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

PROTOCOL NO.: A4021016

PROTOCOL TITLE: Randomized, Open Label, Phase III Trial of CP-751,871 in Combination With Paclitaxel and Carboplatin Versus Paclitaxel and Carboplatin in Patients With Non-Small Cell Lung Cancer

Study Centers: A total of 164 centers in 25 countries randomized subjects: Australia (2); Austria (2); Brazil (2); Bulgaria (4); Canada (2); the Czech Republic (3); Finland (2); France (9); Germany (5); Greece (4); Hong Kong (3); Hungary (5); India (5); Italy (4); Japan (10); the Republic of Korea (4); Poland (7); the Russian Federation (6); Slovakia (3); Spain (6); Switzerland (2); Taiwan (4); Turkey (2); Ukraine (5); United States (US, [63]).

Study Initiation Date, Primary Completion Date and Final Completion Date:

Study Initiation Date: First Subject First Visit (FSFV): 15 April 2008

Primary Completion Date: 31 March 2011

Study Completion Date: Last Subject Last Visit (LSLV): 25 September 2012

The study was terminated prematurely.

Phase of Development: Phase 3

Study Objectives:

The trial objectives were to assess the efficacy and safety of figitumumab administered in combination with paclitaxel plus carboplatin chemotherapy as first-line treatment of subjects with locally advanced (Stage IIIB with pleural effusion) or metastatic (Stage IV or recurrent) non-small cell lung cancer (NSCLC) of non-adenocarcinoma histology and to compare it to the efficacy and safety of paclitaxel plus carboplatin chemotherapy alone.

Primary Objective:

Determine whether the addition of figitumumab, an insulin-like growth factor 1 receptorinhibitor, in combination with paclitaxel plus carboplatin prolongs survival in subjects with non-adenocarcinoma NSCLC.

Secondary Objectives:

- Assess progression free survival in each arm.
- Evaluate the safety and tolerability of figitumumab in combination with paclitaxel and carboplatin.
- Assess the overall response rate in each arm.
- Assess health-related quality of life (HRQoL) outcomes and health states in both treatment arms.
- Collect pharmacokinetics (PK) data of figitumumab for population PK meta-analysis.
- Monitor for the occurrence of any antidrug antibody (ADA) in response to figitumumab treatment.
- Explore the association of pretreatment insulin-like growth factor 1 (IGF-1) and change in IGF-1 with survival.
- Collection of anonymized samples for molecular profiling.

METHODS

Study Design: This was an open-label, 2-arm study. Subjects were randomized in a 1:1 ratio to either the investigational treatment arm (Arm A) or the control treatment arm (Arm B). Subject randomization was stratified according to the following known prognostic factors: prior adjuvant chemotherapy (yes/no), gender, and histology (squamous versus other [ie, large cell and adenosquamous]).

- Investigational Treatment Arm (Arm A): Standard platinum-based doublet chemotherapy consisting of paclitaxel and carboplatin plus figitumumab administered in 3-week cycles. Chemotherapy treatment was continued for a maximum of 6 cycles. After completion or discontinuation of chemotherapy, for reasons other than disease progression (DP), subjects in Arm A continued to receive single agent figitumumab maintenance in 3-week cycles.
- Control Treatment Arm (Arm B): Standard platinum-based doublet chemotherapy consisting of paclitaxel and carboplatin administered in 3-week cycles. Chemotherapy treatment was continued for a maximum of 6 cycles.

Chemotherapy and/or figitumumab was discontinued upon DP, unacceptable treatment-related toxicity, physician decision, or subject refusal to continue study treatment. Figitumumab was administered up to a maximum of 17 cycles as appropriate. Further cycles with figitumumab in responding subjects could be allowed upon agreement between Sponsor and Investigator. A flowchart of study procedure appears below, in Table 1.

Table 1. Schedule of Activities[a]

		Chemotherapy Phase			Maintenance Phase		End of Treatment[b]	End of Study
		Paclitaxel/Carboplatin Figitumumab (3-Week Cycle)			Single Agent Figitumumab (Arm A)	Subjects off Therapy With Stable Disease or Better		Follow-Up[c]
Activity	**Baseline[d]**	**Day 1[e]**	**Day 8**	**Day 15**				**Monthly**
Informed consent	X							
Medical and oncologic history	X							
ECOG performance status	X							
12-Lead ECG[f]	X							
Vital signs[g]	X							
Height	X							
Weight	X	X			X			
Assessments								
Hematology[h]	X	X	X[h]	X[h]	X		X	
Serum chemistry and coagulation[i]	X	X			X		X	
Hgb A1C (arm A only)[j]	X	X					X	
Pregnancy test (serum/urine)[k]	X							
Adverse events assessment[l]		X			X		X	X[l]
Concomitant medications		X						
Tumor assessments[m]	X	Every 6 weeks			Every 6 weeks	Every 6 weeks	X[m]	
Randomization	X							
Study treatment								
EORTC QLQ-C30 and QLQ-LC13[n]		X			X		X	
EQ-5D[n]		X			X		X	
Chemotherapy[o] (Arm A and B)		X						
Figitumumab [p] (Arm A only)		X			X			
Figitumumab plasma concentration (Arm A only)[q]		X					X	
Anti-figitumumab antibody (Arm A only)[r]		X					X	X[r]
Biomarker analysis[s]		X					X	

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Activity	**Baseline[d]**	**Day 1[e]**	**Day 8**	**Day 15**				**Monthly**
Pharmacogenomics[t] (optional)		X						
Subsequent anticancer therapy[u]								X
Survival information[u]								X

AE = adverse event; CRF = case report form; CR = complete response; PR = partial response; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiography; HgbA1C = glycosylated hemoglobin 1C; EQ-5D = a 6-item self-reported questionnaire designed to assess health states in terms of a single idecndex value or utility score. Published weights are available that allow for the creation of a single summary score. Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction; EC/IRB = Ethics Committee/Institutional Review Board; EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; IgG = immunoglobulin G; IGF1 = insulin-like growth factor; labs = laboratory; LC13 = Lung Cancer Module.

a. **Schedule of Activities**: Schedules may vary±3 days to allow flexibility.
b. **End of Treatment**: Assessments only were needed to be performed if the prior assessment was performed >7 days previously. Every effort was made to obtain a final tumor assessment.
c. **Follow-Up**: Started upon disease progression or initiation of a subsequent anticancer therapy. To continue through 150 days post last treatment day.
d. **Baseline**: Assessments were needed to be performed within 7 days of randomization, except tumor assessments, which was performed within 28 days, informed consent and medical history, which was performed within 14 days, and the pregnancy test (if needed), which was performed within 72 hours of treatment.
e. **Day 1**: Cycle 1 Day 1 assessments only needed to be repeated if the assessments were not performed in the previous 7 days. Assessments were done prior to dosing.
f. **ECG**: May be repeated during the course of the study as medically warranted.
g. **Vital Signs**: Included temperature, blood pressure and pulse. Repeated during the course of the study as medically warranted. Results were recorded on CRF.
h **Hematology**: Day 8 and 15 hematology labs were required for the first cycle only. Hematologic evaluation in excess of the required Day 1 labs for each subsequent cycle is at the discretion of the Investigator and per institution guidelines.
i **Serum Chemistry & Coagulation**: Total IgG was measured only at Cycle 1 Day 1 predose and End of Treatment.
j **Hgb A1C**: Hemoglobin A1C was performed at Baseline, prior to Cycle 4 and at the End of Treatment, for all subjects on Arm A only.
k **Pregnancy Test (Serum/Urine)**: This was performed within 72 hours of treatment only for women of childbearing potential. Repeated during the study, if requested by the EC/IRB or if required by local regulations.
l **Adverse Events Assessments**: The reporting period for nonserious AEs terminated 150 days after the last dose of figitumumab treatment or upon initiation of a new anticancer treatment, whichever occurred first. At the end of reporting period, ongoing treatment-related AEs was followed up until resolution, return to baseline, chronicity or initiation of subsequent anticancer treatment. The serious AEs reporting period ends 150 days after the last study treatment

Table 1. Schedule of Activities[a]

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Activity	**Baseline[d]**	**Day 1[e]**	**Day 8**	**Day 15**				**Monthly**

dose, irrespective of start of any new anticancer treatment. Serious-related AEs were reported at any time.

m **Tumor Assessments**: This was done at Baseline within 28 days prior to randomization. Repeated tumor assessment prior to dosing if baseline was >28 days prior to dosing. Subjects with PR or CR had responses confirmed by repeat disease assessment no sooner than 28 days following initial documentation of response. This was repeated at the End of Treatment Visit if >28 days passed since the last evaluation (including CR and PR confirmation, if needed).

n. **EORTC QLQ-C30, QLQ-LC13 and EQ-5D**: Collected prior to any other activities. A member of the staff should be available if a subjects required clarification.

o. **Chemotherapy**: Efforts was made to initiate study treatment within 3 days of randomization.

p. **Figitumumab Injection**: Subjects were observed in the clinic for 1 hour following figitumumab administration. A 3-week interval occurred between last administration of chemotherapy and initiation of single agent figitumumab maintenance (Arm A only).

q. **Figitumumab Plasma Concentrations**: In Arm A subjects only, blood samples were collected within 2 hours prior to figitumumab infusion in Cycles 1, 2, 4, 5, and 6; at 1 hour post infusion in Cycles 1 and 5; and at 28 days and 150 days after the last figitumumab dose.

r. **Anti-Drug Antibodies**: In Arm A subjects only, blood samples were collected within 2 hours prior to figitumumab infusion in cycles 1, 2, and 4; and at 28 days and 150 days after the last figitumumab dose.

s. **Biomarker analysis**: Blood samples were collected within 2 hours prior to chemotherapy and/or figitumumab infusion in cycles 1 and 4, and at the End of Treatment Visit, to assess circulating IGF1 and other biomarkers of interest.

t. Optional blood samples were collected at Baseline for subjects in both Arm A and Arm B.

u. **Subsequent Anticancer Therapy & Survival Information**: Collected monthly after End of Treatment Visit.

Number of Subjects (Planned and Analyzed): A total of 830 subjects were planned for enrollment (415 per arm). Six hundred eighty-one subjects were randomized, 342 to Arm A and 339 to Arm B. Of these, 338 subjects in Arm A and 333 subjects in Arm B received treatment.

Of the 681 randomized subjects, 14 were randomized in Australia; 4 were randomized in Austria ; 3 were randomized in Brazil; 42 were randomized in Bulgaria; 10 were randomized in Canada; 19 were randomized in the Czech Republic; 6 were randomized in Finland; 34 were randomized in France; 20 were randomized in Germany; 14 were randomized in Greece; 7 were randomized in Hong Kong; 55 were randomized in Hungary; 18 were randomized in India; 34 were randomized in Italy; 22 were randomized in Japan; 44 were randomized in the Republic of Korea; 54 were randomized in Poland; 36 were randomized in the Russian Federation; 12 were randomized in Slovakia; 24 were randomized in Spain; 4 were randomized in Switzerland; 21 were randomized in Taiwan; 3 were randomized in Turkey; 54 were randomized in Ukraine; 127 were randomized in the (US).

Diagnosis and Main Criteria for Inclusion:

Subject with age ≥18 years and confirmed diagnosis of NSCLC with a primary histology of predominantly squamous cell, large cell or adenosquamous carcinoma. Advanced NSCLC with documented Stage IIIB (with pleural effusion) or Stage IV or recurrent disease. No prior systemic treatment for NSCLC, except for adjuvant chemotherapy. Adjuvant chemotherapy must have had completed for ≥12 months prior to randomization. Prior surgery or radiation therapy is permitted if completed at least 3 weeks prior to randomization and all acute toxicities have resolved. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1.

Excluded were the subjects with symptomatic central nervous system metastases were not permitted. Subjects requiring chronic steroid use or subjects with uncontrolled diabetes and with other active cancer were not permitted.

