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

PROTOCOL NO.: A4021018

PROTOCOL TITLE: Randomized, Open-Label, Phase 3 Trial of Erlotinib Alone or in Combination With CP-751,871 in Patients With Advanced Non-Small-Cell Lung Cancer of Nonadenocarcinoma Histology

Study Centers: A total of 121 centers took part in the study and randomized subjects; 30 in the United States (US), 12 in Spain, 8 in France, 7 in Italy, 6 each in Russian Federation and Poland, 5 in Ukraine, 4 in Bulgaria, 3 each in the United Kingdom, Taiwan, Serbia, Romania, Republic of Korea, Ireland, Hungary, Czech Republic, and Brazil, 2 each in Switzerland, South Africa, Latvia, Greece, Canada, Indonesia and Belgium and 1 each in Chile and Slovenia.

Study Initiation, Primary Completion and Final Completion Dates:
Study Initiation Date: 23 May 2008
Primary Completion Date: 31 March 2011
Study Completion Date: 26 April 2012

Phase of Development: Phase 3

Study Objectives:

Primary Objective:

- To compare overall survival (OS) in subjects with advanced non-small-cell lung cancer (NSCLC) of nonadenocarcinoma tumor histology who received figitumumab plus erlotinib (Arm A) or erlotinib alone (Arm B). Subjects in Arm B were allowed to receive single-agent figitumumab following progression on erlotinib alone.

Secondary Objectives:

- To compare progression-free survival (PFS) in subjects with advanced NSCLC of nonadenocarcinoma tumor histology who received figitumumab plus erlotinib (Arm A) or erlotinib alone (Arm B);
- To assess the safety and tolerability of multiple doses of figitumumab;
- To assess the efficacy of figitumumab in terms of overall response rate (ORR);

- To collect pharmacokinetic (PK) data of figitumumab for population PK meta-analysis;

- To monitor for the occurrence of antidrug antibody (ADA) in response to figitumumab;

- To test for the presence of plasma insulin-like growth factor 1 receptor (IGF-1R) related markers;

- To assess health-related quality of life outcomes (HRQoL) using the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30/Lung Cancer (LC) 13 and health state utilities using the European Quality of Life Questionnaire (EQ-5D).

METHODS

Study Design: This was a multiple-center, open-label, 2-arm randomized Phase 3 trial in subjects with NSCLC of nonadenocarcinoma (ie, squamous cell, large cell and adenosquamous carcinoma) tumor histology who had received previous treatment with at least 1 platinum-based combination regimen and in whom erlotinib was a reasonable treatment option. Subjects must have had at least 1 target lesion, as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0, that had not been irradiated or that had progressed after irradiation.

At least 900 subjects (450 per arm) were planned for randomization over approximately 3 years, unless stopped early by the Data Safety Monitoring Committee (DSMC). The full population originally planned for this study was not pursued due to a risk for the development of hyperglycemia in individuals with glycated hemoglobin (HbA1c) ≥5.7% and the reasonable assumption that hyperglycemia may have been a contributor to the morbidity of subjects. The screening inclusion criterion of an ≤8% HbA1c was subsequently changed to <5.7% and this restricted population was estimated to comprise approximately one half of the original study population. It was recognized that choosing a subset to reduce serious adverse events (SAEs) in erlotinib + figitumumab treated subjects could introduce some bias into the survival comparison. To mitigate this concern, 300 additional subjects were to be accrued and analyzed separately using a 1-sided 0.05 level testing, for a total of 600 (300 per arm) subjects satisfying the screening HbA1c <5.7% eligibility criterion. Both the results in the 600 subjects meeting the revised HbA1c eligibility criterion and the results in the 300 subjects enrolled according to the original HbA1c criterion had to be positive to conclude a positive outcome of the trial.

One interim analysis of survival for both superiority and futility was planned for after approximately one half (263) of the required number of deaths were observed. The boundary for lack of efficacy per the p-value scale at the interim analysis was 0.39.

The screening for evaluation of disease status (tumor assessments) was to have been completed within 4 weeks prior to randomization. Subjects were randomized (1:1) to receive figitumumab (20 mg/kg as an intravenous [IV] infusion on study Day 1 [Day 1 and 2 in

Cycle 1 only]) and erlotinib (150 mg/day orally [PO]) (Arm A) or erlotinib alone (Arm B). Randomization was according to a central computerized system using the method of permuted blocks balanced according to the following stratification factors: gender (male versus [vs] female), Eastern Cooperative Oncology Group (ECOG) performance status (0-1 vs 2) and region (US/Canada vs European Union vs Rest of World). Subjects in Arm B who experienced disease progression with erlotinib alone were eligible to receive single-agent figitumumab and this was designated Arm B2. Arm A (figitumumab plus erlotinib) subjects for whom either drug was discontinued for any reason, were allowed to continue treatment with the remaining drug.

After the recommendation of the DSMC to close the study, subjects were allowed to continue treatment with figitumumab only if the Investigator and the subject believed that it was providing clinical benefit and continuation was supported by local ethics committee and regulations. Subjects could continue to receive erlotinib as defined in this study. Treatment with single-agent figitumumab was no longer available to subjects who progressed on single-agent erlotinib (crossover). The study visit schedule is shown in Table 1.

Table 1. Visit Schedule

	Screening	Day 1 (Predose)	Day 1 (Postdose)	Day 2 (C1 Only)	Day 3 (C1 Only)	Day 8 (C1 and C2 only)	End of Treatment[a]	Follow-Up[a]
Informed consent	X							
Baseline signs and symptoms	X							
Medical history	X							
EQ-5D[b]		X					X	
Concomitant medications	Assessed throughout the study							
ECOG PS	X	X[c]						
Vital signs (temperature, weight, blood pressure, pulse, and height) [height only at Screening]	X	X[c]					X	X
Physical examination	X	X[c]					X	X
Laboratory (hematology, blood chemistry, coagulation)[d]	X	X[c]			X[d]	X[d]	X	X
ECG[e]	X	X					X	
Erlotinib			PO continuous					
Figutumumab infusion[f]			X	X				
Tumor assessment[g]	X		Performed 6, 9, 12, 15, 18 weeks after randomization and every 6 weeks thereafter					X
AEs	Assessed throughout the study							
IGF-1R related markers[h]	X	X					X	
Anonymized pharmacogenomic sampling		X						
PK[i]		X		X			X	X
ADA[j]		X					X	X
Pregnancy test[k]	X							
Tumor biopsy[l]		X						

ADA = antidrug antibody; AE = adverse event; CT scan = computed tomographic scanning; DAI = dosage and administration instruction; EQ-5D = European Quality of Life Questionnaire; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOT = end of treatment; HbA1c = glycated haemoglobin; IEC = Independent Ethics Committee; IGF-1R; = insulin-like growth factor 1 receptor; IgG = immunoglobulin G; IRB = Institutional Review Board; MRI = magnetic resonance imaging; PK = pharmacokinetic; PO = per oral; RECIST = Response Evaluation Criteria in Solid Tumors.

a. An EOT visit took place 21-28 days after the last dose or sooner if subject started non-study treatment. Crossover Arm B subjects had all the tests/visit required for EOT done prior to figitumumab dosing. A second EOT visit was done 21 to 28 days after the last figitumumab dose. However, no plasma marker samples were collected at this visit. Follow-up study visits were scheduled, as needed, to monitor for any sustained, treatment emergent adverse events or efficacy. Laboratory tests were done prior to new treatment. Follow-up (off-treatment) tumor scans were performed every 8 weeks until objective disease progression. All subjects including those who took non-study anticancer therapy were followed until objective progression. Subjects were followed up for survival monthly via phone until 14 months after accrual was complete.

b. EQ-5D was assessed in both Arms prior to any clinical intervention on Day 1 of Cycles 1-3, every other cycle thereafter, and at the EOT. For subjects in Arm B who

Table 1. Visit Schedule

started to receive figitumumab the questionnaire was to be completed predose crossover Cycle 1, 2, 4, 6, 8, 10, 12, 14 and 16 and at their figitumumab EOT visit.

c. Beginning in Cycle 2, predose activities were done up to 72 h predose. Physical exam and ECOG PS were done up to 1 week before dosing. Vital signs were repeated postdose, if clinically indicated. Weight was measured within 72 hours prior to dosing at each cycle.

d. Hematology, coagulation, and chemistry were done within 1 week (72 hours preferable) prior to dosing on Cycle 1. Total IgG was measured only at Cycle 1 Day 1. HbA1c was measured at Baseline, Cycle 4 Day 1 and EOT only. Chemistry assessments were performed at Cycle 1 on Days 3 and 8 and at Cycle 2 on Day 8. Additional safety assessments were done as per institutional standard of care. Results of these additional tests were recorded on the case report form. Upon documentation of progressive disease, as defined by RECIST, subjects in Arm B continuing on figitumumab as a single-agent (Arm B crossover subjects) were to have a blood sample collected for the measurement HbA1c prior to figitumumab administration in addition to the chemistry, coagulation and hematology panel required at every cycle prior to dosing. Also at the first crossover cycle on Days 3 and 8 and at Cycle 2 Day 8 subjects were to have a blood sample collected for the chemistry panel. Additional HbA1c samples were collected in crossover Arm B subjects at crossover cycle 4 Day 1 and 21-28 days after the last figitumumab dose.

e. A 12-Lead ECG was performed at Screening and on Day 1 predosing at each study cycle and EOT visit. Additional ECGs were done as medically required. Crossover Arm B subjects had an ECG repeated prior to receiving figitumumab, at every cycle prior to dosing and approximately 21-28 days after the last figitumumab infusion.

f. The sites followed the dosage and administration instructions provided for figitumumab dose preparation (DAI). All subjects were weighed within 72 hours prior to dosing for every cycle to ensure they did not experience either a weight loss or gain >10% from the prior weight used to calculate the amount of figitumumab required for dose preparation. Decision to recalculate figitumumab dose based on the weight obtained at each cycle could be in accordance with institutional practice. However, if the subject experienced either a weight loss or gain >10%, the amount of figitumumab required for study drug preparation and administration had to be recalculated using this most recent weight obtained.

