-adenocarcinoma from the 20 mg/kg cohort of the randomized part of the trial were combined with the subjects accrued to the post randomization cohort of non-adenocarcinoma to test whether the initial observation of high response in 10 mg/kg subjects could be verified. The estimate of probability of response for the Stage 1 (10 mg/kg) non-adenocarcinoma subjects was 48.0% (60.0% confirmed plus unconfirmed response, N=25). The estimate of probability of response in the verification cohort (21 from the subjects randomized to 20 mg/kg and 52 non-randomized subjects) was 37.0% (27 responses) (54.8% confirmed plus unconfirmed) with 90 % CI from 27.5 to 47.2. The final results for non-adenocarcinoma NSCLC verification cohort did not reject H_0: p=0.3 at the 0.05 level, p=0.121.

Progression Free Survival (PFS):

Although the trial was not designed as comparative, relative PFS results of Arm A and subset by assigned dose of figitumumab to Arm B were assessed for additional evidence of activity of the combination. Analysis of PFS is complicated because figitumumab treatment was allowed under certain conditions for Arm B subjects (crossover). Twenty-two (22) subjects received subsequent treatment with figitumumab, where 15 of the subjects did not have documented progression when figitumumab treatment was started. A summary of PFS as determined by the Investigator is provided in Table 10.

Overall, 156 events of objective progression or death occurred (44 [75.9%] Arm A 10 mg/kg, 40 [81.6%] Arm A 20 mg/kg, 33 [58.9%] Arm B1 and 39 [69.6%] Arm A non-randomized). The PFS was similar for all groups, and no randomized group had a HR approximately <0.75 relative to Arm B1. All observed medians were consistent with expected median PFS for first line NSCLC. The HR for Arm A 20 mg/kg relative to Arm B was 0.816 (95% CI 0.547, 1.216).

Table 10. Summary of Progression Free Survival (Method 2) by Dose Assigned

	Arm A 10 mg/kg (N=58) n (%)	Arm A 20 mg/kg (N=49) n (%)	Arm B1 (N=56) n (%)	Arm A Non-Randomized[a] (N=56) n (%)
Number of subjects with an event	44 (75.9)	40 (81.6)	33 (58.9)	39 (69.6)
Type of event				
Objective progression	34 (58.6)	35 (71.4)	26 (46.4)	32 (57.1)
Symptomatic deterioration without objective progression	4 (6.9)	3 (6.1)	4 (7.1)	1 (1.8)
Death without objective progression or symptomatic deterioration	6 (10.3)	2 (4.1)	2 (3.6)	6 (10.7)
Started new treatment with progression unknown	0	0	1 (1.8)	0
Number censored	14 (24.1)	9 (18.4)	23 (41.1)	17 (30.4)
Reason for censorship				
In follow-up for progression	5 (8.6)	0	3 (5.4)	3 (5.4)
Withdrew consent for additional follow-up	5 (8.6)	2 (4.1)	2 (3.6)	7 (12.5)
Lost to follow-up	1 (1.7)	1 (2.0)	0	0
Started new treatment without progression	0	0	14 (25.0)	0
Unacceptable gap (>14 weeks) between PD or Death to the most recent prior adequate assessment	3 (5.2)	6 (12.2)	4 (7.1)	7 (12.5)
Probability of being event-free at 6 months[b] (90% CI[c])	30.9 [20.1, 42.5]	33.0 [21.2, 45.4]	27.1 [14.3, 41.6]	34.3[22.5, 46.5]
Kaplan-Meier estimates of time-to-event (month) quartiles (90% CI)[d]				
25%	2.6 [1.9, 3.2]	2.9 [2.6, 3.9]	2.7 [1.5, 3.6]	3.1 [1.8, 3.9]
50%	4.4 [3.8, 5.6]	4.5 [3.9, 5.6]	4.3 [3.9, 5.4]	5.1 [4.0, 5.8]
75%	6.4 [5.6, 6.9]	6.4 [5.6, 7.9]	6.9 [5.1, 9.7]	7.5 [5.8, 11.1]
Versus Arm B1				
Hazard ratio[e]	1.041	0.816		0.741
90% CI of hazard ratio	0.708-1.531	0.547-1.216		0.494-1.111

Crossover date was considered as the new anti-cancer therapy date to analyze only the main therapy.
CI = confidence interval; N = total number of subjects in a given treatment group, n = number of subjects in category; PD = progression of disease.

a. Non-randomized extension cohort treated with 20 mg/kg
b. Estimated from the Kaplan-Meier curve.
c. Calculated from the product-limit method.
d. Based on the Brookmeyer and Crowley Method.
e. Based on the Cox Proportional hazards model.

HAHA Results: No serum samples were positive for HAHA among available results.

Safety Results:

Phase 1b: TEAEs (All causalities) are summarized in Table 11. Diarrhea, hyperglycemia, mucosal inflammation, rash, dry skin and stomatitis were reported more frequently in the erlotinib cohort; all these AEs were expected. All grade, treatment-related TEAEs are provided in Table 12. The most frequently reported study treatment-related (all grades) AEs were fatigue, diarrhea and hyperglycemia.

Table 11. Treatment-Emergent Adverse Events Occurring in Any Cohort: All Causalities, All Grades

System Organ Class and Preferred Term	Number (%) of Subjects								
	Figitumumab 0.05 mg/kg	Figitumumab 0.1 mg/kg	Figitumumab 0.8 mg/kg	Figitumumab 1.5 mg/kg	Figitumumab 3 mg/kg	Figitumumab 6 mg/kg	Figitumumab 10 mg/kg	Figitumumab 20 mg/kg	Erlotinib Cohort
Number (%) of subjects:									
Evaluable for adverse events	3	2	4	3	3	3	17	7	17
With adverse events	3 (100.0)	2 (100.0)	4 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	17 (100.0)	7 (100.0)	17 (100.0
Blood and lymphatic system disorders	0	2 (100.0)	1 (25.0)	0	3 (100.0)	1 (33.3)	7 (41.2)	4 (57.1)	10 (58.8)
Anaemia	0	1 (50.0)	1 (25.0)	0	2 (66.7)	0	1 (5.9)	4 (57.1)	9 (52.9)
Leukopenia	0	1 (50.0)	0	0	0	0	1 (5.9)	0	2 (11.8)
Neutropenia	0	1 (50.0)	0	0	3 (100.0)	1 (33.3)	6 (35.3)	0	6 (35.3)
Thrombocytopenia	0	0	0	0	0	0	1 (5.9)	2 (28.6)	4 (23.5)
Cardiac disorders	0	1 (50.0)	0	0	1 (33.3)	0	2 (11.8)	1 (14.3)	2 (11.8)
Bradycardia	0	1 (50.0)	0	0	0	0	0	0	0
Cardiac failure congestive	0	0	0	0	1(33.3)	0	0	0	0
Cyanosis	0	0	0	0	0	0	0	0	1 (5.9)
Extrasystoles	0	0	0	0	0	0	1 (5.9)	0	0
Left ventricular dysfunction	0	0	0	0	0	0	0	1 (14.3)	0
Pericardial effusion	0	0	0	0	0	0	0	0	1 (5.9)
Tachycardia	0	0	0	0	0	0	1 (5.9)	0	0
Ear and labyrinth disorders	0	0	0	0	0	1 (33.3)	3 (17.6)	1 (14.3)	3 (17.6)
Ear congestion	0	0	0	0	0	0	0	0	1 (5.9)
Ear disorder	0	0	0	0	0	0	1 (5.9)	0	0
Hearing impaired	0	0	0	0	0	0	0	0	1 (5.9)
Hypoacusis	0	0	0	0	0	0	0	0	1 (5.9)
Tinnitus	0	0	0	0	0	1 (33.3)	1 (5.9)	1 (14.3)	0
Vertigo	0	0	0	0	0	0	1 (5.9)	0	0
Eye disorders	1 (33.3)	0	0	0	0	2 (66.7)	4 (23.5)	1 (14.3)	4 (23.5)
Blepharospasm	0	0	0	0	0	0	1 (5.9)	0	0
Chalazion	0	0	0	0	0	0	1 (5.9)	0	0

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System Organ Class and Preferred Term	Number (%) of Subjects								
	Figitumumab 0.05 mg/kg	Figitumumab 0.1 mg/kg	Figitumumab 0.8 mg/kg	Figitumumab 1.5 mg/kg	Figitumumab 3 mg/kg	Figitumumab 6 mg/kg	Figitumumab 10 mg/kg	Figitumumab 20 mg/kg	Erlotinib Cohort
Conjunctivitis	0	0	0	0	0	0	0	0	1 (5.9)
Dry eye	0	0	0	0	0	0	0	0	1 (5.9)
Eye disorder	0	0	0	0	0	0	0	0	1 (5.9)
Eye irritation	0	0	0	0	0	0	0	0	1 (5.9)
Eye pain	0	0	0	0	0	1 (33.3)	0	0	1 (5.9)
Eye swelling	0	0	0	0	0	1 (33.3)	1 (5.9)	0	0
Lacrimation increased	0	0	0	0	0	0	1 (5.9)	0	0
Ocular hyperaemia	0	0	0	0	0	0	0	0	1 (5.9)
Vision blurred	1(33.3)	0	0	0	0	1 (33.3)	2 (11.8)	1 (14.3)	0
Visual impairment	1(33.3)	0	0	0	0	1 (33.3)	0	0	0
Xerophthalmia	0	0	0	0	0	0	0	1 (14.3)	0
Gastrointestinal disorders	3 (100.0)	1 (50.0)	3 (75.0)	3 (100.0)	3 (100.0)	3 (100.0)	16 (94.1)	6 (85.7)	16 (94.1)
Abdominal discomfort	0	0	0	0	1 (33.3)	0	0	0	0
Abdominal distension	0	0	0	0	1 (33.3)	0	0	0	0
Abdominal pain	1(33.3)	0	0	1 (33.3)	0	0	2 (11.8)	1 (14.3)	1 (5.9)
Abdominal pain lower	0	0	0	0	1 (33.3)	0	0	0	0
Abdominal pain upper	0	0	0	1 (33.3)	1 (33.3)	0	0	0	2 (11.8)
Abdominal tenderness	0	0	0	1 (33.3)	0	0	0	0	0
Aphthous stomatitis	0	0	0	0	0	0	0	0	1 (5.9)
Cheilitis	0	0	0	0	0	0	1 (5.9)	0	0
Constipation	1 (33.3)	0	0	1(33.3)	0	0	5 (29.4)	0	2 (11.8)
Diarrhoea	1 (33.3)	0	2(50.0)	0	2 (66.7)	2 (66.7)	9 (52.9)	3 (42.9)	11 (64.7)
Dry mouth	0	0	0	0	0	0	0	0	1 (5.9)
Dyspepsia	0	0	1 (25.0)	1(33.3)	2 (66.7)	1 (33.3)	4 (23.5)	1 (14.3)	0
Dysphagia	2 (66.7)	0	0	0	0	1 (33.3)	1 (5.9)	0	3 (17.6)

Table 11. Treatment-Emergent Adverse Events Occurring in Any Cohort: All Causalities, All Grades