Study Treatment: Subjects in the 2 study arms (Arms A and B) received treatment. Figitumumab was supplied as a liquid intravenous solution and was administered at 20 mg/kg infused over 1 hour. Subjects remained under observation for 1-hour post-infusion. Note: initially the infusion was over a period of 2.5 hours, however data were provided during the study to confirm that this could be reduced to 1 hour. . Paclitaxel was diluted to a final concentration of 0.3 to 1.2 mg/mL and administered at a dose of 200 mg/m^2 in a 3-hour infusion. Study treatment regimen is shown in Table 2.

Table 2. Treatment Regimen

Designation	Treatment Regimen	Schedule
Arm A	Figitumumab 20 mg/kg in combination with carboplatin (AUC=6) and paclitaxel (200 mg/m^2)	Every 3 weeks, up to 6 cycles, followed by maintenance with single-agent figitumumab administered every 3 weeks up to a maximum of 17 cycles total
Arm B	Carboplatin (AUC=6) and paclitaxel (200 mg/m^2)	Every 3 weeks, up to 6 cycles

AUC = area under the curve.

Efficacy, Pharmacokinetic and Safety Endpoints:

Primary Endpoint:

- Overall survival defined as the time from randomization to the date of death due to any cause

Secondary Endpoints:

- Progression free survival (PFS) defined as the time from randomization to the date of progression as defined by independent review, or death due to any cause, whichever occurs first
- Overall safety profile characterized by type, frequency, severity as graded using common terminology criteria for adverse events (CTCAE), v3.0 and relationship to study therapy of adverse events (AEs) and laboratory abnormalities
- Patient -reported outcome of HRQoLand disease-related symptoms as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30), and its lung cancer module (LC13) and health states as measured by the EQ-5D
- Pharmacokinetics of figitumumab as measured by peak (C_{max}) and trough (Ctrough) concentrations (Arm A)
- Anti-drug antibody occurrence in response to figitumumab (Arm A only)
- Change in serum IGF-1 levels

Overall confirmed objective response, defined per response evaluation criteria in solid tumors (RECIST) by independent review.

Safety Evaluations: All subjects who started treatment in either arm were considered evaluable for safety. Safety evaluations consisted of blood hematology, serum chemistry, pregnancy test (serum/urine), AEs, and concomitant medications. AEs were graded by worst National Cancer Institute (NCI) CTCAE version 3.0 grade. The reporting period for nonserious AEs terminated 150 days after the last dose of treatment or upon initiation of a

new anticancer treatment, whichever occurred first. At the end of the reporting period, ongoing treatment-related AEs were followed up until resolution, return to baseline, or initiation of subsequent anticancer treatment. The serious adverse event (SAE) reporting period ended 150 days after the last study treatment dose, irrespective of start of any new anticancer treatment. Related SAEs were reported at any time.

Statistical Methods:

Analysis Sets:

Subjects not randomized to the study (ie, screen only subjects) were not be included in any analysis. The conventions used for subjects who qualify for a population, but who have missing data for a particular endpoint.

Full Analysis Set:

All randomized as randomized were all randomized subjects where subjects were classified according to the randomized treatment regardless of what treatment, if any, was received. All primary analyses of efficacy endpoints and subject reported outcomes were based on the all randomized as randomized population.

Safety Analysis Set:

All treated as treated was all subjects that receive at least 1 dose of any agent of the combination. Subjects were classified by the treatment actually received. The primary population for all safety analyses were all treated as treated population.

Treatment Misallocations:

For subjects who were randomized but took incorrect treatment were reported under the randomized treatment group for the all randomized as randomized population, but were reported under the treatment actually received for the all treated as treated population.

The primary efficacy endpoint, OS, was analyzed using a stratified 1-sided log rank test. Two formal OS interim analyses were planned, after approximately one-third and two-thirds of the anticipated number of OS events occurred. A total of 649 events were expected if the trial went to full follow-up. Two-sided p-values were reported.

The secondary efficacy endpoint of PFS was analyzed using an unstratified log-rank test (2-sided). Best overall confirmed objective response was analyzed using Pearson's Chi-square test (2-sided). AEs were classified using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.0 classification system. AEs were summarized by treatment and by the frequency of subjects experiencing treatment emergent AEs corresponding to body systems and MedDRA preferred term. AEs were summarized by relatedness to study treatment and to glycosylated hemoglobin 1c (HbA1c) concentration. Hematology and chemistry laboratory data were summarized by treatment. The laboratory results were graded according to the NCI CTCAE version 3.0 severity grade. The frequencies of the worst severity grade observed were displayed by study treatment. For

parameters for which an NCI CTCAE version 3.0 scale did not exist, the frequency of subjects with values below, within, and above the normal ranges were summarized by treatment.

RESULTS

Subject Disposition and Demography:

A summary of subject randomization and analysis populations is presented in Table 3.

Table 3. Subject Evaluation Groups (All Treated, As Treated)

	Arm A Figitumumab + Paclitaxel and Carboplatin n (%)	Arm B Paclitaxel and Carboplatin n (%)
Assigned to study treatment: N=681		
Treated	338	333
Discontinued study	334 (98.8)	333 (100.0)
Ongoing at date of data cutoff[a]	4 (1.2)	0
Analyzed for safety:		
Adverse events	338 (100.0)	333 (100.0)
Laboratory data	334 (98.8)	324 (97.3)

N = total number of subjects per treatment arm; n = number of subjects evaluated per treatment arm.

a. Of these 4 subjects, 2 remained on treatment with figitumumab, 1 was in the 150-day safety follow-up period, and 1 was at a study center where the amendment to stop collecting overall survival data had not yet been approved.

A summary of reasons for discontinuation from the treatment phase and from the study is presented in Table 4.

Table 4. Reasons for Discontinuation (All Treated, As Treated)

	Arm A Figitumumab + Paclitaxel and Carboplatin N=338 n (%)	Arm B Paclitaxel and Carboplatin N=333 n (%)
Discontinuations From Treatment Phase – Figitumumab		
Subject died	43 (12.7)	0
Related to figitumumab	22 (6.5)	0
Adverse event	22 (6.5)	0
Not related to figitumumab	271 (80.2)	1 (0.3)
Adverse event	32 (9.5)	1 (0.3)[a]
Global deterioration of health status	10 (3.0)	0
Lost to follow-up	2 (0.6)	0
Objective progression or relapse	170 (50.3)	0
Other	22 (6.5)	0
Protocol violation	1 (0.3)	0
Subject refused continued treatment for reason other than adverse event	34 (10.1)	0
Total	336 (99.4)	1 (0.3)
Discontinuations From Treatment Phase – Chemotherapy		
Subject died	40 (11.8)	32 (9.6)
Related to chemotherapy	29 (8.6)	31 (9.3)
Adverse event	29 (8.6)	31 (9.3)
Not related to chemotherapy	140 (41.4)	123 (36.9)
Adverse event	27 (8.0)	13 (3.9)
Global deterioration of health status	9 (2.7)	10 (3.0)
Lost to follow-up	2 (0.6)	1 (0.3)
Objective progression or relapse	78 (23.1)	81 (24.3)
Other	5 (1.5)	8 (2.4)
Protocol violation	1 (0.3)	1 (0.3)
Subject refused continued treatment for reason other than adverse event	18 (5.3)	9 (2.7)
Total	209 (61.8)	186 (55.9)
Discontinuations From Study Phase		
Subject died	256 (75.7)	248 (74.5)
Not related to study drug	78 (23.1)	85 (25.5)
Lost to follow-up	7 (2.1)	11 (3.3)
No longer willing to participate in study	22 (6.5)	12 (3.6)
Other	1 (0.3)	0
Study terminated by sponsor[b]	48 (14.2)	62 (18.6)
Total	334 (98.8)	333 (100)

N = total number of subjects per treatment arm; n = number of subjects discontinued per treatment arm

.a. This subject was randomized to Arm A, but treated with only paclitaxel and carboplatin.

b. Subjects were still alive when data collection stopped.

Demographic characteristics of treated study subjects are summarized in Table 5.

Table 5. Demographic Characteristics (All Randomized, As Randomized)

	Arm A Figitumumab + Paclitaxel and Carboplatin N=342	Arm B Paclitaxel and Carboplatin N=339
Gender (n)		
Male	261	260
Female	81	79
Age (years)		
<65	204 (59.6)	202 (59.6)
65-69	64 (18.7)	64 (18.9)
≥70	74 (21.6)	73 (21.5)
Median	62.0	62.0
Mean (SD)	61.8 (9.0)	61.8 (9.1)
Range	30-90	36-83
Race, n (%)		
White	265 (77.5)	270 (79.6)
Black	9 (2.6)	4 (1.2)
Asian	56 (16.4)	59 (17.4)
Other	12 (3.5)	6 (1.8)
Weight (kg)		
Median	68.0	68.0
Mean (SD)	70.0 (14.8)	70.3 (15.9)
Range	39.0-118.0	40.0-130.0
Body mass index (kg/m^2)		
Mean (SD)	24.3 (4.6)	24.4 (4.6)
Range	15.2-43.8	14.7-42.7
Height (cm)		
Mean (SD)	169.7 (8.2)	169.3 (8.8)
Range	140.0-192.0	136.7-196.0
Smoking status, n (%)		
Never smoked	34 (9.9)	33 (9.7)
Current smoker	142 (41.5)	141 (41.6)
Ex-smoker	166 (48.5)	165 (48.7)

Body mass index is defined as $weight/(height \bullet .01)^2$
N = total number of subjects per treatment arm; n = number of subjects per treatment arm; SD = standard deviation.

Subject baseline characteristics for ECOG performance status and disease stage are presented in Table 6.

Table 6. Subject Baseline Characteristics, ECOG Performance Status and Disease Stage (All Randomized, As Randomized)

	Arm A Figitumumab + Paclitaxel and CarboplatinN=342 n (%)	Arm B Paclitaxel and Carboplatin N=339 n (%)
ECOG performance status		
0	113 (33.0)	115 (33.9)
1	226 (66.1)	217 (64.0)
2, 3, or 4	0	0
Not reported	3 (<1.0)	7 (2.1)
Current disease stage		
Stage IIIB	39 (11.4)	39 (11.5)
Stage IV	302 (88.3)	300 (88.5)
Not reported	1 (<1.0)	0

ECOG = Eastern Cooperative Oncology Group; N = total number of subjects per treatment arm; n = number of subjects per treatment arm.

Efficacy and Pharmacokinetic Results:

Overall Survival:

A total of 510 deaths occurred during this study, 259 (75.7%) in Arm A and 251 (74.0%) in Arm B, and 171 subjects had been censored at last contact, 83 (24.3%) in Arm A and 88 (26.0%) in Arm B.

Details of the OS analysis are presented in Table 7.