g. Screening tumor assessment (baseline CT, MRI scan and bone scan if clinically indicated) was done within 4 weeks prior to randomization. Tumor lesions previously irradiated were considered measurable only if progressing. Clinical symptoms suggestive of brain metastasis were evaluated 2 weeks prior to randomization. Scans were performed every 6 weeks. If clinically indicated, brain tumor assessment of non target brain lesion(s) and bone scans were repeated at every other scheduled assessment. To confirm an objective response tumor measurement, scans were repeated no ≥4 weeks later. Scans were performed every 8 weeks in subjects discontinuing therapy. Additional scans were performed if medically required. Tumor scans were reviewed at the clinical sites. Arm B subjects continuing on figitumumab single-agent therapy (Arm B crossover) were to have new baseline scans performed up to 4 weeks prior to starting figitumumab treatment, if not available.

h. Samples for the measurement of plasma IGF-IR related markers were taken at Screening, at Cycle 2 Day 1 pre dosing and EOT in both study arms. Baseline samples were collected at Cycle 1 predose if not collected at Screening. Crossover (CO) Arm B subjects, had an additional plasma marker sample collected prior to receiving figitumumab as a single-agent.

i. In Arm A, blood samples for evaluation of figitumumab PK were collected during Cycle 1 within 2 hours before the Day 1 figitumumab infusion and at 1 hour post the end of the Day 2 infusion. In subsequent cycles, PK blood samples were collected within 2 hours prior to figitumumab infusion in Cycles 2, 4, 5, and 6; and at 1 hour post the end of figitumumab infusion in Cycle 5. Additional PK blood samples were collected at the EOT and approximately 150 days after the last figitumumab infusion. These samples were collected even if the subject started another treatment for the disease under study, if possible. In Arm B subjects who went on to receive single-agent figitumumab upon progression, PK samples were collected within 2 hours before CO-C1, CO-C2, and CO-C4 figitumumab infusions, at their second EOT visit and approximately 150 days after the last figitumumab infusion even if the subject started another treatment for his/her disease, if possible.

j. Serum samples for measurement of ADAs were collected within 2 hours prior to figitumumab infusion in Cycles 1, 2, and 4, at the EOT and approximately 150 days after the last figitumumab infusion even if the subject starts another cancer treatment, if possible. In Arm B subjects who go on to receive single agent figitumumab upon progression, anti-drug antibody samples will be collected within 2 hours prior to CO-C1, 2, and 4 figitumumab infusions, at their second EOT visit and approximately 150 days from the last figitumumab infusion. If possible this sample was collected even if the subject starts another cancer therapy.

k. Pregnancy test (serum or urine) as appropriate for all women of child bearing potential within a week prior to Cycle 1 dosing. Results were available before dosing. Pregnancy test was repeated during study as per request of Investigator and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or if required by

Table 1. Visit Schedule

local regulations.

l. Tumor tissue was obtained from available diagnostic pathology specimens (a section of the tumor block or slides). This sample was obtained at any time during the study, if consent was obtained. Biopsy procedures were subject to Investigator and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval.

Number of Subjects (Planned and Analyzed): A total of 900 subjects were planned for randomization over approximately 3 years. A total of 583 subjects were enrolled, 293 subjects were randomized to Arm A and 290 to Arm B. Eighty-three subjects, upon progression on erlotinib, subsequently received single-agent figitumumab (Arm B2).

Diagnosis and Main Criteria for Inclusion: Male or female subjects (≥18 years) with histologically or cytopathologically documented NSCLC with a primary histology of squamous cell, large cell or adenosquamous carcinoma and their variants, with metastases (Stage IV), recurrent disease, or locally advanced (Stage IIIB) with malignant pleural effusion were eligible. Subjects in whom erlotinib was a reasonable treatment option but who had not previously received erlotinib or anti-IGF-1R based investigational therapy were eligible. Subjects must have received previous treatment for advanced disease consisting of at least 1 platinum-based combination regimen. Subjects must have had at least 1 measurable lesion (per RECIST) and an ECOG performance status of 0-2. Subjects must have had adequate hematologic, renal and liver function. Subjects could not have had an HbA1c level ≥5.7% (initial criterion was ≤8%).

Study Treatment:

Arm A: Figitumumab (20 mg/kg) + erlotinib (150 mg/day).

The figitumumab treatment in combination with erlotinib was given in 3 week cycles. Figitumumab was administered as an IV infusion on study Days 1 and 2 in Cycle 1, and on Day 1 every 3 weeks (from Day 1) thereafter. The total dose was calculated based on the subject's actual weight. Erlotinib was taken as 1 tablet per day PO (per oral) at least 1 hour before or 2 hours after the ingestion of food.

Unless unmanageable toxicity occurred, subjects were to continue treatment for a total of up to 17 cycles of figitumumab therapy (approximately 1 year) as long as the Investigator considered that the treatment was providing clinical benefit. Upon agreement of the Investigator and Sponsor, treatment could continue beyond 1 year if there was evidence of safety, toleration and clinical benefit. Subjects could receive treatment upon clinical or imaging progression if the Investigator considered that there was a reasonable possibility that the treatment was providing clinical benefit.

Arm B: Erlotinib (150 mg/day).

Erlotinib was taken as 1 tablet per day PO at least 1 hour before or 2 hours after the ingestion of food. If the subject did not experience disease progression after 1 year and the erlotinib treatment was well tolerated, additional cycles could be given upon agreement between the Investigator and the Sponsor. Figitumumab was provided by the Sponsor. Unless otherwise agreed by the Investigator and Sponsor, erlotinib was provided by the clinical site but the cost was covered by the Sponsor.

Efficacy, Pharmacokinetic, Pharmacodynamic and Quality of Life Endpoints:

Primary Efficacy Endpoint: The primary endpoint for efficacy was OS, which was calculated as the time from randomization to date of death due to any cause. Subjects last

known date to be alive were censored at date of last contact. All subjects were to be followed every 4 weeks for survival.

Secondary Efficacy Endpoints: The secondary endpoints for efficacy were PFS and objective response (defined as a best response of complete response [CR] or partial response [PR]).

PFS was calculated from the time of randomization to date of first documentation of progression of disease, or death due to any cause, whichever came first. Subjects last known 1) to be alive, and 2) to be progression-free, and who had a baseline and at least 1 on-study disease assessment, were censored at the date of the last objective disease assessment that verified lack of disease progression.

Response was assessed using the RECIST (version 1.0). Screening tumor assessments were to be done within 4 weeks prior to randomization. Tumor assessment while on treatment was completed at 6, 9, 12, 15, 18 weeks after randomization and every 6 weeks thereafter. To confirm an objective response, a repeat tumor assessment was required to be made no ≥4 weeks after the initial observation of response and the results recorded on the case report form. Off-treatment tumor assessments were performed at least once every 8 weeks until objective disease progression. This included subjects who took non-study anticancer therapy. After progression, all subjects were to be followed every 4 weeks for survival. Information on subsequent anticancer therapy was collected.

Other Secondary Endpoints:

- Figitumumab plasma concentrations;
- Anti-drug antibodies;
- Plasma IGF-1R related markers;
- Patient Reported Outcomes as measured by the EORTC QLQ-C30/LC13;
- Health state utilities as measured by the EQ-5D.

Safety Evaluations: All subjects who started treatment in either arm were considered evaluable for safety. Safety was assessed by collection of 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 (NCI CTCAE) version 3.0. Collection of new non-serious AEs continued until 150 days after the last dose of study therapy, withdrawal of subject consent or initiation of subsequent anticancer therapy, whichever occurred first. Deaths and other SAEs were to have been reported through 150 days following the last dose of study drug, irrespective of any intervening treatment. The reporting period for erlotinib nonserious AEs and SAEs was later changed from 150 days after the last dose of erlotinib to 28 days after the last dose of erlotinib.

Statistical Methods:

Analysis Populations: There were 3 population analysis sets analyzed for this study:

- Full analysis set: All randomized subjects. For this analysis set subjects were analyzed as randomized regardless of treatment received.

- Treated Analysis Set: All randomized subjects who started treatment. For this analysis set subjects were analyzed according to treatment received. Subjects who were not treated were not included in the analysis.

- Treatment Misallocations: For randomized subjects who received the incorrect treatment arm safety, biomarker, antibody and patient reported outcome data was reported according to the arm received. For survival, response and PFS analyses, subjects were analyzed according to the assigned arm regardless.

All randomized subjects were considered evaluable for efficacy.

Primary Efficacy Endpoint: The primary endpoint for efficacy was OS. The primary analysis of OS was a stratified log-rank test comparing Arm A vs Arm B. OS was calculated as the time from randomization to date of death due to any cause. Subjects last known date to be alive were censored at date of last contact. Overall level for survival testing was 1-sided 0.024. The study was designed to have 1 interim analysis for efficacy and futility after approximately one half (263) of the number of events, and a final analysis for survival. A formal efficacy boundary for rejecting the null hypothesis and futility boundary for rejecting the alternative hypothesis (nonbinding) were constructed using the spending function methodology of Lan and DeMets with O'Brien-Fleming stopping bounds.

Secondary Efficacy Endpoints: The key secondary endpoint for efficacy was PFS. PFS and response were initially assessed by both independent central review and the study Investigators. The contract with the central review entity was terminated when the study was determined to have crossed the statistical boundary for futility. Central review was no longer necessary at that point as its primary purpose would have been to support a regulatory submission which was no longer feasible. All response and PFS data reported herein are based on Investigator assessments.

The primary analysis of PFS was a 0.001 level stratified log-rank test comparing Arm A versus Arm B (overall level for the study was 0.025, with 0.024 allocated to OS and 0.001 allocated to PFS). PFS was calculated from the time of randomization to progression of disease, or death due to any cause, whichever came first. Subjects last known 1) to be alive, and 2) to be progression-free, and who had a baseline and at least 1 on-study disease assessment, were censored at the date of the last objective disease assessment that verified lack of disease progression. Subjects with no on-study disease assessments were censored at the randomization date unless death occurred prior to the first planned assessment (in which case the death was an event). Subjects with inadequate baseline disease assessment were censored at the randomization date. Subjects with documentation of progression or death

after an unacceptably long interval (>9 weeks) since the last tumor assessment were censored at the time of last objective assessment prior to the event.