System Organ Class and Preferred Term	Number (%) of Subjects								
	Figitumumab 0.05 mg/kg	Figitumumab 0.1 mg/kg	Figitumumab 0.8 mg/kg	Figitumumab 1.5 mg/kg	Figitumumab 3 mg/kg	Figitumumab 6 mg/kg	Figitumumab 10 mg/kg	Figitumumab 20 mg/kg	Erlotinib Cohort
Faecal incontinence	0	0	0	0	0	0	1 (5.9)	0	0
Flatulence	0	0	0	0	1(33.3)	0	1 (5.9)	0	1 (5.9)
Gastrointestinal pain	0	0	0	0	0	0	0	0	1 (5.9)
Gastrooesophageal reflux disease	0	0	0	0	0	0	0	0	1 (5.9)
Gingival pain	0	0	0	0	0	0	1 (5.9)	1 (14.3)	1 (5.9)
Haemorrhoids	0	0	0	0	0	0	0	0	1 (5.9)
Melaena	0	0	0	0	0	0	0	0	1 (5.9)
Mucous stools	0	0	0	0	0	0	1 (5.9)	0	0
Nausea	1 (33.3)	1 (50.0)	1(25.0)	0	3 (100.0)	0	10 (58.8)	2 (28.6)	11 (64.7)
Odynophagia	0	0	0	0	0	0	1 (5.9)	0	1 (5.9)
Oral pain	0	0	0	0	0	0	0	1 (14.3)	0
Proctalgia	0	0	0	0	1(33.3)	0	0	0	0
Rectal haemorrhage	0	0	0	0	0	0	0	0	1 (5.9)
Regurgitation	0	0	1(25.0)	0	0	0	0	0	0
Retching	0	0	0	0	0	0	0	0	1 (5.9)
Stomatitis	2 (66.7)	1 (50.0)	0	0	0	1 (33.3)	4 (23.5)	1 (14.3)	7 (41.2)
Toothache	0	0	0	0	0	0	0	1 (14.3)	1 (5.9)
Vomiting	0	1 (50.0)	2 (50.0)	0	2(66.7)	0	5 (29.4)	2 (28.6)	9 (52.9)
General disorders and administration site conditions	3 (100.0)	2 (100.0)	2 (50.0)	3 (100.0)	3 (100.0)	3 (100.0)	14 (82.4)	6 (85.7)	15 (88.2)
Adverse drug reaction	0	1 (50)	1 (25.0)	0	0	0	0	0	0
Asthenia	0	0	0	0	1(33.3)	0	4 (23.5)	1 (14.3)	6 (35.3)
Catheter site pain	0	0	0	0	0	0	0	0	1 (5.9)
Chest discomfort	1(33.3)	0	0	0	0	0	1 (5.9)	0	0
Chest pain	1 (33.3)	0	0	0	0	0	2 (11.8)	2 (28.6)	1 (5.9)
Chills	0	1(50.0)	0	0	1 (33.3)	0	1 (5.9)	0	0
Fatigue	3 (100.0)	2(100)	1 (25.0)	3 (100.0)	3 (100.0)	2 (66.7)	10 (58.8)	5 (71.4)	8 (47.1)
Feeling cold	0	0	0	1 (33.3)	0	0	0	0	0
Gait disturbance	0	0	0	0	0	0	1 (5.9)	0	0

Table 11. Treatment-Emergent Adverse Events Occurring in Any Cohort: All Causalities, All Grades

System Organ Class and Preferred Term	Number (%) of Subjects								
	Figitumumab 0.05 mg/kg	Figitumumab 0.1 mg/kg	Figitumumab 0.8 mg/kg	Figitumumab 1.5 mg/kg	Figitumumab 3 mg/kg	Figitumumab 6 mg/kg	Figitumumab 10 mg/kg	Figitumumab 20 mg/kg	Erlotinib Cohort
General physical health deterioration	0	0	0	0	0	0	0	0	1 (5.9)
Infusion site pain	0	0	0	0	1(33.3)	0	0	0	0
Malaise	0	0	0	0	0	0	1 (5.9)	0	0
Mucosal inflammation	0	0	0	0	0	0	3 (17.6)	0	8 (47.1)
Nodule	0	0	0	0	0	1 (33.3)	0	0	0
Oedema peripheral	0	0	0	0	0	0	1 (5.9)	0	0
Pain	0	0	0	0	0	1 (33.3)	1 (5.9)	0	0
Pyrexia	1 (33.3)	0	1 (25.0)	1 (33.3)	1 (33.3)	0	1 (5.9)	0	2 (11.8)
Hepatobiliary disorders	0	0	0	0	0	1 (33.3)	0	0	1 (5.9)
Hepatomegaly	0	0	0	0	0	1 (33.3)	0	0	0
Hyperbilirubinaemia	0	0	0	0	0	0	0	0	1 (5.9)
Immune system disorders	0	0	0	0	0	0	1 (5.9)	1 (14.3)	0
Drug hypersensitivity	0	0	0	0	0	0	1 (5.9)	0	0
Multiple allergies	0	0	0	0	0	0	0	1 (14.3)	0
Infections and infestations	1 (33.3)	1 (50.0)	0	1 (33.3)	1 (33.3)	1 (33.3)	5 (29.4)	1 (14.3)	8 (47.1)
Bronchitis	1 (33.3)	0	0	0	0	0	0	0	0
Bronchopneumonia	1 (33.3)	0	0	0	0	0	0	0	0
Ear infection	0	0	0	0	0	0	0	0	1 (5.9)
Empyema	0	0	0	0	0	1 (33.3)	0	0	0
Gastrointestinal viral infection	1 (33.3)	0	0	0	0	0	0	0	0
Herpes zoster	0	0	0	1(33.3)	0	0	0	0	0
Infection	0	1(50.0)	0	0	0	0	0	0	0
Laryngitis	0	0	0	0	1 (33.3)	0	0	0	0
Localised infection	0	0	0	0	1 (33.3)	0	0	0	2 (11.8)
Lung infection	0	0	0	0	0	0	1 (5.9)	0	0
Nasopharyngitis	0	0	0	1(33.3)	1 (33.3)	0	0	1 (14.3)	1 (5.9)
Oral candidiasis	0	0	0	0	0	0	1 (5.9)	0	0

Table 11. Treatment-Emergent Adverse Events Occurring in Any Cohort: All Causalities, All Grades

System Organ Class and Preferred Term	Number (%) of Subjects								
	Figitumumab 0.05 mg/kg	Figitumumab 0.1 mg/kg	Figitumumab 0.8 mg/kg	Figitumumab 1.5 mg/kg	Figitumumab 3 mg/kg	Figitumumab 6 mg/kg	Figitumumab 10 mg/kg	Figitumumab 20 mg/kg	Erlotinib Cohort
Oral fungal infection	0	0	0	0	0	0	1 (5.9)	0	0
Pharyngitis	1(33.3)	0	0	0	0	0	0	0	0
Pneumonia	1 (33.3)	0	0	0	0	0	1 (5.9)	0	0
Rhinitis	1 (33.3)	0	0	0	0	0	0	0	0
Sinusitis	1 (33.3)	0	0	0	0	0	0	0	1 (5.9)
Skin infection	0	0	0	0	0	0	1 (5.9)	0	0
Tooth infection	1 (33.3)	0	0	0	0	0	0	0	0
Upper respiratory tract infection	1 (33.3)	0	0	0	0	0	0	0	1 (5.9)
Urinary tract infection	0	0	0	0	0	0	2 (11.8)	0	4 (23.5)
Injury, poisoning and procedural complications	0	0	1 (25.0)	0	2 (66.7)	0	0	0	2 (11.8)
Contusion	0	0	0	0	0	0	0	0	1 (5.9)
Excoriation	0	0	0	0	1 (33.3)	0	0	0	1 (5.9)
Laceration	0	0	0	0	1 (33.3)	0	0	0	0
Peroneal nerve injury	0	0	1 (25.0)	0	0	0	0	0	0
Investigations	3 (100.0)	2(100)	2 (50.0)	1 (33.3)	2(66.7)	2 (66.7)	10 (58.8)	2 (28.6)	12 (70.6)
Alanine aminotransferase	0	1(50.0)	0	0	0	0	0	0	0
Alanine aminotransferase increased	0	0	0	0	1 (33.3)	0	0	0	2 (11.8)
Aspartate aminotransferase	0	0	0	0	0	1 (33.3)	1 (5.9)	0	0
Aspartate amino transerase increased	0	0	0	0	1 (33.3)	0	0	0	0
Blood alkaline phosphatase	0	1 (50.0)	0	0	0	0	1 (5.9)	0	0
Blood bicarbonate decreased	0	0	0	0	0	0	0	0	4 (23.5)

Table 11. Treatment-Emergent Adverse Events Occurring in Any Cohort: All Causalities, All Grades

System Organ Class and Preferred Term	Number (%) of Subjects								
	Figitumumab 0.05 mg/kg	Figitumumab 0.1 mg/kg	Figitumumab 0.8 mg/kg	Figitumumab 1.5 mg/kg	Figitumumab 3 mg/kg	Figitumumab 6 mg/kg	Figitumumab 10 mg/kg	Figitumumab 20 mg/kg	Erlotinib Cohort
Blood bilirubin increased	0	0	0	0	0	0	0	0	2 (11.8)
Blood calcium decreased	0	0	0	0	0	0	0	0	2 (11.8)
Blood chloride decreased	0	0	0	0	0	0	0	0	2 (11.8)
Blood creatinine	0	0	0	0	0	0	0	0	1 (5.9)
Blood creatinine increased	0	0	0	1(33.3)	0	0	0	0	3 (17.6)
Blood lactate dehydrogenase	0	0	0	0	0	0	0	1 (14.3)	0
Blood magnesium decreased	0	0	0	0	0	0	1 (5.9)	0	0
Blood phosphorus decreased	1(33.3)	0	0	0	0	0	0	0	0
Blood phosphorus increased	0	0	0	0	0	0	1 (5.9)	0	1 (5.9)
Blood potassium increased	0	0	0	0	1 (33.3)	0	0	0	0
Blood urea increased	0	0	0	0	0	0	0	1 (14.3)	1 (5.9)
Blood uric acid increased	0	0	0	0	0	0	0	0	1 (5.9)
Gamma-glutamyltransferase	0	1 (50.0)	0	0	0	0	1 (5.9)	0	0
Gamma-glutamyltransferase increased	1 (33.3)	0	0	0	0	0	0	0	2 (11.8)
Haemoglobin	0	1 (50.0)	0	0	0	1 (33.3)	0	0	1 (5.9)
Haemoglobin decreased	0	0	0	0	0	0	2 (11.8)	1 (14.3)	4 (23.5)
Neutrophil count decreased	0	0	0	0	0	0	1 (5.9)	0	3 (17.6)

Table 11. Treatment-Emergent Adverse Events Occurring in Any Cohort: All Causalities, All Grades