Table 7. Summary of Overall Survival (All Randomized, As Randomized)

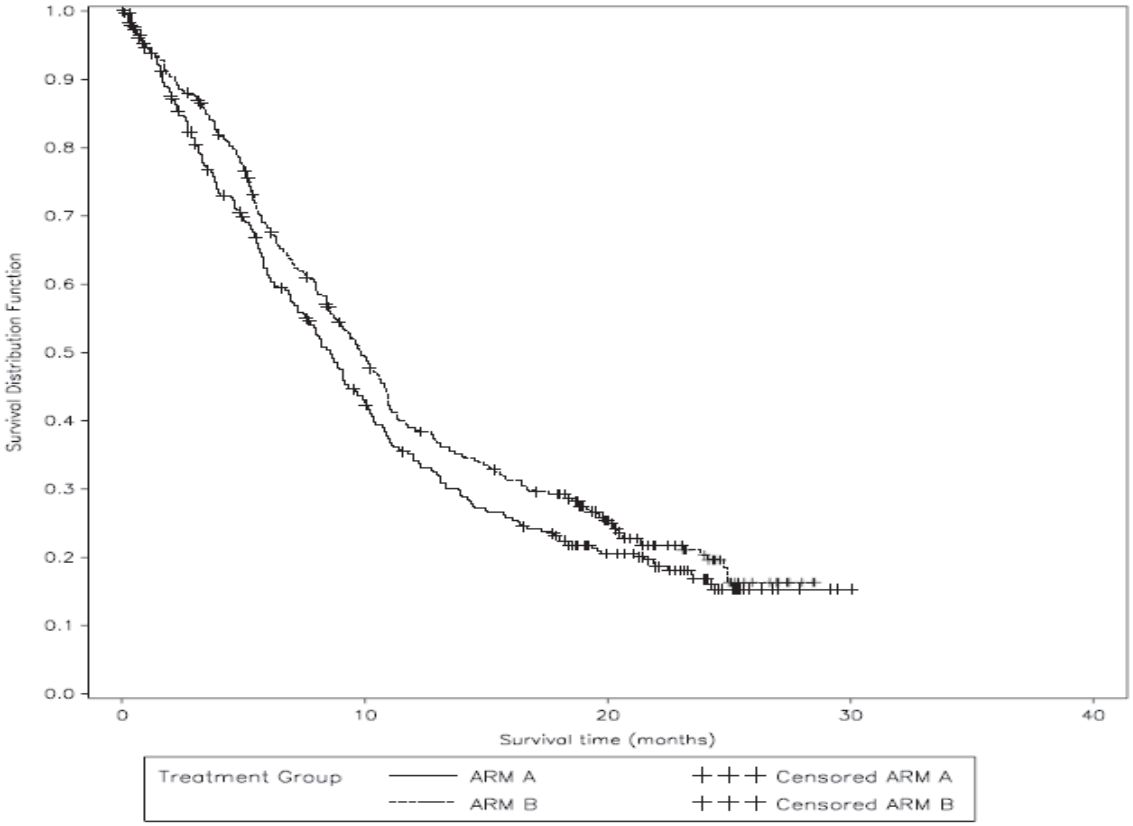
	Arm A Figitumumab + Paclitaxel and Carboplatin N=342 n (%)	Arm B Paclitaxel and Carboplatin N=339 n (%)
Number of deaths	259 (75.7)	251 (74.0)
Cause of death		
Disease under study	222 (64.9)	224 (66.1)
Study treatment toxicity	15 (4.4)	3 (<1.0)
Unknown	3 (<1.0)	7 (2.1)
Other	19 (5.6)	17 (5.0)
Number censored	83 (24.3)	88 (26.0)
Reason for censorship		
Alive	53 (15.5)	63 (18.6)
Subject no longer willing to participate	23 (6.7)	14 (4.1)
Lost to follow-up	7 (2.0)	11 (3.2)
Number of subjects with last contact date >1 year prior to data cutoff date	28 (8.2)	20 (5.9)
Survival probability at Month 6[a] (95% CI[b])	61.3 (55.8, 66.4)	68.2 (62.8, 72.9)
Kaplan-Meier estimates of time-to-event (month) quartiles (95% CI)[c]		
25%	3.8 (3.2, 4.9)	5.2 (4.7, 5.6)
50%	8.6 (7.4, 9.3)	9.8 (8.6, 10.9)
75%	16.4 (13.9, 21.3)	20.2 (16.7, 24.1)
Versus Arm B		
Hazard ratio[d]	1.179	-
95% CI of hazard ratio	0.990-1.404	-
p-Value[e]	0.064	-

N = total number of subjects per treatment arm; n = number of subjects per treatment arm; CI = confidence interval.

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, histology, and prior adjuvant
e. 2-sided p-value from the log rank test stratified by gender, prior adjuvant chemotherapy, and histology.

The Kaplan-Meier estimate of OS for all subjects randomized, as randomized, with censored subjects indicated, is provided in Figure 1.

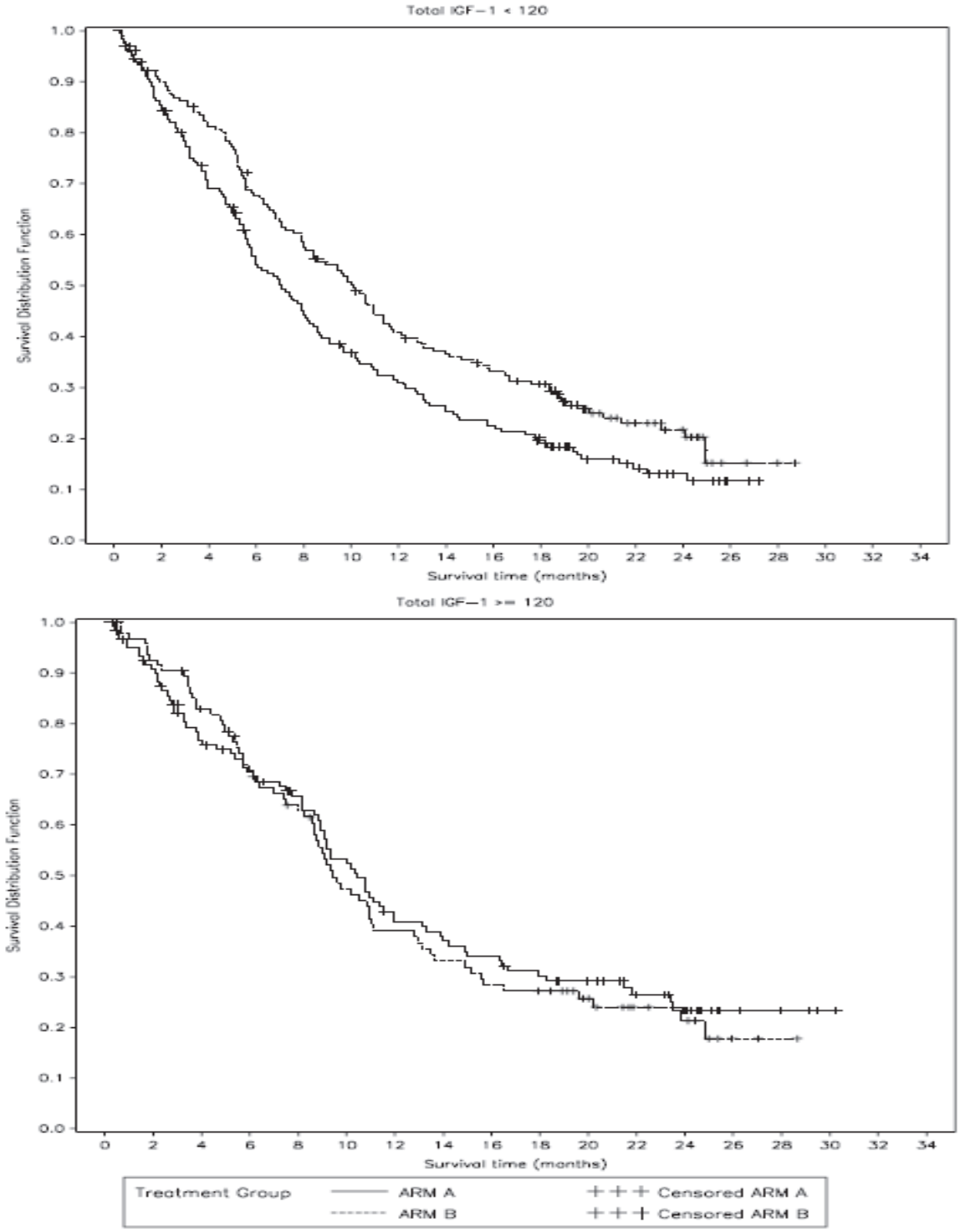
Figure 1. Kaplan-Meier Plot of Overall Survival (All Randomized, As Randomized)



Arm A = figitumumab + Paclitaxel and Carboplatin; Arm B = Paclitaxel and Carboplatin.

The Kaplan-Meier estimate of OS for all subjects randomized, as randomized, by baseline total IGF-1 subgroups, with censored subjects indicated, is provided in Figure 2.

Figure 2. Kaplan-Meier Plot of Overall Survival for Subjects With Baseline Total IGF-1 <120 ng/mL (Top) and ≥120 ng/mL (Bottom) (All Randomized, As Randomized)



Arm A = figitumumab + Paclitaxel and Carboplatin; Arm B = Paclitaxel and Carboplatin.

IGF-1 = insulin-like growth factor-1.

Progression-Free Survival:

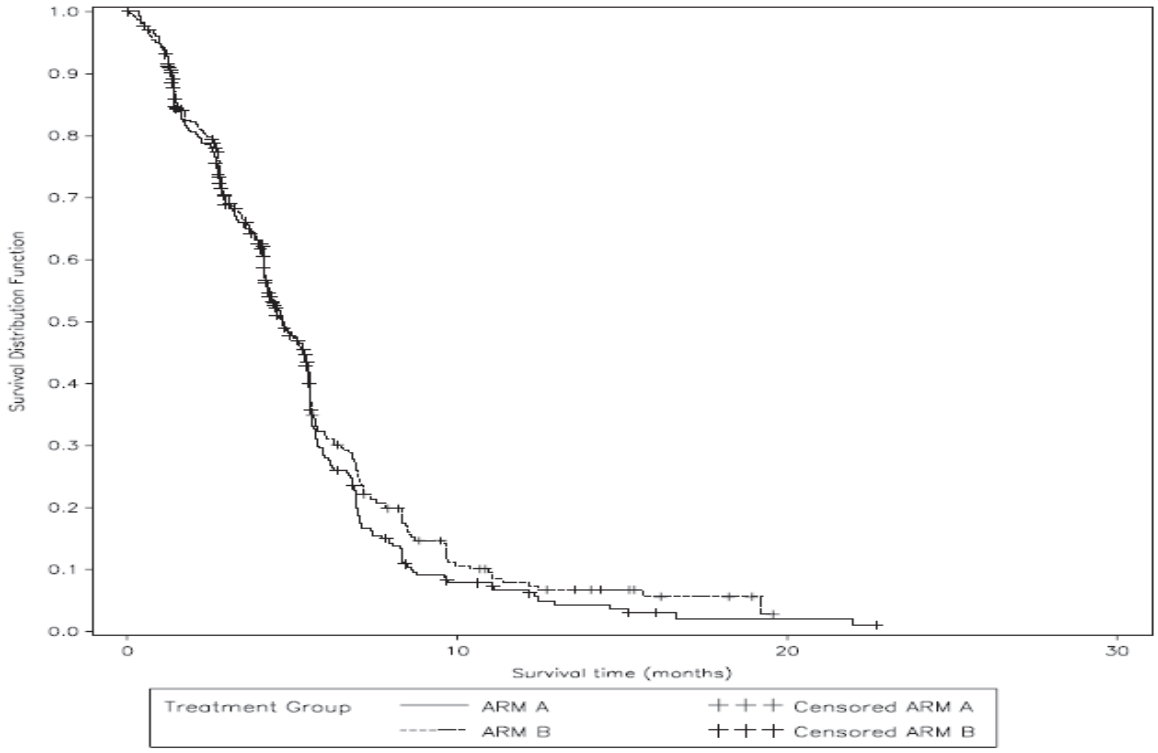
A summary of PFS as determined by the Investigator is provided in Table 8 and the Kaplan-Meier plot is displayed in Figure 3.

Table 8. Progression-Free Survival (All Randomized, As Randomized)

	Arm A Figitumumab + Paclitaxel and Carboplatin N=342 n (%)	Arm B Paclitaxel and Carboplatin N=339 n (%)
Number of subjects with an event	261 (76.3)	241 (71.1)
Type of event		
Objective progression	206 (60.2)	197 (58.1)
Death without objective progression	55 (16.1)	44 (13.0)
Number censored	81 (23.7)	98 (28.9)
Reason for censorship		
No adequate baseline assessments	12 (3.5)	12 (3.5)
No on-study assessments	20 (5.8)	18 (5.3)
Given new anticancer treatment prior to tumor progression	16 (4.7)	27 (8.0)
Withdrew consent for follow-up	8 (2.3)	4 (1.2)
Lost to follow-up	1 (<1.0)	1 (<1.0)
Unacceptable gap (>12 weeks) between PD or death to the most recent prior adequate assessment	15 (4.4)	23 (6.8)
In follow-up for progression[a]	9 (2.6)	13 (3.8)
Probability of being event-free at 6 months[b] (95% CI[c])	28.4 (23.1, 33.9)	31.6 (26.0, 37.4)
Kaplan-Meier estimates of time-to-event (month) quartiles (95% CI)[d]		
25%	2.8 (2.2, 3.0)	2.8 (2.3, 2.9)
50%	4.7 (4.2, 5.4)	4.6 (4.2, 5.4)
75%	6.8 (5.7, 7.0)	7.0 (6.2, 8.3)
Versus Arm B		
Hazard ratio[e]	1.103	
95% CI of hazard ratio	0.925-1.315	
p-Value[f]	0.270	

CI = confidence interval; N = total number of subjects per treatment arm; n = number of subjects per treatment.
a. In follow-up for progression, or scans until progressive disease were not completed.
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.
f. 2-sided p-value from the unstratified log-rank test.