Response was assessed using the RECIST (version 1.0). Best response, CR, PR, stable/no response, progressive disease, indeterminate, early death) and percent of subjects with an objective response (CR or PR) were reported by treatment arm and treatment differences were tested using chi-square tests.

Other Secondary Endpoints:

Figitumumab concentration-time and ADA data were provided as listings.

Circulating tumor cell IGF-1R positive cell counts were included in the laboratory data listing.

Data for HRQoL based on the EORTC QLQ-C30/LC13 were not collected as the majority of subjects had already been enrolled prior to the requirement for scoring HRQoL based on this measure, and the DSMC recommended closure of the study shortly after this requirement was implemented. Subjects completed an EQ-5D Questionnaire and by-subject listings were generated but summary statistics were not.

RESULTS

Subject Disposition and Demography: Two hundred and ninety-three subjects were randomized to Arm A and 290 to Arm B. Eighty-three subjects, upon progression on erlotinib, subsequently received single-agent figitumumab (Arm B2). In tables that include Arm B2, Arm B1 refers to subjects on Arm B, whether or not they received figitumumab. For subjects who did receive figitumumab, Arm B1 includes results up to the start of figitumumab. For subjects who did not receive figitumumab, Arm B1 includes all Arm B results. Disposition and safety data were analyzed separately for the subjects in Arm B2; all other data analyses include all subjects in Arm B.

Overall, all but 4 subjects received study treatment and only 1 subject received study drug from the arm other than the 1 randomized to. A summary of subject randomization and evaluable populations is presented in Table 2.

Table 2. Subject Evaluation Groups

Subject Evaluation Groups		Arm A Figitumumab 20 mg/kg + Erlotinib 150 mg n (%)	Arm B1 Erlotinib 150 mg n (%)	Arm B2 Figitumumab 20 mg/kg n (%)
Assigned to study treatment: N	583			
Treated		289	290	83
Discontinued		282 (97.6)	206 (71.0)	82 (98.8)
Ongoing at time of data cut-off		7 (2.4)	1 (0.3)	1 (1.2)
Crossover		0	83 (28.6)	0
Not treated		3 (1.0)	1 (<1.0)	0
Randomized drug not drug received		1 (<1.0)	0	0
Analyzed for safety:				
Adverse events		289 (100.0)	290 (100.0)	83 (100.0)
Laboratory data		266 (92.0)	280 (96.6)	71 (85.5)

Arm B1 includes all Arm B2 subjects without regard to treatment status at the time of data cut off.
N = number of subjects; n = number of subjects with specified criteria.

The largest proportion of subjects in each treatment arm discontinued the treatment phase of the study due to objective progression or relapse. Twenty-one subjects (20 [6.9%] Arm A, 1 [1.2%] Arm B2) discontinued treatment due to figitumumab-related AEs, and 31 subjects (24 [8.3%] Arm A, 7 [2.4%] Arm B1) discontinued treatment due to erlotinib-related AEs. A summary of reasons for discontinuation from the treatment phase and from the study is presented in Table 3.

Table 3. Reasons for Discontinuation – All Treated Subjects, As Treated

	Arm A Figitumumab 20 mg/kg + Erlotinib 150 mg N=289 n (%)	Arm B1 Erlotinib 150 mg N=290 n (%)	Arm B2 Figitumumab 20 mg/kg N=83 n (%)
Discontinuations from treatment phase – figitumumab			
Subject died	40 (13.8)	0	10 (12.0)
Related to figitumumab	20 (6.9)	0	1 (1.2)
Adverse event	20 (6.9)	0	1 (1.2)
Not related to figitumumab	227 (78.5)	1 (0.3)[a]	71 (85.5)
Adverse event	26 (9.0)	0	1 (1.2)
Global deterioration of health status	25 (8.7)	0	10 (12.0)
Lost to follow-up	0	0	2 (2.4)
Objective progression or relapse	141 (48.8)	0	52 (62.7)
Other	9 (3.1)	1 (0.3)	4 (4.8)
Subject refused continued treatment for reason other than adverse event	26 (9.0)	0	2 (2.4)
Total	287 (99.3)	1 (0.3)	82 (98.8)
Discontinuations from treatment phase – erlotinib			
Subject died	40 (13.8)	18 (6.2)	0
Related to erlotinib	24 (8.3)	7 (2.4)	0
Adverse event	24 (8.3)	7 (2.4)	0
Not related to erlotinib	222 (76.8)	263 (90.7)	1 (1.2)
Adverse event	23 (8.0)	15 (5.2)	0
Global deterioration of health status	30 (10.4)	23 (7.9)	1 (1.2)
Lost to follow-up	0	1 (0.3)	0
Objective progression or relapse	139 (48.1)	209 (72.1)	0
Other	7 (2.4)	7 (2.4)	0
Subject refused continued treatment for reason other than adverse event	23 (8.0)	8 (2.8)	0
Total	286 (99.0)	288 (99.3)	1 (1.2)
Discontinuations from study			
Subject died[b]	234 (81.0)	167 (57.6)	71 (85.5)
Not related to study treatment	48 (16.6)	39 (13.4)	11 (13.3)
Lost to follow-up	9 (3.1)	5 (1.7)	3 (3.6)
No longer willing to participate in study	25 (8.7)	18 (6.2)	5 (6.0)
Other	1 (0.3)	2 (0.7)	0
Study terminated by Sponsor	13 (4.5)	14 (4.8)	3 (3.6)
Total	282 (97.6)	206 (71.0)	82 (98.8)

N = number of subjects; n = number of subjects with specified criteria; OS = overall survival.

a. Subject was randomized to Arm A but only received erlotinib.

b. For Arm B subjects who received figitumumab, the discontinuations from study are reported under Arm B2. Therefore the Arm B1 tabulation does not include all discontinuations from study for subjects randomized to Arm B.

Demographic characteristics (Table 4) were similar across treatment arms. The majority of subjects in each treatment arm were male (228 [77.8%] Arm A, 225 [77.6%] Arm B), <70 years of age (226 [77.1%] Arm A, 222 [76.6%] Arm B), and White (249 [85.0%] Arm A, 238 [82.1%] Arm B).

Table 4. Demographic Characteristics - All Randomized, As Randomized

	Arm A Figitumumab 20 mg/kg + Erlotinib 150 mg N=293 n (%)	Arm B Erlotinib 150 mg N=290 n (%)
Gender:		
Male	228 (77.8)	225 (77.6)
Female	65 (22.2)	65 (22.4)
Age (years):		
<70	226 (77.1)	222 (76.6)
≥70	67 (22.9)	68 (23.4)
Median	62.0	62.0
Mean	62.4	62.3
SD	9.3	9.2
Range	33-85	29-87
Race:		
White	249 (85.0)	238 (82.1)
Black	7 (2.4)	7 (2.4)
Asian	21 (7.2)	23 (7.9)
Other	15 (5.1)	19 (6.6)
Unspecified	1 (0.3)	3 (1.0)
Weight (kg):		
Median	70.0	72.0
Mean	71.1	72.3
SD	13.8	15.8
Range	33.0-110.0	41.0-124.0
N	292 (99.7)	288 (99.3)
Height (cm):		
Mean	169.3	169.2
SD	8.8	8.8
Range	140.0-195.0	143.0-188.0
N	292 (99.7)	290 (100.0)
Smoking Status:		
Never smoked	16 (5.5)	26 (9.0)
Current smoker	94 (32.1)	101 (34.8)
Ex-smoker	183 (62.5)	163 (56.2)

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

Efficacy Results:

Overall Survival: Based on data received as of the data cutoff date, for the final OS analysis, 483 deaths had occurred (241 [82.3%] Arm A, 242 [83.4%] Arm B) and 100 subjects were censored at last contact (52 [17.7%] Arm A, 48 [16.6%] Arm B). The primary analysis of OS was adjusted for the randomization stratification factors of gender, performance status, and region. A survival benefit for subjects treated in Arm A was not demonstrated relative to those treated in Arm B (hazard ratio = 1.091, stratified Cox model) and the difference between the arms was not significant (p = 0.350, 2-sided stratified log-rank test). The Kaplan-Meier estimate of the median OS was 5.7 months (95% confidence interval [CI] 4.8, 6.7) in Arm A and 6.2 months (95% CI 5.8, 7.2) in Arm B (Table 5). The survival probability at 6 months was 48.4% (95% CI 42.4%, 54.1%) in Arm A and 53.5% (95% CI 47.4%, 59.2%) in Arm B.

Table 5. Overall Survival - All Randomized, As Randomized

	Arm A Figitumumab 20 mg/kg + Erlotinib 150 mg N=293 n (%)	Arm B Erlotinib 150 mg N=290 n (%)
Number of deaths	241 (82.3)	242 (83.4)
Cause of death		
Disease under study	212 (72.4)	218 (75.2)
Study treatment toxicity	4 (1.4)	4 (1.4)
Unknown	8 (2.7)	6 (2.1)
Other	20 (6.8)	18 (6.2)
Number censored	52 (17.7)	48 (16.6)
Reason for censorship		
Alive	21 (7.2)	20 (6.9)
Subject withdrew consent for additional follow-up	21 (7.2)	20 (6.9)
Lost to follow-up	10 (3.4)	8 (2.8)
Number of subjects with last contact date >1 year prior to data cut-off date	24 (8.2)	25 (8.6)
Survival probability at 6 months[a] (95% CI[b])	48.4 (42.4, 54.1)	53.5 (47.4, 59.2)
Kaplan-Meier estimates of time-to-event (month) quartiles (95% CI)[c]		
25%	2.4 (1.9, 3.0)	3.4 (3.2, 4.0)
50%	5.7 (4.8, 6.7)	6.2 (5.8, 7.2)
75%	10.8 (9.7, 14.9)	12.1 (10.3, 14.0)
Versus Arm B		
Hazard ratio[d]	1.091	
95% CI of hazard ratio	0.909-1.310	
p-value[e]	0.350	

CI = confidence interval; N = number of subjects; n = number of subjects with specified criteria.
a. Estimated from the Kaplan-Meier curve.
b. Calculated from the product-limit method.
c. Based on the Brookmeyer and Crowley Method.
d. Based on the Cox proportional hazards model stratified by gender, performance status, and region.
e. 2-sided p-value from the log-rank test stratified by gender, performance status, and region.