System Organ Class and Preferred Term	Number (%) of Subjects								
	Figitumumab 0.05 mg/kg	Figitumumab 0.1 mg/kg	Figitumumab 0.8 mg/kg	Figitumumab 1.5 mg/kg	Figitumumab 3 mg/kg	Figitumumab 6 mg/kg	Figitumumab 10 mg/kg	Figitumumab 20 mg/kg	Erlotinib Cohort
Neutrophil count increased	0	0	0	0	0	0	0	0	1 (5.9)
Platelet count decreased	0	1(50.0)	0	0	0	1 (33.3)	2 (11.8)	0	5 (29.4)
Prothrombin time prolonged	0	0	0	1 (33.3)	0	0	0	0	0
Troponin	0	0	0	0	0	0	0	0	1 (5.9)
Weight decreased	0	1 (50.0)	2(50.0)	0	0	0	5 (29.4)	1 (14.3)	6 (35.3)
Weight increased	1 (33.3)	0	0	0	0	0	0	0	0
White blood cell count decreased	2 (66.7)	0	0	0	1 (33.3)	0	0	0	3 (17.6)
White blood cell count increased	0	0	0	0	0	0	0	0	1 (5.9)
Metabolism and nutrition disorders	2 (66.7)	2 (100.0)	2 (50.0)	1 (33.3)	3 (100.0)	2 (66.7)	11 (64.7)	3 (42.9)	16 (94.1)
Cachexia	0	0	1 (25.0)	0	0	0	0	0	0
Decreased appetite	1(33.3)	1 (50.0)	2 (50.0)	0	1 (33.3)	0	9 (52.9)	2 (28.6)	8 (47.1)
Dehydration	0	0	0	1 (33.3)	1 (33.3)	0	2 (11.8)	1 (14.3)	2 (11.8)
Gout	1 (33.3)	0	0	0	0	0	1 (5.9)	0	0
Hypercalcaemia	0	0	0	0	0	0	0	0	1 (5.9)
Hypercholesterolaemia	1(33.3)	0	0	0	0	0	0	0	1 (5.9)
Hyperglycaemia	0	1 (50.0)	0	0	0	2 (66.7)	6 (35.3)	3 (42.9)	11 (64.7)
Hypermagnesaemia	0	0	0	0	0	0	1 (5.9)	0	0
Hyperuricaemia	0	0	0	0	0	0	1 (5.9)	0	0
Hypoalbuminaemia	0	0	0	0	0	0	0	0	3 (17.6)
Hypocalcaemia	0	0	0	0	0	0	1 (5.9)	0	2 (11.8)
Hypokalaemia	0	1 (50.0)	0	0	0	0	0	0	2 (11.8)
Hypomagnesaemia	0	1 (50.0)	0	0	1 (33.3)	0	1 (5.9)	2 (28.6)	3(17.6)
Hyponatraemia	0	1 (50.0)	0	1 (33.3)	0	0	0	0	6 (35.3)

Table 11. Treatment-Emergent Adverse Events Occurring in Any Cohort: All Causalities, All Grades

System Organ Class and Preferred Term	Number (%) of Subjects								
	Figitumumab 0.05 mg/kg	Figitumumab 0.1 mg/kg	Figitumumab 0.8 mg/kg	Figitumumab 1.5 mg/kg	Figitumumab 3 mg/kg	Figitumumab 6 mg/kg	Figitumumab 10 mg/kg	Figitumumab 20 mg/kg	Erlotinib Cohort
Musculoskeletal and connective tissue disorders	3 (100.0)	2 (100.0)	1 (25.0)	3 (100.0)	1 (33.3)	3 (100.0)	14 (82.4)	4 (57.1)	13 (76.5)
Arthralgia	3 (100.0)	1 (50.0)	1 (25.0)	1 (33.3)	0	2 (66.7)	6 (35.3)	3 (42.9)	8 (47.1)
Arthropathy	1 (33.3)	0	0	0	0	0	0	0	0
Back pain	0	0	0	1 (33.3)	0	1 (33.3)	1 (5.9)	1 (14.3)	1 (5.9)
Bone pain	0	0	0	0	0	0	1 (5.9)	0	1 (5.9)
Flank pain	0	0	0	0	0	0	0	1 (14.3)	0
Lower extremity mass	0	0	0	0	0	0	1 (5.9)	0	0
Muscle rigidity	0	0	0	0	0	0	0	0	1 (5.9)
Muscle spasms	1 (33.3)	0	0	1 (33.3)	0	0	3 (17.6)	2 (28.6)	4 (23.5)
Muscle twitching	0	0	0	0	0	0	1 (5.9)	0	0
Muscular weakness	0	0	0	1(33.3)	0	0	1 (5.9)	0	0
Musculoskeletal chest pain	1 (33.3)	0	0	0	0	0	1 (5.9)	1 (14.3)	0
Musculoskeletal pain	0	1(50.0)	0	0	0	1 (33.3)	1 (5.9)	2 (28.6)	3 (17.6)
Myalgia	3 (100.0)	0	1(25.0)	0	0	1 (33.3)	3 (17.6)	2 (28.6)	7 (41.2)
Pain in extremity	1 (33.3)	0	0	2 (66.7)	1 (33.3)	1 (33.3)	4 (23.5)	0	1 (5.9)
Tendonitis	1 (33.3)	0	0	0	0	0	0	0	0
Nervous system disorders	3 (100.0)	2 (100.0)	4 (100.0)	0	2 (66.7)	1 (33.3)	14 (82.4)	6 (85.7)	13 (76.5)
Ataxia	0	0	0	0	0	0	0	0	1 (5.9)
Balance disorder	0	1 (50.0)	0	0	0	0	0	0	0
Cerebral disorder	0	0	0	0	0	0	0	0	1 (5.9)
Cognitive disorder	0	0	0	0	0	0	0	0	1 (5.9)
Convulsion	0	0	0	0	0	0	2 (11.8)	0	0
Dizziness	2 (66.7)	0	0	0	1 (33.3)	0	1 (5.9)	3 (42.9)	4 (23.5)
Dysgeusia	1 (33.3)	0	0	0	1 (33.3)	1 (33.3)	5 (29.4)	4 (57.1)	5 (29.4)
Headache	2 (66.7)	1 (50.0)	0	0	1 (33.3)	0	2 (11.8)	0	2 (11.8)
Hemiparesis	0	0	1 (25.0)	0	0	0	0	0	0
Hydrocephalus	0	0	0	0	0	0	0	0	1 (5.9)

Table 11. Treatment-Emergent Adverse Events Occurring in Any Cohort: All Causalities, All Grades

System Organ Class and Preferred Term	Number (%) of Subjects								
	Figitumumab 0.05 mg/kg	Figitumumab 0.1 mg/kg	Figitumumab 0.8 mg/kg	Figitumumab 1.5 mg/kg	Figitumumab 3 mg/kg	Figitumumab 6 mg/kg	Figitumumab 10 mg/kg	Figitumumab 20 mg/kg	Erlotinib Cohort
Hyperaesthesia	0	0	0	0	0	0	0	0	1 (5.9)
Hypoaesthesia	0	0	0	0	0	0	1 (5.9)	1 (14.3)	0
Motor dysfunction	0	0	0	0	0	0	0	0	1 (5.9)
Neuropathy peripheral	1 (33.3)	1 (50.0)	2 (50.0)	0	1 (33.3)	0	6 (35.3)	3 (42.9)	4 (23.5)
Neurotoxicity	0	0	0	0	0	0	0	0	1 (5.9)
Nystagmus	0	0	0	0	0	0	0	0	1 (5.9)
Paraesthesia	1 (33.3)	0	1 (25.0)	0	1 (33.3)	0	1 (5.9)	1 (14.3)	0
Parosmia	0	0	0	0	0	0	0	1 (14.3)	0
Peripheral sensory neuropathy	0	1 (50.0)	0	0	0	0	3 (17.6)	0	5 (29.4)
Peroneal nerve palsy	0	0	1 (25.0)	0	0	0	0	0	0
Psychomotor hyperactivity	0	0	0	0	0	0	1 (5.9)	0	0
Sensory disturbance	0	0	0	0	0	0	1 (5.9)	0	0
Sensory loss	0	0	0	0	0	0	0	0	1 (5.9)
Somnolence	0	0	0	0	1 (33.3)	0	1 (5.9)	0	0
Syncope	0	0	0	0	0	0	1 (5.9)	0	1 (5.9)
Tremor	1 (33.3)	0	0	0	0	0	1 (5.9)	0	1 (5.9)
Visual field defect	0	0	0	0	0	0	1 (5.9)	0	0
Psychiatric disorders	1(33.3)	2 (100.0)	3 (75.0)	1 (33.3)	1 (33.3)	1 (33.3)	6 (35.3)	0	3 (17.6)
Anxiety	0	0	1 (25.0)	1 (33.3)	1 (33.3)	1 (33.3)	0	0	0
Confusional state	0	0	1(25.0)	0	0	0	2 (11.8)	0	1 (5.9)
Depression	1(33.3)	2 (100.0)	0	1 (33.3)	0	1 (33.3)	1 (5.9)	0	2 (11.8)
Insomnia	1(33.3)	1(50.0)	1 (25.0)	0	0	0	4 (23.5)	0	0
Mood altered	0	0	0	0	0	0	0	0	1 (5.9)
Restlessness	0	0	0	0	0	0	0	0	1 (5.9)
Renal and urinary disorders	0	0	0	0	1 (33.3)	0	3 (17.6)	0	3 (17.6)
Dysuria	0	0	0		0	0	1 (5.9)	0	1 (5.9)
Haematuria	0	0	0	0	0	0	1 (5.9)	0	0
Pollakiuria	0	0	0	0	0	0	1 (5.9)	0	0

Table 11. Treatment-Emergent Adverse Events Occurring in Any Cohort: All Causalities, All Grades

System Organ Class and Preferred Term	Number (%) of Subjects								
	Figitumumab 0.05 mg/kg	Figitumumab 0.1 mg/kg	Figitumumab 0.8 mg/kg	Figitumumab 1.5 mg/kg	Figitumumab 3 mg/kg	Figitumumab 6 mg/kg	Figitumumab 10 mg/kg	Figitumumab 20 mg/kg	Erlotinib Cohort
Proteinuria	0	0	0	0	0	0	0	0	1 (5.9)
Urinary incontinence	0	0	0	0	0	0	0	0	0
Urinary retention	0	0	0	0	1 (33.3)	0	0	0	0
Urogenital haemorrhage	0	0	0	0	0	0	0	0	1 (5.9)
Reproductive systemand breast disorders	1 (33.3)	0	0	0	0	0	0	0	2 (11.8)
Erectile dysfunction	1 (33.3)	0	0	0	0	0	0	0	0
Pelvic pain	0	0	0	0	0	0	0	0	1 (5.9)
Scrotal erythema	0	0	0	0	0	0	0	0	1 (5.9)
Skin and subcutaneous tissue disorders	3 (100.0)	2 (100.0)	2 (50.0)	3 (100.0)	3 (100.0)	3 (100.0)	13 (76.5)	4 (57.1)	17 (100.0)
Acne	0	0	0	0	1 (33.3)	0	0	0	0
Alopecia	3(100.0)	2 (100.0)	1 (25.0)	2 (66.7)	3 (100.0)	3 (100.0)	10 (58.8)	3 (42.9)	10 (58.8)
Dermatitis	0	0	0	0	0	0	1 (5.9)	0	1 (5.9)
Dry skin	0	0	0	1 (33.3)	0	0	6 (35.3)	2 (28.6)	7 (41.2)
Eczema	1 (33.3)	0	0	0	0	0	0	0	0
Erythema	0	0	0	1 (33.3)	0	0	0	0	0
Hair growth abnormal	0	0	0	0	0	0	1 (5.9)	0	0
Hair texture abnormal	0	0	0	0	0	0	1 (5.9)	0	0
Hirsutism	0	0	0	0	0	0	0	1 (14.3)	0
Hyperhidrosis	1 (33.3)	0	0	0	0	0	0	0	0
Ingrowing nail	1 (33.3)	0	0	0	0	0	0	1 (14.3)	2 (11.8)
Nail disorder	1 (33.3)	0	0	0	0	1 (33.3)	0	0	1 (5.9)
Nail toxicity	0	0	0	0	0	0	0	0	1 (5.9)
Palmar erythema	0	0	0	0	0	0	1 (5.9)	0	0
Palmar-plantar erythrodysaesthesia syndrome	0	0	0	0	0	0	0	0	1 (5.9)

Table 11. Treatment-Emergent Adverse Events Occurring in Any Cohort: All Causalities, All Grades