Figure 3. Kaplan-Meier Plot of Progression-Free Survival (All Randomized, As Randomized)



Arm A = figitumumab + Paclitaxel and Carboplatin; Arm B = Paclitaxel and Carboplatin.

Best Overall Response:

A summary of best OR per Investigator for each arm is provided in Table 9.

Table 9. Best Overall Response Per Investigator (All Randomized, As Randomized)

	Arm A Figitumumab + Paclitaxel and Carboplatin N=342 n (%)	Arm B Paclitaxel and Carboplatin N=339 n (%)
Complete response	2 (<1.0)	3 (<1.0)
Partial response	111 (32.5)	114 (33.6)
Stable/no response	126 (36.8)	120 (35.4)
Objective progression	42 (12.3)	44 (13.0)
Early death	21 (6.1)	21 (6.2)
Indeterminate	40 (11.7)	37 (10.9)
Objective response rate (CR + PR)	113 (33.0)	117 (34.5)
95% exact CI[a]	(28.1, 38.3)	(29.5, 39.8)
Versus Arm B		
Treatment difference[b]	-1.472	-
95% CI of the difference[b]	(-8.6, 5.6)	-
p-Value[c]	0.685	-

CI = confidence interval; CR = complete response; N = total number of subjects per treatment arm; n = number of subjects per treatment; 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 Antidrug Antibody (ADA) Results: Figitumumab plasma concentration-time data were available from 332 Arm A subjects. ADA samples were collected from 364 subjects receiving figitumumab (332 in Arm A and 32 in Arm B). Of the 1054 ADA samples tested in the screening assay, 1051 samples were negative for ADA, as indicated by a titer measurement of <6.64. There were 3 samples with a low titer measurement of 22.5, 11.21, and 10.99, respectively.

The positive ADA observed for the Cycle 1 predose sample was likely a false positive result from the assay. While 2 samples from a subject, were tested positive for ADA, the other 3 samples obtained from this subject at Cycle 2 predose, Cycle 4 predose, and 28 days after the last dose showed ADA titers of <6.64. Additionally, there was no evidence suggesting that figitumumab plasma concentrations in the subject were different from those observed in other subjects.

The study was terminated prematurely.

Safety Results:

Safety analysis was based on the treatment received. A total of 3 subjects had additions or changes to AE data. However, no additional Grade 3 or Grade 4 AEs were reported after the previous database snapshot on 04 August 2011. Subjects with treatment emergent nonserious AEshaving frequency ≥2% is presented in Table 10.

Table 10. Treatment Emergent Nonserious Adverse Events Having Frequency ≥2%

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v14.0) Preferred Term	Arm A n (%)	Arm B n (%)
Number (%) of subjects:		
Evaluable for adverse events	338	333
With adverse events	316 (93.5)	303 (91.0)
Blood and lymphatic system disorders	159 (47.0)	157 (47.1)
Anaemia	93 (27.5)	85 (25.5)
Febrile neutropenia	2 (0.6)	7 (2.1)
Leucopenia	18 (5.3)	33 (9.9)
Neutropenia	74 (21.9)	78 (23.4)
Thrombocytopenia	60 (17.8)	49 (14.7)
Cardiac disorders	13 (3.8)	17 (5.1)
Tachycardia	2 (0.6)	7 (2.1)
Ear and labyrinth disorders	33 (9.8)	7 (2.1)
Tinnitus	11 (3.3)	1 (0.3)
Vertigo	11 (3.3)	5 (1.5)
Gastrointestinal disorders	211 (62.4)	158 (47.4)
Abdominal pain	14 (4.1)	10 (3.0)
Abdominal pain upper	10 (3.0)	11 (3.3)
Constipation	60 (17.8)	61 (18.3)
Diarrhoea	95 (28.1)	45 (13.5)
Dry mouth	13 (3.8)	5 (1.5)
Dyspepsia	8 (2.4)	11 (3.3)
Dysphagia	18 (5.3)	9 (2.7)
Mouth ulceration	7 (2.1)	2 (0.6)
Nausea	132 (39.1)	101 (30.3)
Stomatitis	30 (8.9)	10 (3.0)
Vomiting	82 (24.3)	46 (13.8)
General disorders and administration site conditions	203 (60.1)	177 (53.2)
Asthenia	71 (21.0)	59 (17.7)
Chest pain	45 (13.3)	34 (10.2)
Chills	7 (2.1)	5 (1.5)
Fatigue	112 (33.1)	85 (25.5)
General physical health deterioration	14 (4.1)	4 (1.2)
Mucosal inflammation	27 (8.0)	9 (2.7)
Oedema peripheral	10 (3.0)	24 (7.2)
Pain	11 (3.3)	13 (3.9)
Pyrexia	26 (7.7)	33 (9.9)
Immune system disorders	10 (3.0)	12 (3.6)
Hypersensitivity	8 (2.4)	9 (2.7)
Infections and infestations	82 (24.3)	67 (20.1)
Nasopharyngitis	5 (1.5)	7 (2.1)
Pneumonia	12 (3.6)	14 (4.2)
Urinary tract infection	8 (2.4)	4 (1.2)
Investigations	122 (36.1)	74 (22.2)
Blood creatinine increased	13 (3.8)	0
Haemoglobin decreased	14 (4.1)	13 (3.9)
Neutrophil count decreased	11 (3.3)	10 (3.0)
Platelet count decreased	16 (4.7)	6 (1.8)
Weight decreased	65 (19.2)	29 (8.7)
Metabolism and nutrition disorders	198 (58.6)	101 (30.3)
Decreased appetite	128 (37.9)	75 (22.5)

Table 10. Treatment Emergent Nonserious Adverse Events Having Frequency ≥2%

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v14.0) Preferred Term	Arm A n (%)	Arm B n (%)
Dehydration	28 (8.3)	10 (3.0)
Hypercalcaemia	14 (4.1)	5 (1.5)
Hyperglycaemia	74 (21.9)	16 (4.8)
Hyperkalaemia	17 (5.0)	5 (1.5)
Hyperuricaemia	14 (4.1)	1 (0.3)
Hypokalaemia	4 (1.2)	10 (3.0)
Hypomagnesaemia	10 (3.0)	8 (2.4)
Hyponatraemia	13 (3.8)	5 (1.5)
Musculoskeletal and connective tissue disorders	144 (42.6)	147 (44.1)
Arthralgia	47 (13.9)	57 (17.1)
Back pain	19 (5.6)	19 (5.7)
Bone pain	13 (3.8)	16 (4.8)
Muscle spasms	19 (5.6)	5 (1.5)
Muscular weakness	7 (2.1)	7 (2.1)
Musculoskeletal chest pain	10 (3.0)	13 (3.9)
Musculoskeletal pain	20 (5.9)	17 (5.1)
Myalgia	39 (11.5)	44 (13.2)
Pain in extremity	33 (9.8)	23 (6.9)
Nervous system disorders	182 (53.8)	180 (54.1)
Dizziness	37 (10.9)	32 (9.6)
Dysgeusia	26 (7.7)	13 (3.9)
Headache	37 (10.9)	22 (6.6)
Hypoaesthesia	9 (2.7)	7 (2.1)
Neuropathy peripheral	62 (18.3)	56 (16.8)
Neurotoxicity	6 (1.8)	7 (2.1)
Paraesthesia	29 (8.6)	35 (10.5)
Peripheral sensory neuropathy	40 (11.8)	50 (15.0)
Psychiatric disorders	65 (19.2)	64 (19.2)
Anxiety	17 (5.0)	17 (5.1)
Depression	13 (3.8)	11 (3.3)
Insomnia	31 (9.2)	30 (9.0)
Respiratory, thoracic and mediastinal disorders	146 (43.2)	147 (44.1)
Cough	66 (19.5)	59 (17.7)
Dysphonia	11 (3.3)	8 (2.4)
Dyspnoea	56 (16.6)	65 (19.5)
Epistaxis	26 (7.7)	3 (0.9)
Haemoptysis	32 (9.5)	21 (6.3)
Hiccups	9 (2.7)	8 (2.4)
Oropharyngeal pain	13 (3.8)	6 (1.8)
Productive cough	11 (3.3)	9 (2.7)
Skin and subcutaneous tissue disorders	172 (50.9)	167 (50.2)
Alopecia	138 (40.8)	146 (43.8)
Dry skin	11 (3.3)	7 (2.1)
Nail disorder	9 (2.7)	2 (0.6)
Pruritus	26 (7.7)	18 (5.4)
Rash	28 (8.3)	20 (6.0)
Vascular disorders	50 (14.8)	44 (13.2)
Hypertension	14 (4.1)	13 (3.9)
Hypotension	16 (4.7)	11 (3.3)

Table 10. Treatment Emergent Nonserious Adverse Events Having Frequency ≥2%

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v14.0) Preferred Term	Arm A n (%)	Arm B n (%)

Subjects are only counted once per treatment for each row.
Includes data up to 150 days after last dose of study drug.
MedDRA (v14.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with specific event; v = version.

CTCAE grade by treatment arm, and preferred term, all AEs of CTCAE Grade 3 or higher that occurred in ≥5% of subjects in either arm are summarized in Table 11.

Table 11. Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term and CTCAE Grade, for CTCAE Grade ≥3 and Occurrence ≥5% in Either Arm (All Causalities, All Cycles)

	CTCAE Grade			Total
	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	n (%)
Arm A (N=338)				
Any adverse event	70 (20.7)	44 (13.0)	165 (48.8)	279 (82.5)
Disease progression	0	1 (0.3)	114 (33.7)	115 (34.0)
Neutropenia	20 (5.9)	45 (13.3)	1 (0.3)	66 (19.5)
Hyperglycaemia	35 (10.4)	7 (2.1)	0	42 (12.4)
Asthenia	23 (6.8)	4 (1.2)	0	27 (8.0)
Thrombocytopenia	17 (5.0)	10 (3.0)	0	27 (8.0)
Decreased appetite	23 (6.8)	0	0	23 (6.8)
Fatigue	19 (5.6)	2 (0.6)	0	21 (6.2)
Pneumonia	9 (2.7)	5 (1.5)	6 (1.8)	20 (5.9)
Anaemia	15 (4.4)	4 (1.2)	0	19 (5.6)
Dehydration	17 (5.0)	2 (0.6)	0	19 (5.6)
Leukopaenia	8 (2.4)	4 (1.2)	0	12 (3.6)
Dyspnea	8 (2.4)	4 (1.2)	0	12 (3.6)
Febrile neutropenia	3 (0.9)	3 (0.9)	0	6 (1.8)
Arm B (N=333)				
Any adverse event	64 (19.2)	51 (15.3)	125 (37.5)	240 (72.1)
Disease progression	0	0	90 (27.0)	90 (27.0)
Neutropenia	31 (9.3)	33 (9.9)	0	64 (19.2)
Anaemia	20 (6.0)	0	0	20 (6.0)
Thrombocytopenia	15 (4.5)	5 (1.5)	0	20 (6.0)
Dyspnea	15 (4.5)	3 (0.9)	1 (0.3)	19 (5.7)
Febrile neutropenia	12 (3.6)	6 (1.8)	0	18 (5.4)
Leukopaenia	14 (4.2)	4 (1.2)	0	18 (5.4)
Asthenia	15 (4.5)	1 (0.3)	0	16 (4.8)
Fatigue	11 (3.3)	2 (0.6)	0	13 (3.9)
Pneumonia	8 (2.4)	2 (0.6)	3 (0.9)	13 (3.9)
Decreased appetite	7 (2.1)	0	0	7 (2.1)
Dehydration	1 (0.3)	0	1 (0.3)	2 (0.6)
Hyperglycaemia	2 (0.6)	0	0	2 (0.6)

Within each arm, events are listed in order of decreasing overall frequency.
MedDRA (version 14.0) coding dictionary applied.
CTCAE = common terminology criteria for adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects per treatment arm; n = number of subjects per treatment.