Progression-Free Survival: A summary of PFS is provided in Table 6. As of the data cutoff date, for the final PFS analysis, 479 events of objective progression or death had occurred (228 [77.8%] Arm A, 251 [86.6%] Arm B) and 104 subjects were censored at last contact (65 [22.2%] Arm A, 39 [13.4%] Arm B). The Kaplan-Meier estimate of the median PFS was 2.1 months (95% CI 1.9, 2.6) in Arm A and 2.6 months (95% CI 2.1, 2.8) in Arm B. The hazard ratio was 1.075, and the difference between the arms was not significant (2-sided p=0.426). The probability of being event free at 6 months was 15.3% (95% CI 10.9%, 20.3%) in Arm A and 19.2% (95% CI 14.5%, 24.3%) in Arm B.

Table 6. Progression-Free Survival - All Randomized, As Randomized

	Arm A Figitumumab 20 mg/kg + Erlotinib 150 mg N=293 n (%)	Arm B Erlotinib 150 mg N=290 n (%)
Number of subjects with an event	228 (77.8)	251 (86.6)
Type of event		
Objective progression	166 (56.7)	225 (77.6)
Death without objective progression	62 (21.2)	26 (9.0)
Number censored	65 (22.2)	39 (13.4)
Reason for censorship		
No adequate baseline assessments	7 (2.4)	4 (1.4)
No on-study assessments	22 (7.5)	11 (3.8)
Withdrew consent for follow-up	7 (2.4)	6 (2.1)
Lost to follow-up	1 (<1.0)	3 (1.0)
Unacceptable gap (>9 weeks) between progression or death to the most recent prior adequate assessment	22 (7.5)	13 (4.5)
In follow-up for progression	6 (2.0)	2 (<1.0)
Probability of being event-free at 6 months[a] (95% CI[b])	15.3 (10.9, 20.3)	19.2 (14.5, 24.3)
Kaplan-Meier estimates of time-to-event (month) quartiles (95% CI)[c]		
25%	1.3 (1.2, 1.4)	1.3 (1.2, 1.4)
50%	2.1 (1.9, 2.6)	2.6 (2.1, 2.8)
75%	4.5 (3.7, 5.0)	5.4 (4.1, 5.8)
Versus Arm B		
Hazard ratio[d]	1.075	
95% CI of hazard ratio	0.898-1.287	
p-Value[e]	0.426	

CI = confidence interval; N = number of subjects; n = number of subjects with specified criteria.
a. Estimated from the Kaplan-Meier curve.
b. Calculated from the product-limit method.
c. Based on the Brookmeyer and Crowley Method.
d. Based on the Cox proportional hazards model stratified by gender, performance status, and region.
e. 2-sided p-value from the log-rank test stratified by gender, performance status, and region.

Best Overall Response: A summary of best overall response for each arm is provided in Table 7. The ORR was 5.5% (n=16) in Arm A and 3.8% (n=11) in Arm B. One subject had a CR (Arm B), all other responses were PRs.

Table 7. Best Overall Response

	Arm A Figitumumab 20 mg/kg + Erlotinib 150 mg N=293 n (%)	Arm B Erlotinib 150 mg N=290 n (%)
Complete response	0	1 (<1.0)
Partial response	16 (5.5)	10 (3.4)
Stable/no response	113 (38.6)	130 (44.8)
Objective progression	90 (30.7)	117 (40.3)
Early death	30 (10.2)	12 (4.1)
Indeterminate	44 (15.0)	20 (6.9)
Objective response rate (CR + PR)	16 (5.5)	11 (3.8)
95% CI[a]	(3.2, 8.7)	(1.9, 6.7)
Versus Arm B		
Treatment difference[b]	1.668	
95% CI of the difference[b]	(-1.7, 5.1)	
p-Value[c]	0.338	

CI = confidence interval; CR = complete response; N = number of subjects; n = number of subjects with specified criteria; PR = partial response.
a. Using exact method based on binomial distribution.
b. Calculated based on a normal distribution.
c. p-value is from a Pearson chi-square test.

Pharmacokinetic and Pharmacodynamic Results:

Figitumumab plasma concentration-time data were available from 375 subjects. The original plan to include the figitumumab concentration-time data from multiple late-stage protocols in a population PK meta-analysis did not proceed due to changed program status.

ADA samples were collected from 360 subjects receiving figitumumab. Of the 906 ADA samples tested using the screening assay, 903 samples (>99%) were negative for ADAs, as indicated by an endpoint titer of <6.64 in all samples. There were 3 samples with low titer measurements of 17.39 (Arm A Subject, Cycle 1 predose), 11.15 (Arm B2 Subject, predose of the first figitumumab infusion), and 10.89 (Arm B2 Subject, at the EOT), respectively. The ADA measurements observed prior to start of figitumumab dosing from the screening assay for 2 Subjects were likely false positive results. Figitumumab plasma concentration data were available for 2 of the 3 subjects with positive ADA samples; figitumumab plasma concentrations in these subjects were consistent with those observed in other subjects.

Free IGF-1R samples were collected from 176 subjects receiving figitumumab.

Safety Results:

Subjects were analyzed for safety according to the treatment received.

Exposure: Subjects in Arm A completed a median of 3 cycles of figitumumab and 2 cycles of erlotinib. Fourteen subjects (4.8%) in Arm A had at least 1 dose reduction of figitumumab and 61 (21.1%) had at least 1 dose reduction of erlotinib. Subjects in Arm B1 completed a median of 4 cycles of erlotinib. Forty-two (14.5%) of these subjects had at least 1 dose reduction of erlotinib. Subjects who crossed over to Arm B2 completed a median of 2 cycles of figitumumab, with 2 (2.4%) requiring at least 1 dose reduction of figitumumab.

Adverse Events:

Table 8 displays a summary of the safety by arm regardless of causality. The majority of subjects in each arm experienced AEs (Arm A and B1 both 97.2%, Arm B2 98.8%). A lower percentage of subjects in Arm B1 had SAEs or Grade 5 events (52.8%, 46.6%, respectively) compared to Arm A (70.6%, 59.5%, respectively) or Arm B2 (75.9%, 67.5%, respectively). Part of the explanation for the apparent fewer deaths noted for Arm B1 is related to the reporting of the AEs for subjects in Arm B who received figitumumab. For these subjects, Arm B1 treatment emergence ceased when the figitumumab treatment started. Therefore, any AEs that started after the figitumumab treatment, including deaths, are reported under Arm B2. Note that some Arm B2 AEs/deaths that were within the 150 days from the last figitumumab dose, were not within 150 days from the last erlotinib dose, so total deaths within 150 days of last erlotinib dose cannot be determined from this table.

Table 8. Treatment-Emergent Adverse Events – All Causalities, As Treated

	Arm A Figitumumab 20 mg/kg + Erlotinib 150 mg N=289 n (%)	Arm B1 Erlotinib 150 mg N=290 n (%)	Arm B2 Figitumumab 20 mg/kg N=83 n (%)
Subjects evaluable for adverse events	289	290	83
Number of adverse events	2424	1839	656
Number of serious adverse events	365	246	95
Subjects with adverse events	281 (97.2)	282 (97.2)	82 (98.8)
Subjects with serious adverse events	204 (70.6)	153 (52.8)	63 (75.9)
Subjects with Grade 3 or 4 adverse events	180 (62.3)	136 (46.9)	47 (56.6)
Subjects with Grade 5 adverse events	172 (59.5)	135 (46.6)	56 (67.5)
Subjects discontinued figitumumab due to adverse events	89 (30.8)	3 (1.0)[a]	19 (22.9)
Subjects discontinued erlotinib due to adverse events	95 (32.9)	67 (23.1)	6 (7.2)
Subjects temporarily discontinued figitumumab due to adverse events	67 (23.2)	3 (1.0)[b,c]	12 (14.5)
Subjects temporarily discontinued erlotinib due to adverse events	98 (33.9)	56 (19.3)	4 (4.8)
Subjects with dose reduction of figitumumab due to adverse events	7 (2.4)	0	2 (2.4)
Subjects with dose reduction of erlotinib due to adverse events	43 (14.9)	33 (11.4)	5 (6.0)

Adverse events and serious adverse events are not separated out in this table.
Includes data up to 150 days after last dose of study drug. Except for the number of AEs subjects are counted only once per treatment in each row.
Serious adverse events - according to the Investigator's assessment.
MedDRA (v14.0) coding dictionary applied.
AE = adverse event; CRF = case report form; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects with specified criteria; v = version.

a. None of these 3 subjects received figitumumab, however, the CRF for each marked permanently discontinued due to AE for both erlotinib and figitumumab.
b. Two of these subjects crossed over to Arm B2, however, the first dose of figitumumab was held due to AEs for both subjects and was counted as while the subjects were still in Arm B1 prior to crossover.
c. One of these subjects never received figitumumab, however, the CRF was marked temporarily discontinued due to AE for figitumumab.

Table 9 presents a summary of the most frequently reported treatment-emergent non-serious AEs. The AEs listed are those that occurred in ≥5% of subjects in any arm. The most frequently experienced AEs each of Arms A, B1, and B2 were rash and diarrhea.