System Organ Class and Preferred Term	Number (%) of Subjects								
	Figitumumab 0.05 mg/kg	Figitumumab 0.1 mg/kg	Figitumumab 0.8 mg/kg	Figitumumab 1.5 mg/kg	Figitumumab 3 mg/kg	Figitumumab 6 mg/kg	Figitumumab 10 mg/kg	Figitumumab 20 mg/kg	Erlotinib Cohort
Petechiae	0	0	0	0	0	0	1 (5.9)	0	0
Pruritus	1 (33.3)	0	0	1 (33.3)	1 (33.3)	0	3 (17.6)	0	1 (5.9)
Pruritus generalised	0	0	0	0	0	0	0	0	1 (5.9)
Rash	2 (66.7)	1 (50.0)	0	0	0	1 (33.3)	5 (29.4)	1 (14.3)	13 (76.5)
Rash pruritic	1 (33.3)	0	0	0	0	0	0	0	0
Scab	0	0	0	0	0	0	1 (5.9)	0	0
Skin fissures	0	0	0	0	0	0	0	0	1 (5.9)
Skin lesion	0	0	0	0	0	0	1 (5.9)	0	0
Skin ulcer	0	0	1 (25.0)	1 (33.3)	0	0	0	0	1 (5.9)
Urticaria	0	1 (50.0)	0	0	0	0	0	0	0
Surgical and medical procedures	0	0	0	0	0	0	0	1 (14.3)	0
Tooth extraction	0	0	0	0	0	0	0	1 (14.3)	0
Vascular disorders	1(33.3)	1 (50.0)	2 (50.0)	2 (66.7)	2 (66.7)	0	5 (29.4)	2 (28.6)	6 (35.3)
Flushing	0	1 (50.0)	0	0	1 (33.3)	0	3 (17.6)	0	0
Hot flush	0	0	0	0	0	0	0	1 (14.3)	1 (5.9)
Hypertension	1(33.3)	0	1 (25.0)	1(33.3)	0	0	1 (5.9)	0	1 (5.9)
Hypotension	0	0	1 (25.0)	0	0	0	1 (5.9)	0	3 (17.6)
Orthostatic hypotension	0	0	0	1(33.3)	1 (33.3)	0	0	1 (14.3)	0
Pallor	0	0	0	0	0	0	0	1 (14.3)	1 (5.9)
Peripheral coldness	0	0	0	0	0	0	0	1 (14.3)	0
Thrombosis	1 (33.3)	0	0	0	0	0	0	0	0

MedDRA = Medical Dictionary for Regulatory Activities
Subjects are only counted once per treatment for each row.
Includes data up to 150 days after last dose of study drug.
MedDRA (v14.1) coding dictionary applied.

Table 12. Treatment-Emergent Adverse Events by MedDRA Preferred Term (Treatment Related, All Cycles)

Preferred Term	Number (%) of Subjects								
	Figitumumab 0.05 mg/kg	Figitumumab 0.1 mg/kg	Figitumumab 0.8 mg/kg	Figitumumab 1.5 mg/kg	Figitumumab 3 mg/kg	Figitumumab 6 mg/kg	Figitumumab 10 mg/kg	Figitumumab 20 mg/kg	Erlotinib Cohort
	(N=3)	(N=2)	(N=4)	(N=3)	(N=3)	(N=3)	(N=17)	(N=7)	(N=17)
Any AEs	3 (100.0)	2 (100.0)	1 (25.0)	2 (66.7)	3 (100.0)	2 (66.7)	11 (64.7)	5 (71.4)	16 (94.1)
White blood cell count decreased	2 (66.7)	0	0	0	1 (33.3)	0	0	0	0
Alopecia	1 (33.3)	0	0	0	0	0	0	0	0
Dysgeusia	1 (33.3)	0	0	0	0	0	1 (5.9)	2 (28.6)	0
Fatigue	1 (33.3)	1 (50.0)	0	1 (33.3)	1 (33.3)	2 (66.7)	3 (17.6)	2 (28.6)	6 (35.3)
Musculoskeletal pain	0	1 (50.0)	0	0	0	0	0	0	0
Headache	1 (33.3)	0	0	0	1 (33.3)	0	0	0	1 (5.9)
Dyspepsia	0	0	1 (25.0)	0	0	0	1 (5.9)	1 (14.3)	0
Regurgitation	0	0	1 (25.0)	0	0	0	0	0	0
Orthostatic hypotension	0	0	0	1 (33.3)	0	0	0	0	0
Abdominal discomfort	0	0	0	0	1 (33.3)	0	0	0	0
Abdominal pain lower	0	0	0	0	1 (33.3)	0	0	0	0
Anaemia	0	0	0	0	1 (33.3)	0		2 (28.6)	1 (5.9)
Diarrhoea	0	0	0	0	1 (33.3)	1 (33.3)	4 (23.5)	2 (28.6)	2 (11.8)
Flushing	0	0	0	0	1 (33.3)	0	0	0	
Nausea	0	0	0	0	1 (33.3)	0	0	0	4 (23.5)
Pruritus	0	0	0	0	1 (33.3)	0	1 (5.9)	0	0
Rash	0	0	0	0	0	1 (33.3)	0	1 (14.3)	1 (5.9)
Visual impairment	0	0	0	0	0	1 (33.3)	0	0	0
Decreased appetite	0	0	0	0	0	0	2 (11.8)	1 (14.3)	3 (17.6)
Weight decreased	0	0	0	0	0	0	2 (11.8)	1 (14.3)	1 (5.9)
Arthralgia	0	0	0	0	0	0	1 (5.9)	1 (14.3)	3 (17.6)
Asthenia	0	0	0	0	0	0	1 (5.9)	1 (14.3)	2 (11.8)
Blood magnesium decreased	0	0	0	0	0	0	1 (5.9)	0	0
Dehydration	0	0	0	0	0	0	1 (5.9)	0	0

Table 12. Treatment-Emergent Adverse Events by MedDRA Preferred Term (Treatment Related, All Cycles)

Preferred Term	Number (%) of Subjects								
	Figitumumab 0.05 mg/kg	Figitumumab 0.1 mg/kg	Figitumumab 0.8 mg/kg	Figitumumab 1.5 mg/kg	Figitumumab 3 mg/kg	Figitumumab 6 mg/kg	Figitumumab 10 mg/kg	Figitumumab 20 mg/kg	Erlotinib Cohort
Dry skin	0	0	0	0	0	0	1 (5.9)	0	0
Dysuria	0	0	0	0	0	0	1 (5.9)	0	0
Failure to thrive	0	0	0	0	0	0	1 (5.9)	0	0
Flatulence	0	0	0	0	0	0	1 (5.9)	0	0
Gamma-glutamyl transferase	0	0	0	0	0	0	1 (5.9)	0	0
Gingival pain	0	0	0	0	0	0	1 (5.9)	0	0
Hair growth abnormal	0	0	0	0	0	0	1 (5.9)	0	0
Hair texture abnormal	0	0	0	0	0	0	1 (5.9)	0	0
Hyperglycaemia	0	0	0	0	0	0	1 (5.9)	1 (14.3)	8 (47.1)
Neutropenia	0	0	0	0	0	0	1 (5.9)		3 (17.6)
Platelet count decreased	0	0	0	0	0	0	1 (5.9)		2 (11.8)
Dizziness	0	0	0	0	0	0	0	1 (14.3)	1 (5.9)
Hirsutism	0	0	0	0	0	0	0	1 (14.3)	
Hypomagnesaemia	0	0	0	0	0	0	0	1 (14.3)	
Left ventricular dysfunction	0	0	0	0	0	0	0	1 (14.3)	
Muscle spasms	0	0	0	0	0	0	0	1 (14.3)	3 (17.6)
Parosmia	0	0	0	0	0	0	0	1 (14.3)	
Stomatitis	0	0	0	0	0	0	0	1 (14.3)	1 (5.9)
Thrombocytopenia	0	0	0	0	0	0	0	1 (14.3)	1 (5.9)
Myalgia	0	0	0	0	0	0	0	0	3 (17.6)
Vomiting	0	0	0	0	0	0	0	0	3 (17.6)
Epistaxis	0	0	0	0	0	0	0	0	2 (11.8)
Gamma-glutamyltransferase increased	0	0	0	0	0	0	0	0	2 (11.8)
Haemoglobin decreased	0	0	0	0	0	0	0	0	2 (11.8)

Table 12. Treatment-Emergent Adverse Events by MedDRA Preferred Term (Treatment Related, All Cycles)

Preferred Term	Number (%) of Subjects								
	Figitumumab 0.05 mg/kg	Figitumumab 0.1 mg/kg	Figitumumab 0.8 mg/kg	Figitumumab 1.5 mg/kg	Figitumumab 3 mg/kg	Figitumumab 6 mg/kg	Figitumumab 10 mg/kg	Figitumumab 20 mg/kg	Erlotinib Cohort
Mucosal inflammation	0	0	0	0	0	0	0	0	2 (11.8)
Peripheral sensory neuropathy	0	0	0	0	0	0	0	0	2 (11.8)
Abdominal pain	0	0	0	0	0	0	0	0	1 (5.9)
Alanine aminotransferase increased	0	0	0	0	0	0	0	0	1 (5.9)
Aphthous stomatitis	0	0	0	0	0	0	0	0	1 (5.9)
Blood bilirubin increased	0	0	0	0	0	0	0	0	1 (5.9)
Blood uric acid increased	0	0	0	0	0	0	0	0	1 (5.9)
Conjunctivitis	0	0	0	0	0	0	0	0	1 (5.9)
Constipation	0	0	0	0	0	0	0	0	1 (5.9)
Cyanosis	0	0	0	0	0	0	0	0	1 (5.9)
Febrile neutropenia	0	0	0	0	0	0	0	0	1 (5.9)
Gastrooesophageal reflux disease	0	0	0	0	0	0	0	0	1 (5.9)
Hydrocephalus	0	0	0	0	0	0	0	0	1 (5.9)
Leukopenia	0	0	0	0	0	0	0	0	1 (5.9)
Motor dysfunction	0	0	0	0	0	0	0	0	1 (5.9)
Oropharyngeal pain	0	0	0	0	0	0	0	0	1 (5.9)
Pallor	0	0	0	0	0	0	0	0	1 (5.9)
Retching	0	0	0	0	0	0	0		1 (5.9)
Troponin	0	0	0	0	0	0	0		1 (5.9)
Urinary tract infection	0	0	0	0	0	0	0		1 (5.9)

AE = adverse event; N = number of subjects in each treatment group; MedDRA = Medical Dictionary for Regulatory Activities.
MedDRA (v14.1) coding dictionary applied.

Phase 2: Table 13 presents a summary of the most frequently reported TEAEs (all causalities) by treatment arm and preferred term. The most frequently experienced AEs in each of Arms A, B1, and B2 were fatigue and alopecia. All grade, treatment related TEAEs are provided in Table 14. The most frequently reported study treatment related (all grades) AEs in the treatment Arm A subjects were hyperglycemia, fatigue, diarrhea, anemia, decreased appetite, and thrombocytopenia.

Table 13. Treatment-Emergent Adverse Events by Special Organ Class and Preferred Term (All Causalities) For Events Having a Frequency Rate ≥2.