An analysis was performed to compare AEs between subjects who had a baseline HbA1c <5.7% with subjects who had a baseline HbA1c ≥5.7%. These data are presented by preferred term and CTCAE grade for all events occurring in ≥10% of subjects in either arm in Table 12 (HbA1c <5.7%) and Table 13 (HbA1c ≥5.7%).

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

Preferred Term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Arm A (N=128)						
Any adverse event	5 (3.9)	16 (12.5)	22 (17.2)	17 (13.3)	63 (49.2)	123 (96.1)
Alopecia	19 (14.8)	33 (25.8)	2 (1.6)	1 (0.8)	0	55 (43.0)
Disease progression	0	0	0	0	44 (34.4)	44 (34.4)
Decreased appetite	15 (11.7)	19 (14.8)	6 (4.7)	0	0	40 (31.3)
Nausea	21 (16.4)	14 (10.9)	5 (3.9)	0	0	40 (31.3)
Anaemia	6 (4.7)	24 (18.8)	7 (5.5)	2 (1.6)	0	39 (30.5)
Fatigue	8 (6.3)	22 (17.2)	7 (5.5)	2 (1.6)	0	39 (30.5)
Diarrhoea	13 (10.2)	11 (8.6)	3 (2.3)	1 (0.8)	0	28 (21.9)
Vomiting	7 (5.5)	14 (10.9)	4 (3.1)	0	0	25 (19.5)
Hyperglycaemia	5 (3.9)	9 (7.0)	9 (7.0)	1 (0.8)	0	24 (18.8)
Neutropenia	0	3 (2.3)	6 (4.7)	15 (11.7)	0	24 (18.8)
Cough	12 (9.4)	9 (7.0)	1 (0.8)	0	0	22 (17.2)
Thrombocytopenia	3 (2.3)	10 (7.8)	5 (3.9)	4 (3.1)	0	22 (17.2)
Asthenia	4 (3.1)	11 (8.6)	5 (3.9)	1 (0.8)	0	21 (16.4)
Constipation	12 (9.4)	6 (4.7)	2 (1.6)	0	0	20 (15.6)
Dyspnea	14 (10.9)	3 (2.3)	2 (1.6)	1 (0.8)	0	20 (15.6)
Neuropathy peripheral	7 (5.5)	9 (7.0)	3 (2.3)	0	0	19 (14.8)
Weight decreased	11 (8.6)	8 (6.3)	0	0	0	19 (14.8)
Arthralgia	10 (7.8)	8 (6.3)	0	0	0	18 (14.1)
Chest pain	6 (4.7)	6 (4.7)	3 (2.3)	0	0	15 (11.7)
Headache	7 (5.5)	7 (5.5)	1 (0.8)	0	0	15 (11.7)
Myalgia	8 (6.3)	5 (3.9)	0	0	0	13 (10.2)
Pain in extremity	6 (4.7)	7 (5.5)	0	0	0	13 (10.2)
Peripheral sensory neuropathy	7 (5.5)	2 (1.6)	3 (2.3)	0	0	12 (9.4)
Paresthaesia	3 (2.3)	7 (5.5)	1 (0.8)	0	0	11 (8.6)
Leukopaenia	1 (0.8)	2 (1.6)	4 (3.1)	0	0	7 (5.5)
Haemoptysis	5 (3.9)	1 (0.8)	0	0	0	6 (4.7)
Pyrexia	2 (1.6)	2 (1.6)	0	0	0	4 (3.1)
Arm B (N=138)						
Any adverse event	3 (2.2)	30 (21.7)	26 (18.8)	19 (13.8)	52 (37.7)	130 (94.2)
Alopecia	21 (15.2)	46 (33.3)	2 (1.4)	2 (1.4)	0	71 (51.4)
Nausea	33 (23.9)	13 (9.4)	2 (1.4)	0	0	48 (34.8)
Anemia	6 (4.3)	21 (15.2)	12 (8.7)	0	0	39 (28.3)
Decreased appetite	20 (14.5)	15 (10.9)	4 (2.9)	0	0	39 (28.3)
Fatigue	15 (10.9)	14 (10.1)	4 (2.9)	2 (1.4)	0	35 (25.4)
Disease progression	0	0	0	0	34 (24.6)	34 (24.6)
Neutropenia	1 (0.7)	7 (5.1)	13 (9.4)	11 (8.0)	0	32 (23.2)
Arthralgia	20 (14.5)	7 (5.1)	0	0	0	27 (19.6)
Thrombocytopenia	5 (3.6)	8 (5.8)	9 (6.5)	4 (2.9)	0	26 (18.8)
Constipation	18 (13.0)	6 (4.3)	1 (0.7)	0	0	25 (18.1)
Dyspnea	11 (8.0)	7 (5.1)	5 (3.6)	1 (0.7)	1 (0.7)	25 (18.1)
Cough	17 (12.3)	5 (3.6)	2 (1.4)	0	0	24 (17.4)
Asthenia	4 (2.9)	15 (10.9)	3 (2.2)	1 (0.7)	0	23 (16.7)
Vomiting	17 (12.3)	5 (3.6)	1 (0.7)	0	0	23 (16.7)
Peripheral sensory neuropathy	15 (10.9)	5 (3.6)	2 (1.4)	0	0	22 (15.9)
Diarrhea	12 (8.7)	5 (3.6)	1 (0.7)	0	0	18 (13.0)

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

Preferred Term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Neuropathy peripheral	9 (6.5)	5 (3.6)	4 (2.9)	0	0	18 (13.0)
Pyrexia	13 (9.4)	5 (3.6)	0	0	0	18 (13.0)
Leukopaenia	5 (3.6)	5 (3.6)	4 (2.9)	2 (1.4)	0	16 (11.6)
Myalgia	14 (10.1)	2 (1.4)	0	0	0	16 (11.6)
Paresthaesia	10 (7.2)	5 (3.6)	1 (0.7)	0	0	16 (11.6)
Chest pain	7 (5.1)	7 (5.1)	1 (0.7)	0	0	15 (10.9)
Haemoptysis	7 (5.1)	4 (2.9)	1 (0.7)	0	2 (1.4)	14 (10.1)
Weight decreased	7 (5.1)	7 (5.1)	0	0	0	14 (10.1)
Headache	6 (4.3)	4 (2.9)	2 (1.4)	0	0	12 (8.7)
Pain in extremity	3 (2.2)	4 (2.9)	2 (1.4)	1 (0.7)	0	10 (7.2)
Hyperglycaemia	1 (0.7)	3 (2.2)	2 (1.4)	0	0	6 (4.3)

Within each arm, events are listed in order of decreasing overall frequency.
MedDRA (version 14.0) coding dictionary applied.
CTCAE = Common Terminology Criteria for Adverse Events; HbA1c = glycosylated hemoglobin 1C; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects per treatment arm; n = number of subjects per treatment.

Table 13. Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade Occurring in ≥10% of Subjects in Either Arm With Baseline HbA1c ≥5.7% (All Causalities, All Cycles)

Preferred Term[a]	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Arm A (N=194)						
Any adverse event	4 (2.1)	23 (11.9)	45 (23.2)	25 (12.9)	93 (47.9)	190 (97.9)
Nausea	51 (26.3)	30 (15.5)	6 (3.1)	0	0	87 (44.8)
Decreased appetite	29 (14.9)	39 (20.1)	16 (8.2)	0	0	84 (43.3)
Alopecia	36 (18.6)	39 (20.1)	3 (1.5)	0	0	78 (40.2)
Diarrhoea	31 (16.0)	26 (13.4)	9 (4.6)	1 (0.5)	0	67 (34.5)
Disease progression	0	0	0	1 (0.5)	65 (33.5)	66 (34.0)
Fatigue	19 (9.8)	35 (18.0)	11 (5.7)	0	0	65 (33.5)
Vomiting	31 (16.0)	20 (10.3)	5 (2.6)	0	0	56 (28.9)
Anaemia	12 (6.2)	32 (16.5)	8 (4.1)	2 (1.0)	0	54 (27.8)
Asthenia	10 (5.2)	21 (10.8)	18 (9.3)	3 (1.5)	0	52 (26.8)
Hyperglycaemia	9 (4.6)	12 (6.2)	23 (11.9)	5 (2.6)	0	49 (25.3)
Neutropenia	3 (1.5)	5 (2.6)	14 (7.2)	26 (13.4)	0	48 (24.7)
Weight decreased	14 (7.2)	22 (11.3)	11 (5.7)	0	0	47 (24.2)
Cough	29 (14.9)	9 (4.6)	4 (2.1)	0	0	42 (21.6)
Neuropathy peripheral	21 (10.8)	12 (6.2)	9 (4.6)	0	0	42 (21.6)
Constipation	25 (12.9)	13 (6.7)	1 (0.5)	0	0	39 (20.1)
Dyspnea	10 (5.2)	18 (9.3)	6 (3.1)	3 (1.5)	0	37 (19.1)
Thrombocytopenia	11 (5.7)	8 (4.1)	12 (6.2)	6 (3.1)	0	37 (19.1)
Arthralgia	18 (9.3)	8 (4.1)	2 (1.0)	0	0	28 (14.4)
Chest pain	9 (4.6)	17 (8.8)	2 (1.0)	0	0	28 (14.4)
Dizziness	18 (9.3)	10 (5.2)	0	0	0	28 (14.4)
Haemoptysis	15 (7.7)	7 (3.6)	2 (1.0)	0	4 (2.1)	28 (14.4)
Dehydration	4 (2.1)	11 (5.7)	11 (5.7)	0	0	26 (13.4)
Peripheral sensory neuropathy	12 (6.2)	8 (4.1)	6 (3.1)	0	0	26 (13.4)
Myalgia	16 (8.2)	8 (4.1)	1 (0.5)	0	0	25 (12.9)
Stomatitis	19 (9.8)	4 (2.1)	2 (1.0)	0	0	25 (12.9)
Pyrexia	18 (9.3)	6 (3.1)	0	0	0	24 (12.4)
Dysgaeusia	9 (4.6)	12 (6.2)	0	0	0	21 (10.8)
Mucosal inflammation	9 (4.6)	10 (5.2)	2 (1.0)	0	0	21 (10.8)
Pneumonia	1 (0.5)	6 (3.1)	6 (3.1)	4 (2.1)	3 (1.5)	20 (10.3)
Insomnia	10 (5.2)	8 (4.1)	1 (0.5)	0	0	19 (9.8)
Arm B (N=171)						
Any adverse event	6 (3.5)	34 (19.9)	33 (19.3)	27 (15.8)	64 (37.4)	164 (95.9)
Alopecia	27 (15.8)	38 (22.2)	3(1.8)	0	0	68 (39.8)
Disease progression	0	0	0	0	50 (29.2)	50 (29.2)
Fatigue	22 (12.9)	20 (11.7)	6 (3.5)	0	0	48 (28.1)
Nausea	31 (18.1)	17 (9.9)	0	0	0	48 (28.1)
Anaemia	3 (1.8)	30 (17.5)	8 (4.7)	0	0	41 (24.0)
Neutropenia	1 (0.6)	4 (2.3)	15 (8.8)	19 (11.1)	0	39 (22.8)
Dyspnea	9 (5.3)	19 (11.1)	9 (5.3)	1 (0.6)	0	38 (22.2)
Neuropathy peripheral	13 (7.6)	11 (6.4)	8 (4.7)	2 (1.2)	0	34 (19.9)
Asthenia	9 (5.3)	14 (8.2)	10 (5.8)	0	0	33 (19.3)
Constipation	20 (11.7)	11 (6.4)	1 (0.6)	0	0	32 (18.7)
Decreased appetite	18 (10.5)	11 (6.4)	2 (1.2)	0	0	31 (18.1)
Cough	16 (9.4)	11 (6.4)	1 (0.6)	0	0	28 (16.4)
Arthralgia	10 (5.8)	16 (9.4)	0	0	0	26 (15.2)