Table 9. Treatment-Emergent Non-Serious Adverse Events for Events Having a Frequency ≥5% in any Treatment Arm

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v14.0) Preferred Term	Arm A Figitumumab 20 mg/kg + Erlotinib 150 mg n (%)	Arm B1 Erlotinib 150 mg n (%)	Arm B2 Figitumumab 20 mg/kg n (%)
Number (%) of subjects:			
Evaluable for adverse events	289	290	83
With adverse events	265 (91.7)	265 (91.4)	79 (95.2)
Blood and lymphatic system disorders	44 (15.2)	33 (11.4)	13 (15.7)
Anaemia	28 (9.7)	26 (9.0)	11 (13.3)
Gastrointestinal disorders	188 (65.1)	150 (51.7)	35 (42.2)
Constipation	17 (5.9)	19 (6.6)	9 (10.8)
Diarrhoea	123 (42.6)	106 (36.6)	10 (12.0)
Dysphagia	14 (4.8)	11 (3.8)	6 (7.2)
Mouth ulceration	16 (5.5)	4 (1.4)	1 (1.2)
Nausea	54 (18.7)	36 (12.4)	8 (9.6)
Stomatitis	18 (6.2)	6 (2.1)	0
Vomiting	49 (17.0)	23 (7.9)	7 (8.4)
General disorders and administration site conditions	170 (58.8)	144 (49.7)	54 (65.1)
Asthenia	79 (27.3)	46 (15.9)	25 (30.1)
Chest pain	31 (10.7)	28 (9.7)	21 (25.3)
Fatigue	65 (22.5)	53 (18.3)	16 (19.3)
Mucosal inflammation	33 (11.4)	11 (3.8)	0
Oedema peripheral	8 (2.8)	16 (5.5)	1 (1.2)
Pyrexia	25 (8.7)	18 (6.2)	5 (6.0)
Infections and infestations	72 (24.9)	50 (17.2)	15 (18.1)
Paronychia	17 (5.9)	8 (2.8)	1 (1.2)
Investigations	98 (33.9)	60 (20.7)	28 (33.7)
Weight decreased	65 (22.5)	33 (11.4)	19 (22.9)
Metabolism and nutrition disorders	146 (50.5)	94 (32.4)	46 (55.4)
Decreased appetite	115 (39.8)	70 (24.1)	32 (38.6)
Dehydration	21 (7.3)	6 (2.1)	2 (2.4)
Hyperglycemia	37 (12.8)	13 (4.5)	12 (14.5)
Musculoskeletal and connective tissue disorders	68 (23.5)	66 (22.8)	26 (31.3)
Arthralgia	11 (3.8)	11 (3.8)	5 (6.0)
Back pain	19 (6.6)	25 (8.6)	9 (10.8)
Musculoskeletal chest pain	7 (2.4)	5 (1.7)	6 (7.2)
Musculoskeletal pain	7 (2.4)	9 (3.1)	7 (8.4)
Nervous system disorders	71 (24.6)	50 (17.2)	24 (28.9)
Dizziness	16 (5.5)	4 (1.4)	3 (3.6)
Headache	13 (4.5)	14 (4.8)	9 (10.8)
Psychiatric disorders	34 (11.8)	31 (10.7)	18 (21.7)
Depression	10 (3.5)	6 (2.1)	7 (8.4)
Respiratory thoracic and mediastinal disorders	120 (41.5)	118 (40.7)	46 (55.4)
Cough	43 (14.9)	51 (17.6)	21 (25.3)
Dyspnoea	54 (18.7)	61 (21.0)	24 (28.9)
Epistaxis	22 (7.6)	7 (2.4)	2 (2.4)
Haemoptysis	32 (11.1)	32 (11.0)	8 (9.6)
Skin and subcutaneous tissue disorders	207 (71.6)	208 (71.7)	54 (65.1)
Acne	9 (3.1)	17 (5.9)	6 (7.2)
Dermatitis acneiform	22 (7.6)	14 (4.8)	3 (3.6)
Dry skin	30 (10.4)	24 (8.3)	7 (8.4)
Pruritus	21 (7.3)	31 (10.7)	3 (3.6)
Rash	140 (48.4)	152 (52.4)	33 (39.8)

Subjects are only counted once per treatment for each row.
Includes data up to 150 days after last dose of study drug.
MedDRA (version 14.0) coding dictionary applied.
n = Number of subjects; MedDRA = Medical Dictionary for Regulatory Activities.

Most subjects in each arm experienced treatment-related AEs (Arm A 83.4%, Arm B1 82.1%, Arm B2 78.3%). The most frequently reported treatment-related AEs (reported by ≥5% of subjects in any treatment arm) are presented in Table 10.

Table 10. Treatment-Emergent (Treatment-Related) Adverse Events For Events Having a Frequency ≥5% in Any Treatment Arm

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v14.0) Preferred Term	Arm A Figitumumab 20 mg/kg + Erlotinib 150 mg (N=289) n (%)	Arm B1 Erlotinib 150 mg (N=290) n (%)	Arm B2 Figitumumab 20 mg/kg (N=83) n (%)
Any AEs	241 (83.4)	238 (82.1)	65 (78.3)
Blood and lymphatic system disorders	16 (5.5)	11 (3.8)	6 (7.2)
Anaemia	7 (2.4)	10 (3.4)	6 (7.2)
Gastrointestinal disorders	155 (53.6)	131 (45.2)	21 (25.3)
Diarrhoea	118 (40.8)	102 (35.2)	8 (9.6)
Mouth ulceration	15 (5.2)	4 (1.4)	1 (1.2)
Nausea	41 (14.2)	29 (10.0)	5 (6.0)
Vomiting	33 (11.4)	18 (6.2)	4 (4.8)
General disorders and administration site conditions	105 (36.3)	58 (20.0)	20 (24.1)
Asthenia	46 (15.9)	25 (8.6)	12 (14.5)
Fatigue	40 (13.8)	23 (7.9)	8 (9.6)
Mucosal inflammation	29 (10.0)	7 (2.4)	0
Infections and infestations	35 (12.1)	21 (7.2)	3 (3.6)
Paronychia	17 (5.9)	9 (3.1)	1 (1.2)
Investigations	57 (19.7)	29 (10.0)	11 (13.3)
Weight decreased	37 (12.8)	17 (5.9)	7 (8.4)
Metabolism and nutrition disorders	116 (40.1)	48 (16.6)	27 (32.5)
Decreased appetite	80 (27.7)	38 (13.1)	15 (18.1)
Dehydration	18 (6.2)	4 (1.4)	1 (1.2)
Hyperglycaemia	37 (12.8)	3 (1.0)	11 (13.3)
Skin and subcutaneous tissue disorders	200 (69.2)	203 (70.0)	52 (62.7)
Acne	9 (3.1)	17 (5.9)	6 (7.2)
Dermatitis acneiform	21 (7.3)	14 (4.8)	3 (3.6)
Dry skin	26 (9.0)	22 (7.6)	6 (7.2)
Pruritus	19 (6.6)	31 (10.7)	3 (3.6)
Rash	139 (48.1)	149 (51.4)	33 (39.8)

Adverse events and serious adverse events are not separated out.
MedDRA (v14.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory activities; N = total number of subjects; v = version.

Separate AE tables were produced for subjects based on the level of HbA1c at Baseline, <5.7% or ≥5.7%. Table 11 presents these data by arm for subjects with HbA1c at Baseline of <5.7% and Table 12 subjects with HbA1c at Baseline of ≥5.7%. The frequencies of most AEs were relatively similar between those subjects with HbA1c at Baseline of <5.7% and subjects with HbA1c at Baseline of ≥5.7%. However, the incidence of hyperglycemia was higher in subjects with HbA1c at Baseline of ≥5.7% (20.1%) compared to subjects with HbA1c at Baseline of <5.7% (8.1%). As stated earlier, due to a risk for the development of hyperglycemia in individuals with HbA1c ≥5.7%, eligibility criterion was changed to <5.7%.

Table 11. Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade Occurring in ≥10% of Subjects in any Arm With Baseline HbA1c <5.7% (All Causalities, All Cycles), As Treated