System Organ Class and MedDRA Preferred Term	Number (%) of Subjects		
	Arm A	Arm B1	Arm B2
Number (%) of subjects:			
Evaluable for adverse events	163	56	22
With adverse events	162 (99.4)	55 (98.2)	22 (100.0)
Blood and lymphatic system disorders	93 (57.1)	24 (42.9)	6 (27.3)
Anaemia	56 (34.4)	15 (26.8)	4 (18.2)
Leukopenia	13 (8.0)	2 (3.6)	0
Neutropenia	52 (31.9)	13 (23.2)	1 (4.5)
Thrombocytopenia	43 (26.4)	12 (21.4)	3 (13.6)
Ear and labyrinth disorders	26 (16.0)	1 (1.8)	2 (9.1)
Cerumen impaction	0	0	1 (4.5)
Deafness	6 (3.7)	0	2 (9.1)
Ear disorder	1 (0.6)	0	1 (4.5)
Hypoacusis	7 (4.3)	0	0
Tinnitus	8 (4.9)	1 (1.8)	1 (4.5)
Vertigo	3 (1.8)	0	1 (4.5)
Vestibular disorder	0	0	1 (4.5)
Eye disorders	23 (14.1)	4 (7.1)	0
Dry eye	4 (2.5)	0	0
Vision blurred	4 (2.5)	0	0
Gastrointestinal disorders	145 (89.0)	41 (73.2)	13 (59.1)
Abdominal discomfort	1 (0.6)	0	1 (4.5)
Abdominal pain	17 (10.4)	2 (3.6)	0
Abdominal pain upper	3 (1.8)	1 (1.8)	1 (4.5)
Constipation	49 (30.1)	17 (30.4)	5 (22.7)
Diarrhoea	65 (39.9)	12 (21.4)	5 (22.7)
Dry mouth	11 (6.7)	6 (10.7)	1 (4.5)
Dyspepsia	19 (11.7)	5 (8.9)	3 (13.6)
Dysphagia	15 (9.2)	1 (1.8)	2 (9.1)
Flatulence	7 (4.3)	1 (1.8)	0
Gingival bleeding	0	0	1 (4.5)
Haemorrhoids	7 (4.3)	0	0
Nausea	84 (51.5)	24 (42.9)	1 (4.5)
Rectal haemorrhage	5 (3.1)	1 (1.8)	0
Stomatitis	30 (18.4)	1 (1.8)	0
Vomiting	48 (29.4)	11 (19.6)	1 (4.5)
General disorders and administration site conditions	141 (86.5)	40 (71.4)	20 (90.9)
Asthenia	27 (16.6)	5 (8.9)	1 (4.5)
Chest pain	18 (11.0)	1 (1.8)	2 (9.1)
Chills	3 (1.8)	1 (1.8)	1 (4.5)
Fatigue	107 (65.6)	26 (46.4)	14 (63.6)
Gait disturbance	0	1 (1.8)	2 (9.1)
Mucosal inflammation	27 (16.6)	5 (8.9)	2 (9.1)
Oedema	5 (3.1)	4 (7.1)	2 (9.1)
Oedema peripheral	6 (3.7)	6 (10.7)	5 (22.7)
Pain	17 (10.4)	7 (12.5)	2 (9.1)
Pyrexia	24 (14.7)	7 (12.5)	1 (4.5)
Temperature intolerance	4 (2.5)	0	0
Immune system disorders	6 (3.7)	1 (1.8)	0
Hypersensitivity	5 (3.1)	1 (1.8)	0

Table 13. Treatment-Emergent Adverse Events by Special Organ Class and Preferred Term (All Causalities) For Events Having a Frequency Rate ≥2.

System Organ Class and MedDRA Preferred Term	Number (%) of Subjects		
	Arm A	Arm B1	Arm B2
Infections and infestations	69 (42.3)	19 (33.9)	10 (45.5)
Bronchitis	3 (1.8)	0	1 (4.5)
Dermatitis infected	0	1 (1.8)	1 (4.5)
Ear lobe infection	0	0	1 (4.5)
Herpes simplex	0	1 (1.8)	1 (4.5)
Infection	17 (10.4)	2 (3.6)	3 (13.6)
Nasopharyngitis	8 (4.9)	1 (1.8)	0
Oral candidiasis	6 (3.7)	1 (1.8)	0
Oral herpes	1 (0.6)	2 (3.6)	0
Pneumonia	5 (3.1)	2 (3.6)	0
Rhinitis	7 (4.3)	7 (12.5)	5 (22.7)
Sinusitis	4 (2.5)	1 (1.8)	0
Upper respiratory tract infection	6 (3.7)	1 (1.8)	0
Urinary tract infection	8 (4.9)	1 (1.8)	2 (9.1)
Injury, poisoning and procedural complications	10 (6.1)	0	2 (9.1)
Contusion	5 (3.1)	0	0
Fall	0	0	1 (4.5)
Femur fracture	0	0	1 (4.5)
Hip fracture	0	0	1 (4.5)
Investigations	102 (62.6)	24 (42.9)	17 (77.3)
Activated partial thromboplastin time	0	0	1 (4.5)
Alanine aminotransferase increased	16 (9.8)	2 (3.6)	2 (9.1)
Aspartate aminotransferase increased	10 (6.1)	2 (3.6)	1 (4.5)
Blood albumin decreased	2 (1.2)	2 (3.6)	1 (4.5)
Blood alkaline phosphatase decreased	0	1 (1.8)	1 (4.5)
Blood alkaline phosphatase increased	12 (7.4)	1 (1.8)	1 (4.5)
Blood bicarbonate decreased	3 (1.8)	2 (3.6)	3 (13.6)
Blood chloride decreased	5 (3.1)	0	0
Blood creatinine increased	21 (12.9)	1 (1.8)	2 (9.1)
Blood glucose increased	5 (3.1)	1 (1.8)	0
Blood lactate dehydrogenase increased	5 (3.1)	1 (1.8)	0
Blood magnesium decreased	11 (6.7)	6 (10.7)	5 (22.7)
Blood phosphorus increased	4 (2.5)	0	0
Blood uric acid increased	10 (6.1)	0	2 (9.1)
Gamma-glutamyltransferase	3 (1.8)	0	1 (4.5)
Gamma-glutamyltransferase increased	27 (16.6)	6 (10.7)	2 (9.1)
Haemoglobin	5 (3.1)	0	0
Haemoglobin decreased	10 (6.1)	4 (7.1)	4 (18.2)
Neutrophil count	4 (2.5)	2 (3.6)	0
Neutrophil count decreased	5 (3.1)	4 (7.1)	1 (4.5)
Platelet count decreased	9 (5.5)	4 (7.1)	3 (13.6)
Weight decreased	35 (21.5)	2 (3.6)	4 (18.2)
White blood cell count	0	2 (3.6)	1 (4.5)
White blood cell count decreased	4 (2.5)	3 (5.4)	1 (4.5)
Metabolism and nutrition disorders	121 (74.2)	29 (51.8)	17 (77.3)
Decreased appetite	69 (42.3)	15 (26.8)	9 (40.9)
Dehydration	14 (8.6)	2 (3.6)	2 (9.1)
Hypercalcaemia	6 (3.7)	1 (1.8)	0
Hyperglycaemia	67 (41.1)	9 (16.1)	8 (36.4)

Table 13. Treatment-Emergent Adverse Events by Special Organ Class and Preferred Term (All Causalities) For Events Having a Frequency Rate ≥2.

System Organ Class and MedDRA Preferred Term	Number (%) of Subjects		
	Arm A	Arm B1	Arm B2
Hyperkalaemia	11 (6.7)	0	0
Hyperuricaemia	10 (6.1)	0	1 (4.5)
Hypoalbuminaemia	2 (1.2)	1 (1.8)	2 (9.1)
Hypokalaemia	9 (5.5)	3 (5.4)	1 (4.5)
Hypomagnesaemia	6 (3.7)	4 (7.1)	5 (22.7)
Hyponatraemia	17 (10.4)	2 (3.6)	4 (18.2)
Hypophosphataemia	0	2 (3.6)	0
Hypouricaemia	0	1 (1.8)	1 (4.5)
Increased appetite	0	1 (1.8)	1 (4.5)
Musculoskeletal and connective tissue disorders	107 (65.6)	36 (64.3)	16 (72.7)
Arthralgia	48 (29.4)	18 (32.1)	7 (31.8)
Arthritis	4 (2.5)	0	0
Back pain	25 (15.3)	4 (7.1)	2 (9.1)
Bone pain	7 (4.3)	2 (3.6)	2 (9.1)
Muscle spasms	15 (9.2)	3 (5.4)	1 (4.5)
Muscular weakness	4 (2.5)	7 (12.5)	3 (13.6)
Musculoskeletal chest pain	2 (1.2)	2 (3.6)	1 (4.5)
Musculoskeletal pain	18 (11.0)	4 (7.1)	4 (18.2)
Myalgia	32 (19.6)	13 (23.2)	5 (22.7)
Pain in extremity	27 (16.6)	6 (10.7)	4 (18.2)
Nervous system disorders	137 (84.0)	42 (75.0)	20 (90.9)
Ataxia	1 (0.6)	0	1 (4.5)
Dizziness	27 (16.6)	4 (7.1)	4 (18.2)
Dysgeusia	43 (26.4)	7 (12.5)	6 (27.3)
Dyskinesia	0	2 (3.6)	1 (4.5)
Headache	30 (18.4)	2 (3.6)	4 (18.2)
Memory impairment	5 (3.1)	0	1 (4.5)
Neuropathy peripheral	57 (35.0)	22 (39.3)	14 (63.6)
Paraesthesia	16 (9.8)	4 (7.1)	1 (4.5)
Peripheral motor neuropathy	3 (1.8)	1 (1.8)	1 (4.5)
Peripheral sensory neuropathy	38 (23.3)	10 (17.9)	2 (9.1)
Syncope	5 (3.1)	1 (1.8)	0
Tremor	4 (2.5)	0	0
Psychiatric disorders	32 (19.6)	12 (21.4)	7 (31.8)
Anxiety	9 (5.5)	4 (7.1)	1 (4.5)
Confusional state	7 (4.3)	0	0
Depression	5 (3.1)	2 (3.6)	2 (9.1)
Insomnia	13 (8.0)	4 (7.1)	3 (13.6)
Stress	0	0	1 (4.5)
Renal and urinary disorders	24 (14.7)	1 (1.8)	2 (9.1)
Dysuria	9 (5.5)	0	0
Urinary incontinence	5 (3.1)	0	2 (9.1)
Reproductive system and breast disorders	5 (3.1)	1 (1.8)	1 (4.5)
Vaginal haemorrhage	1 (0.6)	1 (1.8)	1 (4.5)
Respiratory, thoracic and mediastinal disorders	102 (62.6)	26 (46.4)	10 (45.5)
Cough	35 (21.5)	7 (12.5)	7 (31.8)
Dysphonia	9 (5.5)	1 (1.8)	1 (4.5)
Dyspnoea	40 (24.5)	15 (26.8)	5 (22.7)

Table 13. Treatment-Emergent Adverse Events by Special Organ Class and Preferred Term (All Causalities) For Events Having a Frequency Rate ≥2.