Table 13. Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade Occurring in ≥10% of Subjects in Either Arm With Baseline HbA1c ≥5.7% (All Causalities, All Cycles)

Preferred Term[a]	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Peripheral sensory neuropathy	12 (7.0)	10 (5.8)	4 (2.3)	0	0	26 (15.2)
Myalgia	15 (8.8)	8 (4.7)	0	0	0	23 (13.5)
Thrombocytopenia	5 (2.9)	12 (7.0)	5 (2.9)	1 (0.6)	0	23 (13.5)
Vomiting	13 (7.6)	7 (4.1)	2 (1.2)	0	0	22 (12.9)
Diarrhoea	10 (5.8)	9 (5.3)	1 (0.6)	0	0	20 (11.7)
Dizziness	15 (8.8)	3 (1.8)	0	0	0	18 (10.5)
Insomnia	13 (7.6)	4 (2.3)	1 (0.6)	0	0	18 (10.5)
Chest pain	5 (2.9)	9 (5.3)	1 (0.6)	0	0	15 (8.8)
Pyrexia	12 (7.0)	3 (1.8)	0	0	0	15 (8.8)
Pneumonia	1 (0.6)	8 (4.7)	3 (1.8)	1 (0.6)	1 (0.6)	14 (8.2)
Weight decreased	10 (5.8)	3 (1.8)	1 (0.6)	0	0	14 (8.2)
Haemoptysis	7 (4.1)	4 (2.3)	0	0	1 (0.6)	12 (7.0)
Hyperglycaemia	3 (1.8)	7 (4.1)	0	0	0	10 (5.8)
Dehydration	1 (0.6)	3 (1.8)	1 (0.6)	0	0	5 (2.9)
Dysgeusia	4 (2.3)	1 (0.6)	0	0	0	5 (2.9)
Stomatitis	5 (2.9)	0	0	0	0	5 (2.9)
Mucosal inflammation	2 (1.2)	0	0	0	0	2 (1.2)

Within each arm, events are listed in order of decreasing overall frequency.
MedDRA (version 14.0) coding dictionary applied.
CTCAE = common terminology criteria for adverse events; HbA1c = glycosylated hemoglobin 1c; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects per treatment arm; n = number of subjects per treatment.

Adverse Events by Baseline Total IGF-1 Subgroup

An analysis was performed to compare AEs between subjects who had a baseline total IGF-1 ≥120 ng/mL with subjects who had a baseline total IGF-1 <120 ng/mL. These data are presented by preferred term and CTCAE grade for all AEs occurring in ≥10% of subjects in either treatment arm in Table 14 (total IGF-1 <120 ng/mL) and Table 15 (total IGF-1 ≥120 ng/mL). When all AEs were considered, regardless of CTCAE grade, the baseline total IGF-1 level did not have any meaningful relationship with the frequency or nature of AEs. However, subjects in Arm A with baseline total IGF-1 <120 ng/mL experienced more Grade 5 AEs than other subjects, predominantly DP (Table 16).

Table 14. Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade Occurring in ≥10% of Subjects in Either Arm With Baseline Total IGF-1 <120 ng/mL (All Causalities, All Cycles)

Preferred Term[a]	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Arm A (N=192)						
Any AE	2 (1.0)	20 (10.4)	37 (19.3)	22 (11.5)	108 (56.3)	189 (98.4)
Decreased appetite	25 (13.0)	38 (19.8)	18 (9.4)	0	0	81 (42.2)
Alopecia	33 (17.2)	42 (21.9)	2 (1.0)	0	0	77 (40.1)
Nausea	38 (19.8)	32 (16.7)	7 (3.6)	0	0	77 (40.1)
Disease progression	0	0	0	0	73 (38.0)	73 (38.0)
Fatigue	19 (9.9)	37 (19.3)	14 (7.3)	1 (0.5)	0	71 (37.0)
Anaemia	12 (6.3)	38 (19.8)	10 (5.2)	4 (2.1)	0	64 (33.3)
Diarrhoea	26 (13.5)	24 (12.5)	7 (3.6)	1 (0.5)	0	58 (30.2)
Vomiting	21 (10.9)	21 (10.9)	4 (2.1)	0	0	46 (24.0)
Asthenia	8 (4.2)	19 (9.9)	15 (7.8)	3 (1.6)	0	45 (23.4)
Hyperglycaemia	9 (4.7)	10 (5.2)	21 (10.9)	4 (2.1)	0	44 (22.9)
Thrombocytopenia	8 (4.2)	14 (7.3)	14 (7.3)	8 (4.2)	0	44 (22.9)
Neutropenia	0	6 (3.1)	12 (6.3)	24 (12.5)	1 (0.5)	43 (22.4)
Cough	28 (14.6)	12 (6.3)	2 (1.0)	0	0	42 (21.9)
Constipation	23 (12.0)	13 (6.8)	3 (1.6)	0	0	39 (20.3)
Weight decreased	13 (6.8)	20 (10.4)	6 (3.1)	0	0	39 (20.3)
Neuropathy peripheral	12 (6.3)	11 (5.7)	8 (4.2)	0	0	31 (16.1)
Dyspnea	11 (5.7)	9 (4.7)	6 (3.1)	3 (1.6)	0	29 (15.1)
Dehydration	3 (1.6)	13 (6.8)	9 (4.7)	2 (1.0)	0	27 (14.1)
Arthralgia	16 (8.3)	8 (4.2)	2 (1.0)	0	0	26 (13.5)
Chest pain	7 (3.6)	19 (9.9)	0	0	0	26 (13.5)
Haemoptysis	15 (7.8)	5 (2.6)	1 (0.5)	0	2 (1.0)	23 (12.0)
Peripheral sensory neuropathy	10 (5.2)	5 (2.6)	7 (3.6)	0	0	22 (11.5)
Pneumonia	0	5 (2.6)	7 (3.6)	5 (2.6)	5 (2.6)	22 (11.5)
Headache	13 (6.8)	8 (4.2)	0	0	0	21 (10.9)
Rash	14 (7.3)	7 (3.6)	0	0	0	21 (10.9)
Insomnia	13 (6.8)	7 (3.6)	0	0	0	20 (10.4)
Dizziness	11 (5.7)	8 (4.2)	0	0	0	19 (9.9)
Myalgia	10 (5.2)	7 (3.6)	1 (0.5)	0	0	18 (9.4)
Paraesthesia	10 (5.2)	8 (4.2)	0	0	0	18 (9.4)
Leukopaenia	1 (0.5)	2 (1.0)	6 (3.1)	4 (2.1)	0	13 (6.8)
Arm B (N=183)						
Any adverse event	4 (2.2)	37 (20.2)	40 (21.9)	29 (15.8)	68 (37.2)	178 (97.3)
Alopecia	26 (14.2)	60 (32.8)	3 (1.6)	1 (0.5)	0	90 (49.2)
Anemia	8 (4.4)	36 (19.7)	13 (7.1)	0	0	57 (31.1)
Fatigue	24 (13.1)	19 (10.4)	8 (4.4)	2 (1.1)	0	53 (29.0)
Nausea	34 (18.6)	17 (9.3)	2 (1.1)	0	0	53 (29.0)
Disease progression	0	0	0	0	48 (26.2)	48 (26.2)
Neutropenia	2 (1.1)	6 (3.3)	18 (9.8)	21 (11.5)	0	47 (25.7)
Decreased appetite	28 (15.3)	14 (7.7)	4 (2.2)	0	0	46 (25.1)
Dyspnea	17 (9.3)	13 (7.1)	11 (6.0)	1 (0.5)	0	42 (23.0)
Asthenia	8 (4.4)	21 (11.5)	8 (4.4)	1 (0.5)	0	38 (20.8)
Constipation	24 (13.1)	9 (4.9)	2 (1.1)	0	0	35 (19.1)
Peripheral sensory neuropathy	19 (10.4)	9 (4.9)	5 (2.7)	0	0	33 (18.0)
Neuropathy peripheral	11 (6.0)	9 (4.9)	9 (4.9)	1 (0.5)	0	30 (16.4)
Thrombocytopenia	10 (5.5)	10 (5.5)	5 (2.7)	5 (2.7)	0	30 (16.4)
Arthralgia	14 (7.7)	14 (7.7)	0	0	0	28 (15.3)

Table 14. Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade Occurring in ≥10% of Subjects in Either Arm With Baseline Total IGF-1 <120 ng/mL (All Causalities, All Cycles)

Preferred Term[a]	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Diarrhoea	15 (8.2)	10 (5.5)	1 (0.5)	0	0	26 (14.2)
Cough	14 (7.7)	10 (5.5)	1 (0.5)	0	0	25 (13.7)
Leukopaenia	7 (3.8)	5 (2.7)	9 (4.9)	3 (1.6)	0	24 (13.1)
Myalgia	15 (8.2)	8 (4.4)	0	0	0	23 (12.6)
Chest pain	7 (3.8)	13 (7.1)	2 (1.1)	0	0	22 (12.0)
Paraesthesia	14 (7.7)	7 (3.8)	1 (0.5)	0	0	22 (12.0)
Vomiting	14 (7.7)	7 (3.8)	1 (0.5)	0	0	22 (12.0)
Dizziness	15 (8.2)	5 (2.7)	0	0	0	20 (10.9)
Insomnia	14 (7.7)	3 (1.6)	1 (0.5)	0	0	18 (9.8)
Haemoptysis	10 (5.5)	6 (3.3)	0	0	1 (0.5)	17 (9.3)
Weight decreased	8 (4.4)	7 (3.8)	0	0	0	15 (8.2)
Pneumonia	2 (1.1)	4 (2.2)	6 (3.3)	1 (0.5)	1 (0.5)	14 (7.7)
Hyperglycaemia	4 (2.2)	8 (4.4)	0	0	0	12 (6.6)
Rash	10 (5.5)	2 (1.1)	0	0	0	12 (6.6)
Headache	6 (3.3)	4 (2.2)	1 (0.5)	0	0	11 (6.1)
Dehydration	0	5 (2.7)	0	0	1 (0.5)	6 (3.3)

Within each arm, events are listed in order of decreasing overall frequency.
MedDRA (version 14.0) coding dictionary applied.
CTCAE = common terminology criteria for adverse events; IGF-1 = insulin like growth factor-1; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects per treatment arm; n = number of subjects per treatment.

Table 15. Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade Occurring in ≥10% of Subjects in Either Arm With Baseline Total IGF-1 ≥120 ng/mL (All Causalities, All Cycles)