Preferred Term[a]	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Arm A (N=135)						
Any AE	5 (3.7)	22 (16.3)	28 (20.7)	3 (2.2)	73 (54.1)	131 (97.0)
Rash	42 (31.1)	25 (18.5)	7 (5.2)	0	0	74 (54.8)
Diarrhoea	35 (25.9)	19 (14.1)	10 (7.4)	0	0	64 (47.4)
Disease progression	0	0	0	1 (0.7)	57 (42.2)	58 (43.0)
Decreased appetite	13 (9.6)	28 (20.7)	13 (9.6)	0	0	54 (40.0)
Asthenia	6 (4.4)	15 (11.1)	19 (14.1)	0	0	40 (29.6)
Weight decreased	7 (5.2)	22 (16.3)	3 (2.2)	0	0	32 (23.7)
Dyspnoea	9 (6.7)	11 (8.1)	6 (4.4)	5 (3.7)	0	31 (23.0)
Fatigue	4 (3.0)	14 (10.4)	9 (6.7)	1 (0.7)	0	28 (20.7)
Nausea	12 (8.9)	9 (6.7)	4 (3.0)	0	0	25 (18.5)
Vomiting	14 (10.4)	9 (6.7)	2 (1.5)	0	0	25 (18.5)
Anaemia	7 (5.2)	7 (5.2)	3 (2.2)	0	0	17 (12.6)
Cough	7 (5.2)	9 (6.7)	1 (0.7)	0	0	17 (12.6)
Mucosal inflammation	9 (6.7)	6 (4.4)	2 (0.7)	0	0	17 (12.6)
Chest pain	4 (3.0)	5 (3.7)	6 (4.4)	0	0	15 (11.1)
Haemoptysis	10 (7.4)	3 (2.2)	2 (1.5)	0	0	15 (11.1)
Pyrexia	12 (8.9)	2 (1.5)	0	0	0	14 (10.4)
Arm B1 (N=115)						
Any AE	13 (11.3)	32 (27.8)	15 (13.0)	3 (2.6)	51 (44.3)	114 (99.1)
Rash	32 (27.8)	29 (25.2)	5 (4.3)	0	0	66 (57.4)
Diarrhoea	33 (28.7)	7 (6.1)	3 (2.6)	0	0	43 (37.4)
Disease progression	0	0	0	1 (0.9)	37 (32.2)	38 (33.0)
Dyspnoea	7 (6.1)	7 (6.1)	8 (7.0)	3 (2.6)	0	25 (21.7)
Decreased appetite	14 (12.2)	6 (5.2)	3 (2.6)	0	0	23 (20.0)
Asthenia	7 (6.1)	8 (7.0)	5 (4.3)	1 (0.9)	0	21 (18.3)
Fatigue	7 (6.1)	12 (10.4)	0	0	0	19 (16.5)
Cough	7 (6.1)	9 (7.8)	1 (0.9)	0	0	17 (14.8)
Haemoptysis	11 (9.6)	2 (1.7)	2 (1.7)	1 (0.9)	1 (0.9)	17 (14.8)
Weight decreased	6 (5.2)	9 (7.8)	1 (0.9)	0	0	16 (13.9)
Nausea	8 (7.0)	6 (5.2)	1 (0.9)	0	0	15 (13.0)
Arm B2 (N=36)						
Any AE	2 (5.6)	8 (22.2)	1 (2.8)	0	25 (69.4)	36 (100.0)
Disease progression	0	0	0	0	22 (61.1)	22 (61.1)
Rash	12 (33.3)	3 (8.3)	0	0	0	15 (41.7)
Decreased appetite	7 (19.4)	4 (11.1)	1 (2.8)	0	0	12 (33.3)
Weight decreased	2 (5.6)	7 (19.4)	2 (5.6)	0	0	11 (30.6)
Asthenia	2 (5.6)	3 (8.3)	4 (11.1)	0	0	9 (25.0)
Dyspnoea	5 (13.9)	3 (8.3)	1 (2.8)	0	0	9 (25.0)
Anaemia	1 (2.8)	5 (13.9)	1 (2.8)	0	0	7 (19.4)
Chest pain	1 (2.8)	3 (8.3)	3 (8.3)	0	0	7 (19.4)
Cough	4 (11.1)	1 (2.8)	2 (5.6)	0	0	7 (19.4)
Fatigue	3 (8.3)	2 (5.6)	2 (5.6)	0	0	7 (19.4)
Hyperglycaemia	1 (2.8)	3 (8.3)	3 (8.3)	0	0	7 (19.4)
Depression	2 (5.6)	3 (8.3)	0	0	0	5 (13.9)
Diarrhoea	3 (8.3)	2 (5.6)	0	0	0	5 (13.9)
Haemoptysis	3 (8.3)	0	1 (2.8)	0	0	4 (11.1)
Musculoskeletal pain	1 (2.8)	3 (8.3)	0	0	0	4 (11.1)
Nausea	2 (5.6)	2 (5.6)	0	0	0	4 (11.1)

Adverse events and serious adverse events are not separated out.
AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects with specified criteria;v = version.
a. MedDRA (v14.0) coding dictionary applied.

Table 12. Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade Occurring in ≥10% of Subjects in any Arm With Baseline HbA1c ≥5.7% (All Causalities, All Cycles), As Treated

Preferred Term[a]	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Arm A (N=139)						
Any AE	2 (1.4)	13 (9.4)	23 (16.5)	7 (5.0)	91 (65.5)	136 (97.8)
Disease progression	0	0	0	0	71 (51.1)	71 (51.1)
Rash	22 (15.8)	27 (19.4)	13 (9.4)	0	0	62 (44.6)
Diarrhoea	28 (20.1)	19 (13.7)	10 (7.2)	0	0	57 (41.0)
Decreased appetite	17 (12.2)	22 (15.8)	16 (11.5)	0	0	55 (39.6)
Asthenia	6 (4.3)	17 (12.2)	10 (7.2)	3 (2.2)	0	36 (25.9)
Fatigue	8 (5.8)	10 (7.2)	12 (8.6)	2 (1.4)	0	32 (23.0)
Weight decreased	16 (11.5)	14 (10.1)	2 (1.4)	0	0	32 (23.0)
Hyperglycaemia	3 (2.2)	13 (9.4)	5 (3.6)	7 (5.0)	0	28 (20.1)
Nausea	14 (10.1)	12 (8.6)	1 (0.7)	0	0	27 (19.4)
Dyspnoea	4 (2.9)	9 (6.5)	10 (7.2)	2 (1.4)	1 (0.7)	26 (18.7)
Cough	14 (10.1)	7 (5.0)	1 (0.7)	0	0	22 (15.8)
Vomiting	10 (7.2)	11 (7.9)	0	0	0	21 (15.1)
Haemoptysis	10 (7.2)	6 (4.3)	3 (2.2)	0	0	19 (13.7)
Dry skin	13 (9.4)	4 (2.9)	0	0	0	17 (12.2)
Mucosal inflammation	8 (5.8)	8 (5.8)	0	0	0	16 (11.5)
Chest pain	4 (2.9)	9 (6.5)	0	2 (1.4)	0	15 (10.8)
Anaemia	5 (3.6)	7 (5.0)	2 (1.4)	0	0	14 (10.1)
Dehydration	2 (1.4)	3 (2.2)	9 (6.5)	0	0	14 (10.1)
Pyrexia	8 (5.8)	6 (4.3)	0	0	0	14 (10.1)
Arm B1 (N=160)						
Any AE	18 (11.3)	31 (19.4)	25 (15.6)	4 (2.5)	75 (46.9)	153 (95.6)
Rash	38 (23.8)	35 (21.9)	8 (5.0)	0	0	81 (50.6)
Disease progression	0	0	0	0	66 (41.3)	66 (41.3)
Diarrhoea	41 (25.6)	14 (8.8)	4 (2.5)	0	0	59 (36.9)
Decreased appetite	22 (13.8)	15 (9.4)	8 (5.0)	0	0	45 (28.1)
Dyspnoea	11 (6.9)	18 (11.3)	7 (4.4)	1 (0.6)	0	37 (23.1)
Cough	14 (8.8)	16 (10.0)	2 (1.3)	0	0	32 (20.0)
Fatigue	12 (7.5)	14 (8.8)	5 (3.1)	0	0	31 (19.4)
Asthenia	9 (5.6)	10 (6.3)	6 (3.8)	1 (0.6)	0	26 (16.3)
Dry skin	13 (8.1)	7 (4.4)	0	0	0	20 (12.5)
Anaemia	7 (4.4)	7 (4.4)	4 (2.5)	1 (0.6)	0	19 (11.9)
Back pain	6 (3.8)	11 (6.9)	2 (1.3)	0	0	19 (11.9)
Pruritus	12 (7.5)	4 (2.5)	3 (1.9)	0	0	19 (11.9)
Haemoptysis	11 (6.9)	5 (3.1)	0	1 (0.6)	1 (0.6)	18 (11.3)
Nausea	13 (8.1)	4 (2.5)	1 (0.6)	0	0	18 (11.3)
Weight decreased	10 (6.3)	3 (1.9)	3 (1.9)	0	0	16 (10.0)
Arm B2 (N=45)						
Any AE	2 (4.4)	7 (15.6)	2 (4.4)	4 (8.9)	29 (64.4)	44 (97.8)
Disease progression	0	0	0	1 (2.2)	21 (46.7)	22 (48.9)
Decreased appetite	8 (17.8)	8 (17.8)	3 (6.7)	0	0	19 (42.2)
Rash	12 (26.7)	6 (13.3)	0	0	0	18 (40.0)
Asthenia	3 (6.7)	7 (15.6)	5 (11.1)	0	0	15 (33.3)
Dyspnoea	4 (8.9)	9 (20.0)	2 (4.4)	0	0	15 (33.3)
Chest pain	2 (4.4)	10 (22.2)	2 (4.4)	0	0	14 (31.1)
Cough	6 (13.3)	7 (15.6)	1 (2.2)	0	0	14 (31.1)
Fatigue	4 (8.9)	3 (6.7)	2 (4.4)	1 (2.2)	0	10 (22.2)
Weight decreased	0	6 (13.3)	2 (4.4)	0	0	8 (17.8)
Back pain	3 (6.7)	4 (8.9)	0	0	0	7 (15.6)
Dry skin	4 (8.9)	3 (6.7)	0	0	0	7 (15.6)
Constipation	4 (8.9)	2 (4.4)	0	0	0	6 (13.3)

Table 12. Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade Occurring in ≥10% of Subjects in any Arm With Baseline HbA1c ≥5.7% (All Causalities, All Cycles), As Treated

Preferred Term[a]	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Haemoptysis	4 (8.9)	2 (4.4)	0	0	0	6 (13.3)
Headache	6 (13.3)	0	0	0	0	6 (13.3)
Hyperglycaemia	2 (4.4)	2 (4.4)	1 (2.2)	1 (2.2)	0	6 (13.3)
Anaemia	1 (2.2)	0	4 (8.9)	0	0	5 (11.1)
Arthralgia	4 (8.9)	1 (2.2)	0	0	0	5 (11.1)
Diarrhoea	3 (6.7)	2 (4.4)	0	0	0	5 (11.1)
Dysphagia	2 (4.4)	2 (4.4)	1 (2.2)	0	0	5 (11.1)

Adverse events and serious adverse events are not separated out.
AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects with specified criteria; v = version.
a. MedDRA (v14.0) coding dictionary applied.

Serious Adverse Events: SAEs (including disease progression with an outcome of death) were reported through and including 150 calendar days after the last administration of any study drug. A summary of SAE regardless of causality is provided in Table 13. The percentage by arm of subjects with SAEs was lower in Arm B1 relative to either of the figitumumab-containing arms (Arm A = 70.6%, Arm B1 = 52.8%, and Arm B2 = 75.9%). The most commonly reported treatment-emergent SAEs, other than disease progression, were pneumonia, dehydration, diarrhea, and dyspnea. A summary of the treatment-emergent SAEs, by system organ class and preferred term (all causalities) is presented in Table 14.