System Organ Class and MedDRA Preferred Term	Number (%) of Subjects		
	Arm A	Arm B1	Arm B2
Epistaxis	26 (16.0)	2 (3.6)	0
Haemoptysis	20 (12.3)	1 (1.8)	2 (9.1)
Hiccups	5 (3.1)	1 (1.8)	0
Nasal congestion	5 (3.1)	0	1 (4.5)
Oropharyngeal pain	4 (2.5)	1 (1.8)	0
Productive cough	6 (3.7)	1 (1.8)	0
Rhinorrhoea	5 (3.1)	1 (1.8)	0
Wheezing	1 (0.6)	2 (3.6)	0
Skin and subcutaneous tissue disorders	107 (65.6)	36 (64.3)	17 (77.3)
Alopecia	91 (55.8)	31 (55.4)	15 (68.2)
Dermatitis acneiform	0	1 (1.8)	1 (4.5)
Dry skin	10 (6.1)	4 (7.1)	2 (9.1)
Ecchymosis	1 (0.6)	0	1 (4.5)
Erythema	3 (1.8)	2 (3.6)	1 (4.5)
Hyperhidrosis	1 (0.6)	2 (3.6)	1 (4.5)
Nail disorder	9 (5.5)	0	0
Night sweats	1 (0.6)	1 (1.8)	1 (4.5)
Pruritus	8 (4.9)	1 (1.8)	1 (4.5)
Rash	33 (20.2)	4 (7.1)	3 (13.6)
Skin hyperpigmentation	0	1 (1.8)	1 (4.5)
Skin ulcer	0	1 (1.8)	1 (4.5)
Urticaria	1 (0.6)	2 (3.6)	0
Vascular disorders	29 (17.8)	5 (8.9)	2 (9.1)
Hypertension	5 (3.1)	0	0
Hypotension	11 (6.7)	1 (1.8)	0
Phlebitis	2 (1.2)	1 (1.8)	1 (4.5)
Thrombophlebitis	0	1 (1.8)	1 (4.5)

MedDRA = Medical Dictionary for Regulatory Activities.
Subjects are only counted once per treatment for each row.
Includes data up to 150 days after last dose of study drug.
MedDRA (v14.1) coding dictionary applied.

Table 14 Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term (Treatment Related, All Cycles).

System Organ Class and MedDRA Preferred Term	Number (%) of Subjects		
	Arm A (N=163)	Arm B1 (N=56)	Arm B2 (N=22)
Any AEs	123 (75.5)	16 (28.6)	17 (77.3)
Blood and lymphatic system disorders	35 (21.5)	1 (1.8)	0
Febrile neutropenia	17 (10.4)	0	0
Leukocytosis	1 (0.6)	0	0
Leukopenia	8 (4.9)	0	0
Neutropenia	14 (8.6)	1 (1.8)	0
Thrombocytopenia	17 (10.4)	0	0
Ear and labyrinth disorders	2 (1.2)	0	1 (4.5)
Tinnitus	1 (0.6)	0	0
Vertigo	1 (0.6)	0	0
Vestibular disorder	0	0	1 (4.5)
Gastrointestinal disorders	44 (27.0)	4 (7.1)	5 (22.7)
Abdominal pain	1 (0.6)	0	0
Constipation	6 (3.7)	1 (1.8)	1 (4.5)
Diarrhoea	27 (16.6)	1 (1.8)	4 (18.2)
Diverticulum	1 (0.6)	0	0
Dry mouth	3 (1.8)	0	0
Flatulence	1 (0.6)	0	0
Nausea	16 (9.8)	1 (1.8)	1 (4.5)
Stomatitis	3 (1.8)	0	0
Vomiting	10 (6.1)	1 (1.8)	0
General disorders and administration site conditions	57 (35.0)	6 (10.7)	8 (36.4)
Adverse drug reaction	1 (0.6)	0	0
Asthenia	9 (5.5)	0	0
Catheter site haemorrhage	1 (0.6)	0	0
Chest pain	1 (0.6)	0	0
Fatigue	46 (28.2)	5 (8.9)	7 (31.8)
Infusion site pain	1 (0.6)	0	0
Mucosal inflammation	4 (2.5)	0	0
Pain	1 (0.6)	0	1 (4.5)
Pyrexia	2 (1.2)	1 (1.8)	0
Immune system disorders	2 (1.2)	0	0
Drug hypersensitivity	1 (0.6)	0	0
Hypersensitivity	1 (0.6)	0	0
Infections and infestations	8 (4.9)	0	0
Candidiasis	1 (0.6)	0	0
Clostridial infection	1 (0.6)	0	0
Cystitis	1 (0.6)	0	0
Infection	1 (0.6)	0	0
Oral candidiasis	2 (1.2)	0	0
Pneumonia	1 (0.6)	0	0
Pneumonia necrotising	1 (0.6)	0	0
Urinary tract infection	2 (1.2)	0	0
Investigations	42 (25.8)	3 (5.4)	5 (22.7)
Alanine aminotransferase	1 (0.6)	0	1 (4.5)
Alanine aminotransferase increased	3 (1.8)	0	1 (4.5)
Aspartate aminotransferase increased	2 (1.2)	0	1 (4.5)
Blood alkaline phosphatase increased	4 (2.5)	0	0

Table 14 Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term (Treatment Related, All Cycles).

System Organ Class and MedDRA Preferred Term	Number (%) of Subjects		
	Arm A (N=163)	Arm B1 (N=56)	Arm B2 (N=22)
Blood chloride decreased	1 (0.6)	0	0
Blood creatinine increased	2 (1.2)	0	0
Blood glucose increased	3 (1.8)	0	0
Blood immunoglobulin G increased	1 (0.6)	0	0
Blood lactate dehydrogenase increased	3 (1.8)	0	0
Blood phosphorus decreased	1 (0.6)	0	0
Blood phosphorus increased	1 (0.6)	0	0
Blood potassium increased	1 (0.6)	0	0
Blood pressure increased	1 (0.6)	0	0
Blood sodium decreased	1 (0.6)	0	0
Blood urea increased	1 (0.6)	0	0
Blood uric acid increased	4 (2.5)	0	1 (4.5)
Coagulation test abnormal	1 (0.6)	0	0
Gamma-glutamyltransferase	2 (1.2)	0	1 (4.5)
Gamma-glutamyltransferase increased	16 (9.8)	3 (5.4)	2 (9.1)
Haemoglobin	2 (1.2)	0	0
Haemoglobin decreased	1 (0.6)	0	0
Neutrophil count decreased	1 (0.6)	0	0
Platelet count decreased	2 (1.2)	0	0
Weight decreased	8 (4.9)	0	0
White blood cell count decreased	1 (0.6)	0	0
Metabolism and nutrition disorders	71 (43.6)	4 (7.1)	9 (40.9)
Decreased appetite	17 (10.4)	0	3 (13.6)
Dehydration	3 (1.8)	0	0
Diabetes mellitus	1 (0.6)	0	0
Hyperglycaemia	51 (31.3)	3 (5.4)	6 (27.3)
Hyperkalaemia	3 (1.8)	0	0
Hypernatraemia	1 (0.6)	1 (1.8)	0
Hyperuricaemia	2 (1.2)	0	0
Hypocalcaemia	1 (0.6)	0	0
Hypoglycaemia	2 (1.2)	0	0
Hypokalaemia	2 (1.2)	1 (1.8)	0
Hypophosphataemia		1 (1.8)	0
Hypomagnesaemia	4 (2.5)	0	0
Hyponatraemia	4 (2.5)	0	0
Type 2 diabetes mellitus	1 (0.6)	0	0
Musculoskeletal and connective tissue disorders	17 (10.4)	2 (3.6)	0
Arthralgia	4 (2.5)	1 (1.8)	0
Arthritis	2 (1.2)	0	0
Bone pain	1 (0.6)	0	0
Muscle spasms	5 (3.1)	1 (1.8)	0
Muscular weakness	2 (1.2)	0	0
Musculoskeletal disorder	1 (0.6)	0	0
Musculoskeletal pain	1 (0.6)	0	0
Myalgia	2 (1.2)	1 (1.8)	0
Pain in extremity	1 (0.6)	1 (1.8)	0
Nervous system disorder	12 (7.4)	0	1 (4.5)
Aphasia	1 (0.6)	0	0

Table 14 Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term (Treatment Related, All Cycles).

System Organ Class and MedDRA Preferred Term	Number (%) of Subjects		
	Arm A (N=163)	Arm B1 (N=56)	Arm B2 (N=22)
Balance disorder	1 (0.6)	0	0
Dizziness	2 (1.2)	0	0
Dysgeusia	7 (4.3)	0	1 (4.5)
Headache	1 (0.6)	0	0
Hypoaesthesia	1 (0.6)	0	0
Neuropathy peripheral	2 (1.2)	0	0
Peripheral motor neuropathy	1 (0.6)	0	0
Syncope	2 (1.2)	0	0
Psychiatric disorders	2 (1.2)	0	0
Depression	1 (0.6)	0	0
Insomnia	1 (0.6)	0	0
Renal and urinary disorders	4 (2.5)	0	0
Dysuria	1 (0.6)	0	0
Nocturia	1 (0.6)	0	0
Pollakiuria	1 (0.6)	0	0
Stress urinary incontinence	1 (0.6)	0	0
Urinary incontinence	1 (0.6)	0	0
Reproductive system and breast disorders	1 (0.6)	0	0
Erectile dysfunction	1 (0.6)	0	0
Respiratory,thoracic and mediastinal disorders	8 (4.9)	0	0
Cough	1 (0.6)	0	0
Dysphonia	1 (0.6)	0	0
Dyspnoea	3 (1.8)	0	0
Epistaxis	3 (1.8)	0	0
Hypoxia	1 (0.6)	0	0
Skin and subcutaneous tissue disorders	16 (9.8)	0	2 (9.1)
Alopecia	4 (2.5)	0	0
Dry skin	1 (0.6)	0	0
Erythema	0	0	1 (4.5)
Exfoliative rash	1 (0.6)	0	0
Hyperhidrosis	1 (0.6)	0	0
Nail disorder	1 (0.6)	0	0
Pruritus	1 (0.6)	0	1 (4.5)
Purpura	1 (0.6)	0	0
Rash	7 (4.3)	0	1 (4.5)
Rash erythematous	1 (0.6)	0	0
Vascular disorders	7 (4.3)	0	0
Hypotension	5 (3.1)	0	0
Orthostatic hypotension	2 (1.2)	0	0

N = number of subjects in each treatment group; MedDRA = Medical Dictionary for Regulatory Activities.
MedDRA (v14.1) coding dictionary applied.

Phase 1: A summary of the treatment-emergent serious adverse events (SAEs) (all causalities) is presented in Table 15. The most frequently reported treatment emergent SAEs were disease progression, dehydration, diarrhea, and vomiting.

Treatment-emergent SAEs (treatment related) is presented in Table 16. In total, 2 subjects each in the figitumumab (10 mg/kg) cohort and erlotinib cohort had 4 treatment-related SAEs.