Preferred Term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Arm A (N=120)						
Any adverse event	5 (4.2)	18 (15.0)	30 (25.0)	17 (14.2)	45 (37.5)	115 (95.8)
Alopecia	22 (18.3)	29 (24.2)	3 (2.5)	1 (0.8)	0	55 (45.8)
Nausea	27 (22.5)	13 (10.8)	4 (3.3)	0	0	44 (36.7)
Decreased appetite	19 (15.8)	18 (15.0)	5 (4.2)	0	0	42 (35.0)
Diarrhoea	17 (14.2)	15 (12.5)	5 (4.2)	0	0	37 (30.8)
Fatigue	11 (9.2)	19 (15.8)	5 (4.2)	1 (0.8)	0	36 (30.0)
Hyperglycemia	6 (5.0)	10 (8.3)	14 (11.7)	3 (2.5)	0	33 (27.5)
Disease progression	0	0	0	1 (0.8)	31 (25.8)	32 (26.7)
Vomiting	15 (12.5)	12 (10.0)	3 (2.5)	0	0	30 (25.0)
Neutropenia	3 (2.5)	2 (1.7)	8 (6.7)	16 (13.3)	0	29 (24.2)
Dyspnea	13 (10.8)	12 (10.0)	2 (1.7)	0	0	27 (22.5)
Neuropathy peripheral	12 (10.0)	10 (8.3)	5 (4.2)	0	0	27 (22.5)
Asthenia	5 (4.2)	12 (10.0)	7 (5.8)	1 (0.8)	0	25 (20.8)
Weight decreased	11 (9.2)	9 (7.5)	4 (3.3)	0	0	24 (20.0)
Anaemia	6 (5.0)	13 (10.8)	4 (3.3)	0	0	23 (19.2)
Cough	11 (9.2)	6 (5.0)	3 (2.5)	0	0	20 (16.7)
Constipation	14 (11.7)	5 (4.2)	0	0	0	19 (15.8)
Arthralgia	11 (9.2)	7 (5.8)	0	0	0	18 (15.0)
Chest pain	8 (6.7)	7 (5.8)	3 (2.5)	0	0	18 (15.0)
Myalgia	14 (11.7)	4 (3.3)	0	0	0	18 (15.0)
Dizziness	12 (10.0)	5 (4.2)	0	0	0	17 (14.2)
Peripheral sensory neuropathy	8 (6.7)	6 (5.0)	2 (1.7)	0	0	16 (13.3)
Thrombocytopenia	5 (4.2)	6 (5.0)	3 (2.5)	2 (1.7)	0	16 (13.3)
Haemoptysis	6 (5.0)	3 (2.5)	2 (1.7)	0	3 (2.5)	14 (11.7)
Headache	8 (6.7)	5 (4.2)	1 (0.8)	0	0	14 (11.7)
Pain in extremity	8 (6.7)	5 (4.2)	1 (0.8)	0	0	14 (11.7)
Pyrexia	8 (6.7)	2 (1.7)	0	0	0	10 (8.3)
Arm B (N=96)						
Any AE	4 (4.2)	21 (21.9)	13 (13.5)	18 (18.8)	35 (36.5)	91 (94.8)
Alopecia	17 (17.7)	20 (20.8)	2 (2.1)	1 (1.0)	0	40 (41.7)
Nausea	25 (26.0)	9 (9.4)	0	0	0	34 (35.4)
Disease progression	0	0	0	0	25 (26.0)	25 (26.0)
Neuropathy peripheral	11 (11.5)	8 (8.3)	4 (4.2)	1 (1.0)	0	24 (25.0)
Cough	14 (14.6)	7 (7.3)	2 (2.1)	0	0	23 (24.0)
Fatigue	10 (10.4)	11 (11.5)	2 (2.1)	0	0	23 (24.0)
Neutropenia	0	1 (1.0)	9 (9.4)	11 (11.5)	0	21 (21.9)
Anaemia	3 (3.1)	14 (14.6)	2 (2.1)	0	0	19 (19.8)
Arthralgia	10 (10.4)	9 (9.4)	0	0	0	19 (19.8)
Constipation	11 (11.5)	7 (7.3)	0	0	0	18 (18.8)
Decreased appetite	6 (6.3)	11 (11.5)	1 (1.0)	0	0	18 (18.8)
Vomiting	11 (11.5)	3 (3.1)	2 (2.1)	0	0	16 (16.7)
Dyspnea	3 (3.1)	8 (8.3)	2 (2.1)	2 (2.1)	0	15 (15.6)
Myalgia	13 (13.5)	2 (2.1)	0	0	0	15 (15.6)
Asthenia	3 (3.1)	7 (7.3)	3 (3.1)	0	0	13 (13.5)
Pyrexia	10 (10.4)	3 (3.1)	0	0	0	13 (13.5)
Thrombocytopenia	2 (2.1)	7 (7.3)	4 (4.2)	0	0	13 (13.5)
Pain in extremity	5 (5.2)	5 (5.2)	1 (1.0)	0	0	11 (11.5)

Table 15. Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade Occurring in ≥10% of Subjects in Either Arm With Baseline Total IGF-1 ≥120 ng/mL (All Causalities, All Cycles)

Preferred Term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Chest pain	5 (5.2)	5 (5.2)	0	0	0	10 (10.4)
Diarrhoea	3 (3.1)	7 (7.3)	0	0	0	10 (10.4)
Peripheral sensory neuropathy	6 (6.3)	4 (4.2)	0	0	0	10 (10.4)
Weight decreased	8 (8.3)	2 (2.1)	0	0	0	10 (10.4)
Dizziness	5 (5.2)	2 (2.1)	0	0	0	7 (7.3)
Haemoptysis	4 (4.2)	2 (2.1)	0	0	0	6 (6.3)
Headache	1 (1.0)	3 (3.1)	1 (1.0)	0	0	5 (5.2)
Hyperglycaemia	0	3 (3.1)	1 (1.0)	0	0	4 (4.2)

Within each arm, events are listed in order of decreasing overall frequency.
MedDRA (version 14.0) coding dictionary applied.
CTCAE = common terminology criteria for adverse events; IGF-1 = insulin-like growth factor-1; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects per treatment arm; n = number of subjects per treatment.

Table 16. Subjects Experiencing CTCAE Grade 5 Treatment-Emergent Adverse Events by Treatment Group and Baseline Total IGF-1 (All Causalities, All Cycles)

Baseline Total IGF-1	Treatment	
	Arm A Figitumumab + Paclitaxel and Carboplatin n/N (%)	Arm B Paclitaxel and Carboplatin n/N (%)
Any Grade 5 TEAE		
<120 ng/mL	108/192 (56.3)	68/183 (37.2)
≥120 ng/mL	45/120 (37.5)	35/96 (36.5)

CTCAE = common terminology criteria for adverse events; -1 = insulin-like growth factor-1; N = total number of subjects per treatment arm; n = number of subjects per treatmentIGF; TEAE = treatment-emergent adverse event

Subjects with treatment-emergent SAE by special organ class and preferred term (all causalities) is presented in Table 17.

Table 17. Treatment-Emergent Serious Adverse Events by Special 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 n (%)	Arm B n (%)
Number (%) of subjects:		
Evaluable for adverse events	338	333
With adverse events	227 (65.7)	170 (51.1)
Blood and lymphatic system disorders	15 (4.4)	26 (7.8)
Anaemia	2 (0.6)	9 (2.7)
Bone marrow failure	1 (0.3)	0
Febrile bone marrow aplasia	0	1 (0.3)
Febrile neutropenia	5 (1.5)	11 (3.3)
Granulocytopaenia	1 (0.3)	2 (0.6)
Leukopenia	1 (0.3)	1 (0.3)
Neutropenia	5 (1.5)	1 (0.3)
Pancytopenia	2 (0.6)	0
Thrombocytopenia	2 (0.6)	5 (1.5)
Cardiac disorders	16 (4.7)	8 (2.4)
Angina pectoris	1 (0.3)	1 (0.3)
Arrhythmia	1 (0.3)	0
Atrial fibrillation	1 (0.3)	1 (0.3)
Cardiac arrest	1 (0.3)	0
Cardiac failure	0	1 (0.3)
Cardiac failure congestive	0	1 (0.3)
Cardio-respiratory arrest	1 (0.3)	1 (0.3)
Cardiopulmonary failure	3 (0.9)	1 (0.3)
Cardiotoxicity	1 (0.3)	0
Cardiovascular disorder	2 (0.6)	0
Myocardial infarction	2 (0.6)	2 (0.6)
Myocardial ischaemia	2 (0.6)	0
Tachyarrhythmia	1 (0.3)	0
Ear and labyrinth disorders	1 (0.3)	0
Vertigo	1 (0.3)	0
Endocrine disorders	2 (0.6)	0
Adrenal insufficiency	1 (0.3)	0
Inappropriate antidiuretic hormone secretion	1 (0.3)	0
Gastrointestinal disorders	25 (7.4)	7 (2.1)
Abdominal pain	1 (0.3)	0
Abdominal pain upper	1 (0.3)	0
Anal fistula	1 (0.3)	0
Diarrhoea	9 (2.7)	0
Duodenal ulcer	0	1 (0.3)
Dysphagia	1 (0.3)	1 (0.3)
Gastric disorder	1 (0.3)	0
Gastric perforation	1 (0.3)	0
Gastrointestinal haemorrhage	2 (0.6)	1 (0.3)
Glossitis	1 (0.3)	0
Haematemesis	0	1 (0.3)
Haemorrhoids	1 (0.3)	0
Nausea	3 (0.9)	2 (0.6)
Oesophageal perforation	1 (0.3)	0
Oesophagitis	1 (0.3)	0
Peptic ulcer	0	1 (0.3)

Table 17. Treatment-Emergent Serious Adverse Events by Special 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 n (%)	Arm B n (%)
Stomatitis	1 (0.3)	0
Upper gastrointestinal haemorrhage	1 (0.3)	0
Vomiting	7 (2.1)	1 (0.3)
General disorders and administration site conditions	136 (40.2)	104 (31.2)
Adverse drug reaction	0	1 (0.3)
Asthenia	11 (3.3)	2 (0.6)
Chest pain	3 (0.9)	0
Condition aggravated	1 (0.3)	0
Death	3 (0.9)	3 (0.9)
Disease progression	115 (34.0)	90 (27.0)
Drug intolerance	0	2 (0.6)
Fatigue	0	2 (0.6)
General physical health deterioration	8 (2.4)	5 (1.5)
Malaise	1 (0.3)	1 (0.3)
Multi-organ failure	1 (0.3)	0
Pain	3 (0.9)	3 (0.9)
Performance status decreased	1 (0.3)	2 (0.6)
Pyrexia	4 (1.2)	4 (1.2)
Sudden death	1 (0.3)	1 (0.3)
Hepatobiliary disorders	2 (0.6)	1 (0.3)
Cholecystitis	1 (0.3)	0
Hyperbilirubinaemia	1 (0.3)	1 (0.3)
Infections and infestations	39 (11.5)	20 (6.0)
Anal abscess	1 (0.3)	0
Bone abscess	0	1 (0.3)
Bronchitis	1 (0.3)	0
Bronchopulmonary aspergillosis	1 (0.3)	0
Candidiasis	1 (0.3)	0
Cellulitis	1 (0.3)	0
Diverticulitis	2 (0.6)	0
Erysipelas	0	1 (0.3)
Gastroenteritis	1 (0.3)	1 (0.3)
Infection	1 (0.3)	1 (0.3)
Lung abscess	1 (0.3)	1 (0.3)
Lung infection	2 (0.6)	0
Neutropenic sepsis	1 (0.3)	0
Oral candidiasis	1 (0.3)	0
Pneumonia	21 (6.2)	12 (3.6)
Pseudomonas infection	1 (0.3)	0
Pyothorax	1 (0.3)	0
Respiratory tract infection	1 (0.3)	1 (0.3)
Sepsis	4 (1.2)	0
Septic shock	3 (0.9)	1 (0.3)
Sputum purulent	1 (0.3)	0
Staphylococcal infection	1 (0.3)	0
Urinary tract infection	0	2 (0.6)
Injury, poisoning and procedural complications	6 (1.8)	3 (0.9)
Fall	1 (0.3)	1 (0.3)
Femoral neck fracture	0	1 (0.3)

Table 17. Treatment-Emergent Serious Adverse Events by Special 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 n (%)	Arm B n (%)
Hip fracture	3 (0.9)	0
Overdose	1 (0.3)	0
Poisoning	0	1 (0.3)
Scapula fracture	1 (0.3)	0
Toxicity to various agents	1 (0.3)	0
Investigations	5 (1.5)	4 (1.2)
Blood creatinine increased	1 (0.3)	1 (0.3)
Blood glucose increased	1 (0.3)	0
Eastern cooperative oncology group performance status worsened	0	1 (0.3)
General physical condition abnormal	1 (0.3)	0
Haemoglobin decreased	0	2 (0.6)
Platelet count decreased	1 (0.3)	0
Weight decreased	2 (0.6)	0
Metabolism and nutrition disorders	32 (9.5)	6 (1.8)
Cachexia	1 (0.3)	0
Decreased appetite	5 (1.5)	0
Dehydration	15 (4.4)	2 (0.6)
Diabetes mellitus	1 (0.3)	0
Failure to thrive	1 (0.3)	0
Hypercalcaemia	3 (0.9)	2 (0.6)
Hyperglycaemia	11 (3.3)	1 (0.3)
Hyperkalaemia	1 (0.3)	0
Hypoglycaemia	0	1 (0.3)
Hypokalaemia	2 (0.6)	0
Hyponatraemia	1 (0.3)	1 (0.3)
Malnutrition	0	1 (0.3)
Type 2 diabetes mellitus	1 (0.3)	0
Musculoskeletal and connective tissue disorders	5 (1.5)	3 (0.9)
Back pain	1 (0.3)	1 (0.3)
Pain in extremity	2 (0.6)	1 (0.3)
Pathological fracture	1 (0.3)	0
Rhabdomyolysis	1 (0.3)	0
Systemic lupus erythematosus	0	1 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10 (3.0)	4 (1.2)
Adenocarcinoma pancreas	0	1 (0.3)
Genitourinary tract neoplasm	1 (0.3)	0
Lung cancer metastatic	1 (0.3)	0
Lung neoplasm malignant	3 (0.9)	0
Metastases to central nervous system	1 (0.3)	0
Metastases to meninges	1 (0.3)	0
Non-small cell lung cancer	2 (0.6)	3 (0.9)
Tongue neoplasm malignant stage unspecified	1 (0.3)	0
Nervous system disorders	13 (3.8)	10 (3.0)
Cerebral haemorrhage	0	1 (0.3)
Cerebral infarction	1 (0.3)	1 (0.3)
Cerebrovascular accident	2 (0.6)	3 (0.9)
Convulsion	2 (0.6)	0