Table 13. Treatment-Emergent Serious Adverse Events – All Causalities, As Treated

	Arm A Figitumumab 20 mg/kg + Erlotinib 150 mg N=289 n (%)	Arm B1 Erlotinib 150 mg N=290 n (%)	Arm B2 Figitumumab 20 mg/kg N=83 n (%)
Number of serious adverse events	365	246	95
Subjects with serious adverse events	204 (70.6)	153 (52.8)	63 (75.9)
Subjects with Grade 3 or 4 serious adverse events	99 (34.3)	66 (22.8)	22 (26.5)
Subjects with Grade 5 adverse events	172 (59.5)	134 (46.2)	56 (67.5)
Subjects discontinued figitumumab due to serious adverse events	64 (22.1)	0	17 (20.5)
Subjects discontinued erlotinib due to serious adverse events	63 (21.8)	45 (15.5)	5 (6.0)
Subjects temporarily discontinued figitumumab due to serious adverse events	22 (7.6)	1 (0.3)	5 (6.0)
Subjects temporarily discontinued erlotinib due to serious adverse events	29 (10.0)	14 (4.8)	1 (1.2)
Subjects with dose reduction of figitumumab due to serious adverse events	0	0	0
Subjects with dose reduction of erlotinib due to serious adverse events	2 (0.7)	2 (0.7)	0

Includes data up to 150 days after last dose of study drug.
Except for the number of adverse events subjects were counted only once per treatment in each row.
Serious adverse events - according to the Investigator's assessment.
MedDRA (v14.0) coding dictionary applied.
N = number of subjects; n = number of subjects with specified criteria;; v = version.

Table 14. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v14.0) Preferred Term	Arm A Figitumumab 20 mg/kg + Erlotinib 150 mg n (%)	Arm B1 Erlotinib 150 mg n (%)	Arm B2 Figitumumab 20 mg/kg n (%)
Number (%) of subjects:			
Evaluable for adverse events	289	290	83
With adverse events	204 (70.6)	153 (52.8)	63 (75.9)
Blood and lymphatic system disorders	4 (1.4)	5 (1.7)	4 (4.8)
Anaemia	3 (1.0)	3 (1.0)	2 (2.4)
Febrile neutropenia	0	1 (0.3)	1 (1.2)
Neutropenia	0	1 (0.3)	1 (1.2)
Thrombocytopenia	1 (0.3)	0	0
Cardiac disorders	5 (1.7)	6 (2.1)	1 (1.2)
Arrhythmia	1 (0.3)	1 (0.3)	0
Atrial tachycardia	0	1 (0.3)	0
Cardiac arrest	1 (0.3)	1 (0.3)	0
Cardiac failure	2 (0.7)	0	1 (1.2)
Cardiac failure congestive	0	1 (0.3)	0
Myocardial infarction	1 (0.3)	0	0
Pericardial effusion	0	1 (0.3)	0
Pericarditis constrictive	0	1 (0.3)	0
Supraventricular tachycardia	0	1 (0.3)	0
Congenital, familial and genetic disorders	1 (0.3)	0	0
Tracheo-oesophageal fistula	1 (0.3)	0	0
Ear and labyrinth disorders	1 (0.3)	0	0
Deafness bilateral	1 (0.3)	0	0
Gastrointestinal disorders	27 (9.3)	13 (4.5)	4 (4.8)
Abdominal pain	2 (0.7)	1 (0.3)	0
Colitis	0	0	1 (1.2)
Diarrhoea	11 (3.8)	3 (1.0)	0
Dysphagia	2 (0.7)	1 (0.3)	0
Gastric ulcer	1 (0.3)	1 (0.3)	0
Gastrointestinal haemorrhage	2 (0.7)	0	0
Ileus	0	2 (0.7)	0
Inguinal hernia	0	1 (0.3)	0
Intestinal ischaemia	1 (0.3)	0	0
Intestinal obstruction	0	1 (0.3)	0
Large intestine perforation	0	0	1 (1.2)
Mouth ulceration	1 (0.3)	0	0
Nausea	1 (0.3)	0	0
Oesophageal stenosis	0	1 (0.3)	0
Oesophagitis	1 (0.3)	0	0
Pancreatitis	0	0	1 (1.2)
Peritonitis	0	0	1 (1.2)
Rectal haemorrhage	1 (0.3)	0	0
Small intestinal obstruction	0	1 (0.3)	0
Stomatitis	1 (0.3)	0	0
Upper gastrointestinal haemorrhage	1 (0.3)	0	0
Vomiting	4 (1.4)	3 (1.0)	1 (1.2)
General disorders and administration site conditions	151 (52.2)	119 (41.0)	52 (62.7)
Asthenia	5 (1.7)	1 (0.3)	0
Chest pain	5 (1.7)	0	1 (1.2)
Chills	1 (0.3)	0	0
Death	2 (0.7)	0	1 (1.2)
Disease progression	136 (47.1)	111 (38.3)	45 (54.2)
Fatigue	2 (0.7)	1 (0.3)	1 (1.2)
General physical health deterioration	3 (1.0)	5 (1.7)	5 (6.0)
Hypothermia	1 (0.3)	0	0

Table 14. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v14.0) Preferred Term	Arm A Figitumumab 20 mg/kg + Erlotinib 150 mg n (%)	Arm B1 Erlotinib 150 mg n (%)	Arm B2 Figitumumab 20 mg/kg n (%)
Mucosal inflammation	0	1 (0.3)	0
Oedema peripheral	1 (0.3)	0	0
Pain	3 (1.0)	0	0
Pyrexia	4 (1.4)	5 (1.7)	1 (1.2)
Hepatobiliary disorders	1 (0.3)	2 (0.7)	0
Cholecystitis	0	1 (0.3)	0
Hepatic function abnormal	1 (0.3)	0	0
Hyperbilirubinaemia	0	1 (0.3)	0
Immune system disorders	1 (0.3)	1 (0.3)	0
Anaphylactic reaction	0	1 (0.3)	0
Hypersensitivity	1 (0.3)	0	0
Infections and infestations	32 (11.1)	25 (8.6)	1 (1.2)
Bacteraemia	1 (0.3)	0	0
Bronchopneumonia	1 (0.3)	0	0
Clostridium difficile colitis	1 (0.3)	0	0
Empyema	0	1 (0.3)	0
Fungaemia	1 (0.3)	0	0
Gangrene	1 (0.3)	0	0
Gastroenteritis	2 (0.7)	1 (0.3)	0
Infection	1 (0.3)	0	0
Lower respiratory tract infection	4 (1.4)	0	1 (1.2)
Lung abscess	1 (0.3)	0	0
Lung infection	1 (0.3)	0	0
Osteomyelitis	1 (0.3)	0	0
Paronychia	0	1 (0.3)	0
Perirectal abscess	1 (0.3)	0	0
Pneumonia	9 (3.1)	12 (4.1)	1 (1.2)
Pneumonia bacterial	1 (0.3)	0	0
Pseudomonas infection	0	1 (0.3)	0
Pulmonary tuberculosis	1 (0.3)	0	0
Pyelonephritis acute	1 (0.3)	0	0
Pyothorax	0	1 (0.3)	0
Respiratory tract infection	4 (1.4)	3 (1.0)	0
Sepsis	2 (0.7)	1 (0.3)	0
Septic shock	1 (0.3)	1 (0.3)	0
Staphylococcal infection	0	1 (0.3)	0
Urinary tract infection	1 (0.3)	2 (0.7)	0
Urosepsis	0	1 (0.3)	0
Injury, poisoning and procedural complications	2 (0.7)	2 (0.7)	2 (2.4)
Collapse of lung	1 (0.3)	0	0
Concussion	0	1 (0.3)	0
Fall	1 (0.3)	0	0
Femoral neck fracture	0	0	2 (2.4)
Road traffic accident	0	1 (0.3)	0
Investigations	8 (2.8)	0	1 (1.2)
Band neutrophil count increased	1 (0.3)	0	0
Blood creatinine increased	1 (0.3)	0	1 (1.2)
Gamma-glutamyltransferase increased	1 (0.3)	0	0
General physical condition abnormal	1 (0.3)	0	0
Haematocrit decreased	1 (0.3)	0	0
Liver function test abnormal	1 (0.3)	0	0
Myocardial strain	1 (0.3)	0	0
Renal function test abnormal	1 (0.3)	0	0
Troponin increased	1 (0.3)	0	0