Table 15. Treatment-Emergent Serious Adverse Events by Special Organ Class and Preferred Term (All Causalities)

System Organ Class and Preferred Term	Number (%) of Subjects								
	Figitumumab 0.05 mg/kg	Figitumumab 0.1 mg/kg	Figitumumab 0.8 mg/kg	Figitumumab 1.5 mg/kg	Figitumumab 3 mg/kg	Figitumumab 6 mg/kg	Figitumumab 10 mg/kg	Figitumumab 20 mg/kg	Erlotinib Cohort
Number (%) of subjects:									
Evaluable for adverse events	3	2	4	3	3	3	17	7	17
With adverse events	0	1 (50.0)	2 (50.0)	1 (33.3)	2 (66.7)	2 (66.7)	7 (41.2)	2 (28.6)	9 (52.9)
Blood and lymphatic system disorders	0	0	0	1 (33.3)	0	0	0	0	1 (5.9)
Febrile neutropenia	0	0	0	0	0	0	0	0	1 (5.9)
Neutropenia	0	0	0	1 (33.3)	0	0	0	0	1 (5.9)
Cardiac disorders	0	0	0	0	0	0	1 (5.9)	0	0
Acute myocardial infarction	0	0	0	0	0	0	1 (5.9)	0	0
Eye disorders	0	0	0	0	0	0	1 (5.9)	0	0
Diplopia	0	0	0	0	0	0	1 (5.9)	0	0
Gastrointestinal disorders	0	0	0	0	1 (33.3)	0	2 (11.8)	0	3 (17.6)
Diarrhoea	0	0	0	0	0	0	1 (5.9)	0	2 (11.8)
Enteritis	0	0	0	0	0	0	0	0	1 (5.9)
Intestinal obstruction	0	0	0	0	1 (33.3)	0	0	0	0
Nausea	0	0	0	0	0	0	2 (11.8)	0	0
Vomiting	0	0	0	0	0	0	1 (5.9)	0	2 (11.8)
General disorders and administration site conditions	0	0	0	1 (33.3)	0	0	1 (5.9)	1 (14.3)	4 (23.5)
Disease progression	0	0	0	1 (33.3)	0	0	0	0	3 (17.6)

Table 15. Treatment-Emergent Serious Adverse Events by Special Organ Class and Preferred Term (All Causalities)

System Organ Class and Preferred Term	Number (%) of Subjects								
	Figitumumab 0.05 mg/kg	Figitumumab 0.1 mg/kg	Figitumumab 0.8 mg/kg	Figitumumab 1.5 mg/kg	Figitumumab 3 mg/kg	Figitumumab 6 mg/kg	Figitumumab 10 mg/kg	Figitumumab 20 mg/kg	Erlotinib Cohort
Mucosal haemorrhage	0	0	0	0	0	0	0	0	1 (5.9)
Pain	0	0	0	0	0	0	1 (5.9)	0	0
Performance status decreased	0	0	0	0	0	0	0	0	1 (5.9)
Pyrexia	0	0	0	0	0	0	0	1 (14.3)	0
Immune system disorders	0	0	0	0	0	0	1 (5.9)	0	0
Anaphylactic reaction	0	0	0	0	0	0	1 (5.9)	0	0
Infections and infestations	0	0	0	1 (33.3)	1 (33.3)	2 (66.7)	0	0	1 (5.9)
Cellulitis	0	0	0	1 (33.3)	0 0 0 0	0	0	0	0
Device related infection	0	0	0	0	0	1 (33.3)	0	0	0
Infection	0	0	0	0	1 (33.3)	1 (33.3)	0	0	0
Pneumonia	0	0	0	0	0	0	0	0	1 (5.9)
Injury, poisoning and procedural complications	0	0	0	1 (33.3)	0	1 (33.3)	0	0	0
Fall	0	0	0	1 (33.3)	0	1 (33.3)	0	0	0
Femur fracture	0	0	0	0	0	1 (33.3)	0	0	0
Investigations	0	0	0	0	0	0	1 (5.9)	0	0
Oxygen saturation decreased	0	0	0	0	0	0	1 (5.9)	0	0
Metabolism and nutrition disorders	0	0	0	0	0	0	3 (17.6)	0	0
Dehydration	0	0	0	0	0	0	3 (17.6)	0	0
Failure to thrive	0	0	0	0	0	0	1 (5.9)	0	0
Hyperglycaemia	0	0	0	0	0	0	1 (5.9)	0	0

Table 15. Treatment-Emergent Serious Adverse Events by Special Organ Class and Preferred Term (All Causalities)

System Organ Class and Preferred Term	Number (%) of Subjects								
	Figitumumab 0.05 mg/kg	Figitumumab 0.1 mg/kg	Figitumumab 0.8 mg/kg	Figitumumab 1.5 mg/kg	Figitumumab 3 mg/kg	Figitumumab 6 mg/kg	Figitumumab 10 mg/kg	Figitumumab 20 mg/kg	Erlotinib Cohort
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	0	0	0	0	1 (5.9)
Metastases to meninges	0	0	0	0	0	0	0	0	1 (5.9)
Nervous system disorders	0	0	0	0	0	0	1 (5.9)	1 (14.3)	2 (11.8)
Cerebrovascular accident	0	0	0	0	0	0	0	1 (14.3)	1 (5.9)
Depressed level of consciousness	0	0	0	0	0	0	1 (5.9)	0	0
Hydrocephalus	0	0	0	0	0	0	0	0	1 (5.9)
Psychiatric disorders	0	1 (50.0)	1 (25.0)	0	0	0	0	0	1 (5.9)
Confusional state	0	0	1 (25.0)	0	0	0	0	0	0
Major depression	0	0	0	0	0	0	0	0	1 (5.9)
Suicidal ideation	0	1 (50.0)	0	0	0	0	0	0	0
Renal and urinary disorders	0	0	0	0	0	0	0	0	2 (11.8)
Renal failure acute	0	0	0	0	0	0	0	0	2 (11.8)
Respiratory, thoracic and mediastinal disorders	0	0	2 (50.0)	0	0	0	0	0	3 (17.6)
Dyspnoea	0	0	1 (25.0)	0	0	0	0	0	0

Table 15. Treatment-Emergent Serious Adverse Events by Special Organ Class and Preferred Term (All Causalities)

System Organ Class and Preferred Term	Number (%) of Subjects								
	Figitumumab 0.05 mg/kg	Figitumumab 0.1 mg/kg	Figitumumab 0.8 mg/kg	Figitumumab 1.5 mg/kg	Figitumumab 3 mg/kg	Figitumumab 6 mg/kg	Figitumumab 10 mg/kg	Figitumumab 20 mg/kg	Erlotinib Cohort
Epistaxis	0	0	0	0	0	0	0	0	2 (11.8)
Pleural effusion	0	0	1 (25.0)	0	0	0	0	0	0
Pulmonary embolism	0	0	0	0	0	0	0	0	1 (5.9)
Vascular disorders	0	0	0	0	1 (33.3)	0	0	0	1 (5.9)
Embolism	0	0	0	0	0 0 0 0	0	0	0	1 (5.9)
Orthostatic hypotension	0	0	0	0	1 (33.3)	0	0	0	0

MedDRA = Medical Dictionary for Regulatory Activities.
Subjects are only counted once per treatment for each row.
Includes data up to 150 days after last dose of study drug.
MedDRA (v14.1) coding dictionary applied.

Table 16. Treatment-Emergent Serious Adverse Events by MedDRA Preferred Term (Treatment Related, All Cycles)

MedDRA Preferred Term	10 mg/kg (N=17) n (%)	Erlotinib Cohort (N=17) n (%)
Any AEs	2 (11.8)	2 (11.8)
Dehydration	1 (5.9)	-
Diarrhoea	1 (5.9)	-
Failure to thrive	1 (5.9)	-
Hyperglycaemia	1 (5.9)	-
Epistaxis	-	1 (5.9)
Febrile neutropenia	-	1 (5.9)
Hydrocephalus	-	1 (5.9)
Neutropenia	-	1 (5.9)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.
MedDRA (v14.1) coding dictionary applied.

Phase 2: A summary of the treatment-emergent SAEs (all causalities) reported in any arm is presented in Table 17.

A summary of the treatment-related SAEs reported in any arm is presented in Table 18. The most frequently reported study treatment related SAEs in the treatment Arm A were hyperglycemia, febrile neutropenia, decreased appetite and dehydration. No study treatment related SAEs were reported for subjects in Arm B1 and Arm B2.

Table 17 Treatment-Emergent Serious Adverse Events by Special Organ Class and Preferred Term (All Causalities) For Events Having a Frequency Rate ≥0.

System Organ Class and MedDRA Preferred Term	Number (%) of Subjects		
	Arm A	Arm B1	Arm B2
Number (%) of subjects:			
Evaluable for adverse events	163	56	22
With adverse events	86 (52.8)	9 (16.1)	3 (13.6)
Blood and lymphatic system disorders	14 (8.6)	2 (3.6)	0
Anaemia	2 (1.2)	0	0
Febrile neutropenia	8 (4.9)	2 (3.6)	0
Neutropenia	5 (3.1)	0	0
Thrombocytopenia	2 (1.2)	0	0
Cardiac disorders	6 (3.7)	3 (5.4)	0
Acute myocardial infarction	0	1 (1.8)	0
Arrhythmia	0	1 (1.8)	0
Atrial fibrillation	2 (1.2)	1 (1.8)	0
Cardiogenic shock	0	1 (1.8)	0
Mitral valve incompetence	1 (0.6)	0	0
Myocardial infarction	2 (1.2)	0	0
Pericardial effusion	0	1 (1.8)	0
Tachycardia	1 (0.6)	0	0
Tricuspid valve incompetence	1 (0.6)	0	0
Congenital, familial and genetic disorders	1 (0.6)	0	0
Tracheo-oesophageal fistula	1 (0.6)	0	0
Gastrointestinal disorders	14 (8.6)	1 (1.8)	0
Abdominal pain	1 (0.6)	0	0
Abdominal pain upper	1 (0.6)	0	0
Constipation	1 (0.6)	0	0
Diarrhoea	3 (1.8)	0	0
Dysphagia	1 (0.6)	0	0
Gastrointestinal haemorrhage	1 (0.6)	0	0
Haematemesis	1 (0.6)	0	0
Intestinal perforation	2 (1.2)	0	0
Nausea	3 (1.8)	1 (1.8)	0
Pancreatitis	1 (0.6)	0	0
Pancreatitis acute	1 (0.6)	0	0
Rectal haemorrhage	1 (0.6)	0	0
Vomiting	4 (2.5)	1 (1.8)	0
General disorders and administration site conditions	26 (16.0)	3 (5.4)	1 (4.5)
Asthenia	3 (1.8)	0	0
Chest pain	3 (1.8)	0	0
Death	1 (0.6)	1 (1.8)	0
Disease progression	11 (6.7)	2 (3.6)	0
Fatigue	2 (1.2)	0	0
General physical health deterioration	2 (1.2)	0	0
Mucosal inflammation	1 (0.6)	0	0
Multi-organ failure	1 (0.6)	0	0
Pain	3 (1.8)	0	1 (4.5)
Pyrexia	4 (2.5)	0	0
Infections and infestations	21 (12.9)	1 (1.8)	1 (4.5)
Abdominal sepsis	1 (0.6)	0	0
Cellulitis	1 (0.6)	0	0
Clostridial infection	1 (0.6)	0	0

Table 17 Treatment-Emergent Serious Adverse Events by Special Organ Class and Preferred Term (All Causalities) For Events Having a Frequency Rate ≥0.