Table 17. Treatment-Emergent Serious Adverse Events by Special 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 n (%)	Arm B n (%)
Dizziness	1 (0.3)	0
Hemiparesis	1 (0.3)	1 (0.3)
Hydrocephalus	1 (0.3)	0
Ischaemic stroke	0	1 (0.3)
Lethargy	1 (0.3)	0
Neuropathy peripheral	1 (0.3)	2 (0.6)
Neurotoxicity	1 (0.3)	0
Spinal cord compression	1 (0.3)	0
Syncope	2 (0.6)	1 (0.3)
Tremor	1 (0.3)	0
Psychiatric disorders	8 (2.4)	2 (0.6)
Completed suicide	0	1 (0.3)
Confusional state	3 (0.9)	0
Delirium	1 (0.3)	1 (0.3)
Depression	1 (0.3)	0
Hallucination	1 (0.3)	0
Insomnia	1 (0.3)	0
Mental status changes	2 (0.6)	0
Renal and urinary disorders	7 (2.1)	4 (1.2)
Haematuria	0	1 (0.3)
Renal colic	1 (0.3)	0
Renal failure	2 (0.6)	2 (0.6)
Renal failure acute	2 (0.6)	1 (0.3)
Renal impairment	1 (0.3)	0
Urinary retention	1 (0.3)	0
Respiratory, thoracic and mediastinal disorders	35 (10.4)	30 (9.0)
Acute respiratory failure	2 (0.6)	1 (0.3)
Asphyxia	0	1 (0.3)
Chronic obstructive pulmonary disease	2 (0.6)	1 (0.3)
Cough	0	1 (0.3)
Dyspnoea	6 (1.8)	6 (1.8)
Dyspnoea exertional	1 (0.3)	0
Emphysema	1 (0.3)	0
Epistaxis	0	1 (0.3)
Haemoptysis	9 (2.7)	5 (1.5)
Hydropneumothorax	1 (0.3)	0
Hydrothorax	1 (0.3)	0
Hypoxia	1 (0.3)	0
Lung disorder	1 (0.3)	1 (0.3)
Mediastinal disorder	1 (0.3)	0
Obstructive airways disorder	0	1 (0.3)
Pleural effusion	1 (0.3)	2 (0.6)
Pneumomediastinum	1 (0.3)	0
Pneumonia aspiration	1 (0.3)	1 (0.3)
Pneumonitis	1 (0.3)	0
Pneumothorax	2 (0.6)	1 (0.3)
Pulmonary embolism	7 (2.1)	6 (1.8)
Pulmonary haemorrhage	2 (0.6)	1 (0.3)
Pulmonary oedema	0	1 (0.3)

Table 17. Treatment-Emergent Serious Adverse Events by Special 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 n (%)	Arm B n (%)
Respiratory failure	2 (0.6)	2 (0.6)
Skin and subcutaneous tissue disorders	1 (0.3)	0
Rash	1 (0.3)	0
Vascular disorders	10 (3.0)	6 (1.8)
Arterial thrombosis limb	0	1 (0.3)
Arteritis	0	1 (0.3)
Deep vein thrombosis	1 (0.3)	2 (0.6)
Haemorrhage	2 (0.6)	0
Hypotension	3 (0.9)	0
Hypovolaemic shock	1 (0.3)	0
Orthostatic hypotension	1 (0.3)	0
Superior vena cava syndrome	0	1 (0.3)
Thrombosis	1 (0.3)	1 (0.3)
Vena cava thrombosis	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 (v14.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with specific event; v = version.

Deaths

Deaths during study treatment or within 28 days of last study treatment are summarized in Table 18. Note that in Arm A, there were an additional 5 treatment-related deaths, not reflected in Table 18, during the safety reporting period between 28 and 150 days after last study treatment. Thus, the total number of treatment related deaths was 17 (5.0%) in Arm A and 4 (1.2%) in Arm B. One additional subject was reported to have died within the safety reporting period since the database snapshot on 04 August 2011. Subject died due to cardiac failure, judged by the investigator as unrelated to any protocol treatment or procedure.

Table 18. Summary of Deaths Within 28 Days of Last Study Treatment—All Treated, As Treated

	Arm A Figitumumab + Paclitaxel and Carboplatin N=338 n (%)	Arm B Paclitaxel and Carboplatin N=333 n (%)
Deaths from all causes	44 (13.0)	31 (9.3)
Cause of death		
Disease under study	24 (7.1)	16 (4.8)
Study treatment toxicity	12 (3.6)	4 (1.2)
Adverse event	8 (2.4)	11 (3.3)
Deaths related to study treatment		
Related to carboplatin	8 (2.4)	4 (1.2)
Related to paclitaxel	7 (2.1)	4 (1.2)
Related to figitumumab	10 (3.0)	0

N = total number of subjects per treatment arm; n = number of subjects with deaths per treatment arm, per specified criteria.

Early study discontinuations due to AEs are presented in Table 4. In Arm A, discontinuations from figitumumab treatment were due to subject death (43 subjects, 12.7%) and objective progression or relapse (170 subjects, 50.3%). Twenty-two subjects (6.5%) in Arm A discontinued from figitumumab treatment due to a treatment-related AE, and 29 subjects (8.6%) in Arm A discontinued chemotherapy due to a chemotherapy drug-related AE. In Arm B, 31 subjects (9.3%) discontinued chemotherapy due to a chemotherapy drug-related AE.

Laboratory Results:

No additional CTCAE Grade 3 or 4 laboratory abnormality was reported. Laboratory results are similar to what has already been reported in last CSR dated and the impact of this additional data to the laboratory summary tables is minimal.

Abnormal hematology laboratory results are summarized by common terminology criteria (CTC) grade and treatment arm in Table 19.

Table 19. Summary of Laboratory Results by Maximum CTC Grade (Hematology, All Cycles)

Parameter	N	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Arm A						
Hemoglobin	334	160 (47.9)	121 (36.2)	23 (6.9)	5 (1.5)	309 (92.5)
Platelets	334	119 (35.6)	27 (8.1)	26 (7.8)	9 (2.7)	181 (54.2)
White blood cells	331	80 (24.2)	64 (19.3)	34 (10.3)	10 (3.0)	188 (56.8)
Neutrophils (absolute)	334	48 (14.4)	48 (14.4)	50 (15.0)	67 (20.1)	213 (63.8)
Lymphocytes (absolute)	334	72 (21.6)	53 (15.9)	31 (9.3)	3 (0.9)	159 (47.6)
Arm B						
Hemoglobin	323	149 (46.1)	115 (35.6)	30 (9.3)	1 (0.3)	295 (91.3)
Platelets	324	89 (27.5)	22 (6.8)	27 (8.3)	3 (0.9)	141 (43.5)
White blood cells	322	85 (26.4)	65 (20.2)	30 (9.3)	7 (2.2)	187 (58.1)
Neutrophils (absolute)	324	45 (13.9)	46 (14.2)	62 (19.1)	54 (16.7)	207 (63.9)
Lymphocytes (absolute)	324	76 (23.5)	56 (17.3)	40 (12.3)	7 (2.2)	179 (55.2)

CTC = Common Terminology Criteria; N = total number of subjects per treatment arm; n = number of subjects per treatment.

The incidence of hyperglycemia by CTC grade and treatment arm is summarized in Table 20.

Table 20. Summary of Hyperglycemia by Maximum CTC Grade (All Cycles, Laboratory and Adverse Event Data Combined)

Parameter	N	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Arm A						
Hyperglycemia	333	140 (42.0)	65 (19.5)	49 (14.7)	11 (3.3)	265 (79.6)
Arm B						
Hyperglycemia	329	139 (42.2)	45 (13.7)	10 (3.0)	0	194 (59.0)

Adverse events preferred terms: hyperglycemia, blood glucose increased, diabetes mellitus, diabetic ketoacidosis, diabetic hyperosmolar coma and AE lower level term: drug-induced hyperglycemia, hyperglycemia steroid-induced from adverse events data have been added to hyperglycemia.
AE=adverse event; CTC = Common Terminology Criteria, n = number of subjects; N = number of subjects who either were evaluable for laboratory glucose (hyperglycemia) or evaluable forAE.

CONCLUSIONS:

Based on review of the efficacy and safety data from a planned interim analysis of the study, the Data Safety Monitoring Committee found sufficient evidence to recommend closure of study A4021016 due to a survival hazard ratio in the experimental arm that crossed the prespecified futility boundary.

None of the efficacy endpoints analyzed (OS, PFS, and best OR) suggested that the addition of figitumumab to standard chemotherapy had any beneficial effect on DP or outcome.

- The study did not meet its primary objective of demonstrating an increase in OS from treatment with figitumumab and paclitaxel-carboplatin over paclitaxel-carboplatin alone in advanced non-adenocarcinoma NSCLC. The Kaplan-Meier estimate of the median OS was 8.6 months in Arm A and 9.8 months in Arm B. The hazard ratio (Arm A compared to Arm B) was 1.179 (95% CI: 0.990-1.404; p=0.064, 2-sided).

- The Kaplan-Meier estimate of the median PFS was 4.7 months in Arm A and 4.6 months in Arm B. The hazard ratio (Arm A compared to Arm B) was 1.103 (95% CI: 0.925-1.315; p=0.270, 2-sided).

In subjects with advanced non-adenocarcinoma NSCLC, figitumumab administered with standard doublet chemotherapy (paclitaxel and carboplatin) the following clinically significant safety findings were noted when compared with standard doublet chemotherapy alone.

- Regardless of causality, a greater percentage of subjects in Arm A had SAEs or Grade 5 AEs than in Arm B (65.7% versus 51.1% for SAEs and 48.8% versus 37.5% for Grade 5 AEs), respectively.

- More subjects in Arm A died of treatment related toxicity than subjects in Arm B, 17 subjects (5.0%) versus 4 subjects (1.2%), respectively.

- A larger percentage of subjects in Arm A had Grade 3/4 SAEs than in Arm B (34.0% versus 21.6%), respectively.

- Hyperglycemia, a known side-effect of figitumumab, occurred in 23.4% of Arm A subjects and 5.1% of Arm B subjects. A larger percentage of Arm A subjects reported Grade 3/4 hyperglycemia than in Arm B (12.4% versus 0.6%). There were no reports of Grade 5 hyperglycemia.

- A higher frequency of all causality AEs was noted for Arm A than Arm B: excluding DP, nausea (39.3% versus 30.9%), decreased appetite (38.5% versus 22.5%), fatigue (33.1% versus 25.8%), diarrhea (29.9% versus 13.5%), vomiting (25.1% versus 14.1%), hyperglycemia (23.4% versus 5.1%), weight decreased (19.5% versus 8.7%), stomatitis (9.2% versus 3.0%), and dehydration (11.5% versus 3.6%).

- Figitumumab in combination with paclitaxel and carboplatin may be more tolerable for subjects with low baseline HbA1c (<5.7%) or high baseline total IGF-1 (≥120 ng/mL) compared to subjects with HbA1c ≥5.7% or baseline total IGF-1 <120 ng/mL.

- Figitumumab has minimal risk of inducing ADAs following repeated administration.