Table 14. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v14.0) Preferred Term	Arm A Figitumumab 20 mg/kg + Erlotinib 150 mg n (%)	Arm B1 Erlotinib 150 mg n (%)	Arm B2 Figitumumab 20 mg/kg n (%)
White blood cell count increased	1 (0.3)	0	0
Metabolism and nutrition disorders	33 (11.4)	13 (4.5)	5 (6.0)
Decreased appetite	4 (1.4)	1 (0.3)	0
Dehydration	14 (4.8)	6 (2.1)	1 (1.2)
Diabetes mellitus	1 (0.3)	0	0
Diabetes mellitus inadequate control	1 (0.3)	0	0
Diabetic ketoacidosis	1 (0.3)	0	0
Failure to thrive	1 (0.3)	2 (0.7)	0
Hypercalcaemia	6 (2.1)	4 (1.4)	1 (1.2)
Hyperglycaemia	7 (2.4)	0	2 (2.4)
Hypoglycaemia	0	1 (0.3)	0
Hyponatraemia	1 (0.3)	1 (0.3)	0
Hypophosphataemia	1 (0.3)	0	0
Malnutrition	0	0	1 (1.2)
Musculoskeletal and connective tissue disorders	1 (0.3)	3 (1.0)	0
Back pain	0	1 (0.3)	0
Muscular weakness	0	1 (0.3)	0
Neck pain	1 (0.3)	1 (0.3)	0
Neoplasms benign, malignant and unspecified (inclusive cysts and polyps)	10 (3.5)	7 (2.4)	3 (3.6)
Lung neoplasm malignant	2 (0.7)	4 (1.4)	1 (1.2)
Neoplasm progression	5 (1.7)	2 (0.7)	2 (2.4)
Non-small-cell lung cancer	2 (0.7)	0	0
Rectal cancer	0	1 (0.3)	0
Sebaceous carcinoma	1 (0.3)	0	0
Nervous system disorders	9 (3.1)	2 (0.7)	2 (2.4)
Balance disorder	0	0	1 (1.2)
Cerebral haemorrhage	0	0	1 (1.2)
Cerebrovascular accident	2 (0.7)	0	0
Convulsion	1 (0.3)	0	0
Dysarthria	0	0	1 (1.2)
Intraventricular haemorrhage	1 (0.3)	0	0
Lethargy	1 (0.3)	0	0
Mental impairment	0	0	1 (1.2)
Spinal cord compression	0	1 (0.3)	0
Syncope	5 (1.7)	1 (0.3)	0
Psychiatric disorders	1 (0.3)	2 (0.7)	2 (2.4)
Completed suicide	0	0	1 (1.2)
Confusional state	0	2 (0.7)	1 (1.2)
Mental status changes	1 (0.3)	0	0
Renal and urinary disorders	4 (1.4)	3 (1.0)	0
Haematuria	0	1 (0.3)	0
Renal failure	2 (0.7)	0	0
Renal failure acute	2 (0.7)	1 (0.3)	0
Urinary retention	0	1 (0.3)	0
Respiratory, thoracic and mediastinal disorders	38 (13.1)	25 (8.6)	11 (13.3)
Acute pulmonary oedema	1 (0.3)	0	0
Acute respiratory distress syndrome	1 (0.3)	0	0
Acute respiratory failure	1 (0.3)	0	0
Alveolitis allergic	1 (0.3)	0	0
Asphyxia	1 (0.3)	0	0
Aspiration	1 (0.3)	1 (0.3)	0
Chronic obstructive pulmonary disease	0	4 (1.4)	0
Dyspnoea	11 (3.8)	2 (0.7)	1 (1.2)

Table 14. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v14.0) Preferred Term	Arm A Figitumumab 20 mg/kg + Erlotinib 150 mg n (%)	Arm B1 Erlotinib 150 mg n (%)	Arm B2 Figitumumab 20 mg/kg n (%)
Dyspnoea at rest	0	0	1 (1.2)
Haemoptysis	4 (1.4)	6 (2.1)	2 (2.4)
Hydropneumothorax	0	0	1 (1.2)
Hypoxia	0	1 (0.3)	0
Oesophagobronchial fistula	0	1 (0.3)	0
Pleural effusion	2 (0.7)	3 (1.0)	1 (1.2)
Pneumonia aspiration	2 (0.7)	1 (0.3)	0
Pneumonitis	1 (0.3)	0	1 (1.2)
Pneumothorax	5 (1.7)	1 (0.3)	2 (2.4)
Pulmonary embolism	0	0	2 (2.4)
Pulmonary haemorrhage	3 (1.0)	3 (1.0)	1 (1.2)
Pulmonary oedema	1 (0.3)	0	0
Respiratory distress	2 (0.7)	1 (0.3)	0
Respiratory failure	5 (1.7)	5 (1.7)	0
Skin and subcutaneous tissue disorders	2 (0.7)	1 (0.3)	0
Drug eruption	0	1 (0.3)	0
Rash	1 (0.3)	0	0
Skin reaction	1 (0.3)	0	0
Vascular disorders	4 (1.4)	2 (0.7)	0
Arterial thrombosis	0	1 (0.3)	0
Deep vein thrombosis	1 (0.3)	0	0
Haemorrhage	1 (0.3)	0	0
Hypertension	1 (0.3)	0	0
Hypotension	1 (0.3)	0	0
Superior vena cava syndrome	1 (0.3)	1 (0.3)	0

Subjects are only counted once per treatment for each row.
Includes data up to 150 days after last dose of study drug.
MedDRA (version 14.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects.

Discontinuations due to AEs: As presented in Table 3, most subjects discontinued study treatment due to disease progression. However, AEs were listed as the reason for discontinuation of treatment with figitumumab in 46 (15.9%) subjects in Arm A and 2 subjects (2.4%) in Arm B2, and as the reason for discontinuation of treatment with erlotinib in 47 (16.3%) subjects in Arm A and 22 subjects (7.6%) in Arm B1. The Medical Dictionary for Regulatory Activities (MedDRA) terms listed as the AE reason for discontinuation from figitumumab included for >1 subject included: hyperglycemia (n=5), diarrhea (n=5), disease progression (n=5), asthenia (n=4), dyspnea (n=4), rash (n=4), fatigue (n=3), syncope (n=2), abdominal pain (n=2), pneumonia (n=2), and failure to thrive (n=2). The MedDRA terms listed for >1 subject as the AE reason for discontinuation from erlotinib included: disease progression (n=5), diarrhea (n=4), hyperglycemia (n=4), rash (n=4), asthenia (n=3), decreased appetite (n=3), dyspnea (n=2), abdominal pain (n=2), and pneumonia (n=2). Typically the same term(s) were reported for both drugs for treatment discontinuation for subjects in Arm A.

Deaths: The majority of subjects who died while on study treatment or within 28 days of their last dose of study treatment died due to their NSCLC. Eight subjects died due to treatment-related toxicity. Four of these deaths occurred in Arm A, 2 were considered

related to both study drugs (pulmonary hemorrhage, acute respiratory distress syndrome), and 2 were considered related to erlotinib only (intestinal ischemia, alveolitis allergic). An additional 2 erlotinib-related deaths occurred in Arm B1 (respiratory failure, pneumonia aspiration/renal failure acute/cardiac arrest), and 2 figitumumab-related deaths occurred in Arm B2 (pulmonary hemorrhage, cerebral hemorrhage).

Laboratory Results:

Hematology: The majority of abnormal hematology laboratory test results were Grades 1 or 2. The incidence of laboratory abnormalities was fairly similar across the treatment arms with the possible exception of abnormal platelet values which occurred more in the arms containing figitumumab (Arm A = 21.4%, Arm B2 = 18.3%) than in Arm B1 with single-agent erlotinib (7.5%).

Chemistries: The most common laboratory abnormality observed in all arms was hyperglycemia, an expected toxicity associated with treatment with figitumumab but unexpected in association with erlotinib. A higher incidence of Grade 3 and Grade 4 hyperglycemia was reported in treatment groups receiving figitumumab (Arm A 9.8% and 3.4% and Arm B2 13.0% and 1.4%, respectively) compared to Arm B1 at 2.9% and 0%, respectively. In addition to hyperglycemia, a higher incidence of elevated creatinine (all grades) was reported in treatment groups receiving figitumumab (Arm A 46.6% and B2 36.6%) compared to Arm B1 at 20.1%.

CONCLUSIONS:

- Based on review of the efficacy and safety data from a planned interim analysis of the study, the DSMC found sufficient evidence to recommend closure of the study due to a survival hazard ratio in the experimental arm that crossed the prespecified futility boundary.

- The study did not meet its primary objective of demonstrating an increase in OS from treatment with figitumumab and erlotinib over erlotinib alone. Median OS was 5.7 months in Arm A and 6.2 months in Arm B resulting in a hazard ratio of 1.091 with a 95% CI of 0.909-1.310, p=0.350.

- Median PFS was 2.1 months in Arm A and 2.6 months in Arm B. The hazard ratio was 1.075 (95% CI 0.898-1.287), the difference between the arms was not significant (p=0.426).

- Both study drugs, figitumumab and erlotinib, in combination and as single agents, were tolerated by the subjects treated in this study. Some summary statistics are difficult to interpret due to the safety reporting period (150 days after treatment), resulting in many Grade 5 AEs of disease progression. Further difficulties in interpretation are introduced due to the option for Arm B subjects to receive figitumumab after progression, resulting in AEs being reported under Arm B2 that would have been reported under Arm B1 if the subject had not received figitumumab.

- Most commonly reported treatment-emergent, all causality, AEs in Arm A and Arm B1, other than disease progression, were rash and diarrhea.

- AEs known to be associated with figitumumab treatment including weight decreased, nausea, and vomiting were reported more frequently on Arm A than on Arm B1.

- A higher percentage of Grade 3 and Grade 4 hyperglycemia was reported in treatment groups receiving figitumumab (Arm A 9.8% and 3.4% and Arm B2 13.0% and 1.4% respectively) than in Arm B1 at 2.9% and 0%.

- A higher percentage of subjects experienced Grade 3 and 4 treatment-emergent, all causality, AEs in Arm A (62.3%) than in Arm B1 (46.9%).

- Fewer subjects experienced SAEs in Arm B1 relative to either of the figitumumab-containing arms (Arm A=70.6%, Arm B1 = 52.8%, and Arm B2 = 75.9%). Other than disease progression, the most frequently reported SAE in Arm A was dehydration, and in Arm B2 was general physical health deterioration.

- The majority of subjects who died while on study treatment or within 28 days of their last dose of study treatment died due to their NSCLC. Eight subjects died due to treatment-related toxicity (4 in Arm A, 2 in Arm B1, and 2 in Arm B2).

- Nine subjects remained in the study at the time of the data cutoff for the primary clinical study report (CSR) dated 15 December 2011 (3 on treatment and 6 in safety follow-up). All 9 subjects left the study and the Supplemental Synopsis CSR dated 28 November 2012 was written to report additional safety information collected after the prior data cutoff.

- Six of the 9 remaining subjects left the study when it was terminated by the Sponsor. Two subjects died (1 in Arm A and 1 in Arm B). One subject was no longer willing to continue study participation. Of the 3 subjects that continued on treatment, 1 subject discontinued erlotinib due to erlotinib-related AEs (diarrhea and vomiting), 1 discontinued erlotinib and figitumumab due to hemoptysis considered unrelated to the study drugs, and 1 subject discontinued erlotinib due to objective progression or relapse.

- Additional AEs were reported and were similar to what had previously been reported. The impact to the AE summary tables was minimal. There were no changes to the conclusions from the A4021018 CSR dated 15 December 2011.