System Organ Class and MedDRA Preferred Term	Number (%) of Subjects		
	Arm A	Arm B1	Arm B2
Diverticulitis	2 (1.2)	0	0
Infection	3 (1.8)	0	1 (4.5)
Lobar pneumonia	1 (0.6)	0	0
Pneumonia	7 (4.3)	1 (1.8)	0
Pneumonia necrotising	1 (0.6)	0	0
Rectal abscess	1 (0.6)	0	0
Respiratory tract infection	2 (1.2)	0	0
Sepsis	1 (0.6)	0	0
Staphylococcal infection	1 (0.6)	0	0
Tooth abscess	1 (0.6)	0	0
Urosepsis	1 (0.6)	0	0
Investigations	2 (1.2)	0	0
Haemoglobin decreased	2 (1.2)	0	0
Platelet count decreased	1 (0.6)	0	0
Metabolism and nutrition disorders	29 (17.8)	1 (1.8)	1 (4.5)
Decreased appetite	2 (1.2)	0	0
Dehydration	12 (7.4)	0	1 (4.5)
Diabetes mellitus	1 (0.6)	0	0
Diabetic complication	1 (0.6)	0	0
Hypercalcaemia	2 (1.2)	0	0
Hyperglycaemia	11 (6.7)	0	0
Hypoglycaemia	1 (0.6)	0	0
Hyponatraemia	4 (2.5)	0	0
Hypophagia	0	1 (1.8)	0
Musculoskeletal and connective tissue disorders	4 (2.5)	0	0
Back pain	1 (0.6)	0	0
Fistula	1 (0.6)	0	0
Muscular weakness	1 (0.6)	0	0
Pain in extremity	1 (0.6)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.8)	0	1 (4.5)
Cancer pain	1 (0.6)	0	0
Malignant pleural effusion	1 (0.6)	0	0
Non-small cell lung cancer	1 (0.6)	0	1 (4.5)
Nervous system disorders	6 (3.7)	1 (1.8)	0
Cerebral ischaemia	1 (0.6)	0	0
Cerebrovascular accident	1 (0.6)	0	0
Convulsion	0	1 (1.8)	0
Depressed level of consciousness	1 (0.6)	0	0
Dizziness	1 (0.6)	0	0
Epilepsy	1 (0.6)	0	0
Peripheral sensory neuropathy	1 (0.6)	0	0
Somnolence	1 (0.6)	0	0
Psychiatric disorders	10 (6.1)	0	0
Catatonia	1 (0.6)	0	0
Completed suicide	1 (0.6)	0	0
Confusional state	5 (3.1)	0	0
Delirium	2 (1.2)	0	0
Depression	3 (1.8)	0	0

Table 17 Treatment-Emergent Serious Adverse Events by Special Organ Class and Preferred Term (All Causalities) For Events Having a Frequency Rate ≥0.

System Organ Class and MedDRA Preferred Term	Number (%) of Subjects		
	Arm A	Arm B1	Arm B2
Mental status changes	1 (0.6)	0	0
Personality disorder	1 (0.6)	0	0
Renal and urinary disorders	3 (1.8)	0	0
Incontinence	1 (0.6)	0	0
Renal failure	2 (1.2)	0	0
Renal failure acute	1 (0.6)	0	0
Respiratory, thoracic and mediastinal disorders	24 (14.7)	5 (8.9)	0
Chronic obstructive pulmonary disease	2 (1.2)	1 (1.8)	0
Cough	1 (0.6)	0	0
Dysphonia	1 (0.6)	0	0
Dyspnoea	6 (3.7)	0	0
Haemoptysis	2 (1.2)	0	0
Hypoxia	3 (1.8)	0	0
Pleural effusion	1 (0.6)	1 (1.8)	0
Pneumothorax	2 (1.2)	0	0
Pulmonary embolism	6 (3.7)	1 (1.8)	0
Respiratory failure	3 (1.8)	2 (3.6)	0
Skin and subcutaneous tissue disorders	2 (1.2)	0	0
Leukocytoclastic vasculitis	1 (0.6)	0	0
Purpura	1 (0.6)	0	0
Vascular disorders	3 (1.8)	2 (3.6)	0
Deep vein thrombosis	1 (0.6)	2 (3.6)	0
Orthostatic hypotension	1 (0.6)	0	0
Thrombosis	0	1 (1.8)	0
Vasculitis	1 (0.6)	0	0

MedDRA = Medical Dictionary for Regulatory Activities.
Subjects are only counted once per treatment for each row.
Includes data up to 150 days after last dose of study drug.
MedDRA (v14.1) coding dictionary applied.

Table 18. Summary of Treatment-Emergent Serious Adverse Events by MedDRA Preferred Term (Treatment Related, All Cycles)

MedDRA Preferred Term	Arm A (N=163) n (%)
Any AEs	22 (13.5)
Hyperglycaemia	8 (4.9)
Febrile neutropenia	3 (1.8)
Decreased appetite	2 (1.2)
Dehydration	2 (1.2)
Asthenia	1 (0.6)
Chest pain	1 (0.6)
Clostridial infection	1 (0.6)
Diabetes mellitus	1 (0.6)
Diarrhoea	1 (0.6)
Dyspnoea	1 (0.6)
Fatigue	1 (0.6)
Hyponatraemia	1 (0.6)
Hypoxia	1 (0.6)
Muscular weakness	1 (0.6)
Nausea	1 (0.6)
Neutropenia	1 (0.6)
Orthostatic hypotension	1 (0.6)
Pneumonia	1 (0.6)
Pneumonia necrotising	1 (0.6)
Purpura	1 (0.6)
Pyrexia	1 (0.6)
Thrombocytopenia	1 (0.6)
Vomiting	1 (0.6)

N = number of subjects in treatment group; MedDRA = Medical Dictionary for Regulatory Activities. MedDRA (v14.1) coding dictionary applied.

Phase 1 Discontinuations due to AEs: Most subjects discontinued study treatment due to disease progression. A total of 9 subjects discontinued due to AEs in the figitumumab dose escalation and extension cohort (1 subject discontinued each in the figitumumab 0.1 mg/kg, 0.8 mg/kg, 6 mg/kg, and 20 mg/kg cohorts; 2 subjects in the CP-751,871, 1.5 mg/kg cohort; and 3 subjects in the figitumumab, 10 mg/kg cohort) and 5 subjects in the erlotinib cohort during the treatment phase.

Phase 2 Discontinuations Due to Treatment Related Adverse Events: Most subjects discontinued study treatment due to disease progression. Among subjects treated in Arm A, 3 subjects discontinued figitumumab due to AE of study treatment related hyperglycemia, 1 subject discontinued figitumumab treatment due to gamma glutamyl-transferase (GGT)

increase (reported as laboratory abnormality), and 1 subject discontinued figitumumab treatment because of study treatment related anemia, neutropenia and thrombocytopenia.

Phase 1 Deaths: No treatment-related (per Investigator) deaths were observed. In total, there were 26 deaths: 1 (50.0%) subject in the figitumumab (0.1 mg/kg) cohort, 3 (75.0%) subjects in the figitumumab (0.8 mg/kg) cohort, 1 (33.3%) subject in the figitumumab (1.5 mg/kg) cohort, 2 (66.7%) subjects in the figitumumab (3 mg/kg) cohort, 2 (66.7%) subjects in the figitumumab (6 mg/kg) cohort, 4 (23.5%) subjects in the figitumumab (10 mg/kg) cohort, 3 (42.9%) subjects in the figitumumab (20 mg/kg) cohort, and 10 (58.8%) subjects in the erlotinib cohort.

Of the 26 deaths, 2 occurred during study treatment or within 28 days of last study treatment: 1 subject (5.9%) each in the figitumumab (10 mg/kg) cohort and erlotinib cohort.

Phase 2 Deaths: No treatment-related (per Investigator) deaths were observed. Ninety-two subjects (56.4%) in Arm A, 33 subjects (58.9%) in Arm B1 and 12 subjects (54.5%) in Arm B2 died during the study period.

Grade 5 AEs were reported in 20 subjects treated in Arm A and were mostly disease progression or NSCLC (13 subjects); the remaining 8 deaths were as a result of (observed in 1 subjects each): completed suicide, death, general physical health deterioration, intestinal perforation, multi-organ failure, myocardial infarction, pneumonia, and respiratory failure

Grade 5 AEs were reported in 4 subjects treated in Arm B1 before figitumumab was started or added: 2 subjects with disease progression (observed in 1 subject each), death and respiratory failure.

A Grade 5 AE of NSCLC was reported in a subject treated in Arm B2.

CONCLUSIONS:

Phase 1

Safety

- MTD was not determined in this study. Based on the safety profile, figitumumab at 10 mg/kg was determined to be the initial RP2D and later changed to 20 mg/kg based on results from other Phase 1 studies.

- Figitumumab in combination with paclitaxel and carboplatin was tolerated by the subjects treated in this study. Overall, the 4-drug regimen (figitumumab in combination with paclitaxel, carboplatin and erlotinib) was less tolerated than the 3-drug regimen (figitumumab in combination with paclitaxel and carboplatin).

- All the subjects in the figitumumab dose escalation and extension cohort and erlotinib cohort experienced TEAEs (any grade, all cycles).

- A total of 12 (28.6%) subjects and 11 (64.7%) subjects in the figitumumab dose escalation and extension cohort; and erlotinib cohort, respectively reported TEAE of hyperglycemia of which 1 was a SAE.

- There were no treatment-related deaths reported in any study treatment cohort.

- The majority of subjects experienced Grade 3 or Grade 4 all causality or treatment-related AEs in all treatment groups. The most frequently reported study treatment-related (all grades) AEs were fatigue, diarrhea and hyperglycemia. Clinically meaningful higher frequency of alopecia, fatigue, nausea, diarrhea and vomiting were observed in the figitumumab dose escalation and extension cohort.

- Similar number of subjects (2 subjects each) in the figitumumab (10 mg/kg) cohort and erlotinib cohort had treatment-related SAEs.

Pharmacokinetic

Increases in plasma figitumumab exposure for the 3-week dosing cycle (AUC_{504}) generally appeared to be dose proportional at doses of 0.8 to 20 mg/kg. Moderate accumulation of approximately 2-fold was observed from Cycle 1 to Cycle 4. Mean terminal $t_{½}$ was approximately 10 days at doses ≥3 mg/kg.

Efficacy

- The ORR (defined as CR + PR) was 33.3% in the figitumumab dose escalation and extension cohort and 25.0% in the erlotinib cohort in combination with paclitaxel and carboplatin.

Phase 2

Efficacy

- The randomized Phase 2 portion of the trial met its primary goal of demonstrating a favorable probability of confirmed response for the Arm A with respect to historical activity in non-small-cell lung cancer subjects. The lower limit of the 90 % CI was 29.2 % and the requirement was >28.0%; p=0.027.

- However, in the non-randomized non-adenocarcinoma cohort (consisting subjects with non-adenocarcinoma histology), greater activity was not demonstrated. The lower limit of the 90 % CI was 27.5% and the requirement was >30 %; p=0.121.

- Median PFS was similar (4.4 in 10 mg Arm A, 4.5 in 20 mg Arm A, 4.3 in Arm B and 5.1 in non-randomized Arm A) in all groups.

Safety

- Figitumumab in combination with paclitaxel and carboplatin, and paclitaxel and carboplatin alone were tolerated by the subjects treated in this study.

- The majority of subjects in Arm A (75.5%) and B2 (77.3%) experienced treatment emergent AEs (any grade all cycles).

- A total of 11 (6.7%) subjects in Arm A reported serious TEAEs of hyperglycemia, of which 4.9% were treatment-related SAEs.

- There were no treatment-related deaths reported in any study treatment cohort. Due to the extended safety reporting period (which was extended to 150 days after treatment for some sites), more Grade 5 AEs of disease progression may have been reported in Arm A. Further difficulties in interpretation are introduced due to the option for Arm B subjects to receive figitumumab resulting in AEs being reported under Arm B2 that would have been reported under Arm B1 if the subject had not received figitumumab.

- More Grade 3/4 (combined) all causality/treatment-related AEs were reported for Arm A (81.0%; 36.2%) than Arm B1 (62.5%; 10.7%) subjects, respectively, although the safety reporting period and Arm B1 also impact interpretation. For the following events, more subjects in Arm A than Arm B1 reported clinically meaningful higher frequency of all causality AEs: fatigue, decreased appetite, hyperglycemia, diarrhea, neutropenia, vomiting, dysgeusia, weight decreased, rash, headache, stomatitis and epistaxis.

- More Arm A (52.8%; 13.5%) than Arm B1 (16.1%; 0%) subjects reported all causality or treatment-related SAEs, respectively, although the safety reporting period and Arm B1 also impact interpretation.