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ORIGINAL REPORT

Randomized, Phase III Trial of First-Line Figitumumab in Combination With Paclitaxel and Carboplatin Versus Paclitaxel and Carboplatin Alone in Patients With Advanced Non–Small-Cell Lung Cancer

Corey J. Langer, Silvia Novello, Keunchil Park, Maciej Krzakowski, Daniel D. Karp, Tony Mok, Rebecca J. Benner, Judith R. Scranton, Anthony J. Olszanski, and Jacek Jassem

Corey J. Langer, University of Pennsylvania; Anthony J. Olszanski, Fox Chase Cancer Center, Philadelphia, PA; Daniel D. Karp, MD Anderson Center, Houston, TX; Rebecca J. Benner, Judith R. Scranton, Pfizer Oncology, Groton, CT; Silvia Novello, University of Turin, Orbassano, Italy; Keunchil Park, Sungkyunkwan University School of Medicine, Seoul, Korea; Maciej Krzakowski, The Maria Sklodowska-Curie Institute of Oncology, Warsaw; Jacek Jassem, Medical University of Gdansk, Gdansk, Poland; Tony Mok, Chinese University, Hong Kong, Special Administrative Region, People's Republic of China.

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Corresponding author: Corey J. Langer, MD, FACP, Professor of Medicine, Hematology-Oncology Division, University of Pennsylvania, 3400 Civic Center Blvd, 2 Perelman Center for Advanced Medicine, Philadelphia, PA 19104; e-mail: corey.langer@uphs.upenn.edu.

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ABSTRACT

Purpose
Figitumumab (CP-751,871), a fully human immunoglobulin G2 monoclonal antibody, inhibits the insulin-like growth factor 1 receptor (IGF-1R). Our multicenter, randomized, phase III study compared figitumumab plus chemotherapy with chemotherapy alone as first-line treatment in patients with advanced non–small-cell lung cancer (NSCLC).

Patients and Methods
Patients with stage IIIB/IV or recurrent NSCLC disease with nonadenocarcinoma histology received open-label figitumumab (20 mg/kg) plus paclitaxel (200 mg/m^2) and carboplatin (area under the concentration-time curve, 6 mg · min/mL) or paclitaxel and carboplatin alone once every 3 weeks for up to six cycles. The primary end point was overall survival (OS).

Results
Of 681 randomly assigned patients, 671 received treatment. The study was closed early by an independent Data Safety Monitoring Committee because of futility and an increased incidence of serious adverse events (SAEs) and treatment-related deaths with figitumumab. Median OS was 8.6 months for figitumumab plus chemotherapy and 9.8 months for chemotherapy alone (hazard ratio [HR], 1.18; 95% CI, 0.99 to 1.40; $P = .06$); median progression-free survival was 4.7 months (95% CI, 4.2 to 5.4) and 4.6 months (95% CI, 4.2 to 5.4), respectively (HR, 1.10; $P = .27$); the objective response rates were 33% and 35%, respectively. The respective rates of all-causality SAEs were 66% and 51%; $P < .01$). Treatment-related grade 5 adverse events were also more common with figitumumab (5% *v* 1%; $P < .01$).

Conclusion
Adding figitumumab to standard chemotherapy failed to increase OS in patients with advanced nonadenocarcinoma NSCLC. Further clinical development of figitumumab is not being pursued.

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INTRODUCTION

Metastatic non–small-cell lung cancer (NSCLC) is rarely curable and, despite significant treatment advances over the last decade, 5-year survival rates remain below 5%.[1] Current therapeutic options include histology-based chemotherapy, antiangiogenic agents, and targeted agents inhibiting epidermal growth factor receptor and anaplastic lymphoma kinase. Insulin-like growth factor 1 (IGF-1) receptor (IGF-1R) is a central component of cancer signal transduction pathways.[2] Expression of IGF-1R is detectable in 39% to 84% of advanced NSCLCs and is more frequently found in squamous cell lung cancer.[3] The prognostic significance of IGF-1R expression remains unclear. Several prospective studies suggest a relationship between circulating IGF-1 and cancer risk.[4,5]

Figitumumab (CP-751,871) is a fully human immunoglobulin G2 monoclonal antibody that inhibits IGF-1R. In phase I trials, it was well tolerated as a single agent and in combination with chemotherapy at 20 mg/kg every 3 weeks.[6,7] In a randomized phase II study of patients with treatment-naive advanced NSCLC, the originally reported objective response rate (ORR) was 54% with figitumumab 10 or 20 mg/kg plus full-dose paclitaxel and carboplatin, and 42% with chemotherapy alone. Median

progression-free survival (PFS) was initially reported as 5.0 months with figitumumab 20 mg/kg and 3.5 months with chemotherapy alone. No unexpected toxicities were observed. These findings prompted a prospective, randomized phase III trial of figitumumab plus paclitaxel and carboplatin compared with chemotherapy alone as first-line treatment for advanced NSCLC. However, the phase II data were subsequently retracted after a reanalysis revealed a lower ORR in both treatment arms (see Discussion).[8]

In this article, we report the results of the phase III trial, which was restricted to patients with nonadenocarcinoma histology based on an initial analysis of the phase II study that indicated potentially increased figitumumab efficacy in this subset.[8]

PATIENTS AND METHODS

Patients

Eligible patients were at least 18 years old with histologically or cytologically confirmed advanced NSCLC; documented American Joint Committee on Cancer[9] stage IIIB or metastatic (stage IV or recurrent) disease not amenable to curative treatment; and a primary histology of predominantly squamous cell, large cell, or adenosquamous carcinoma. Prior systemic treatment for NSCLC and previous or concurrent therapy with IGF-1R inhibitors or growth hormone agonists or antagonists were prohibited. Adjuvant chemotherapy was permitted if completed at least 12 months before randomization. Prior surgery or radiation therapy was permitted if completed at least 3 weeks before randomization, with all acute toxicities resolved to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 grade 1. Patients had to have an Eastern Cooperative Oncology Group performance status of 0 or 1 and adequate organ function. Exclusions included symptomatic CNS metastases, other active malignancies, uncontrolled hypertension, or uncontrolled diabetes (baseline glycosylated hemoglobin [$HbA1_c$] $> 8\%$).

The study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice guidelines, the declaration of Helsinki, and local regulatory requirements and laws. Institutional review board or independent ethics committee approval was required for each investigator and center. Written informed consent was obtained from all patients.

Study Design and Treatment

Patients were randomly assigned in a 1:1 ratio to open-label figitumumab plus paclitaxel and carboplatin (investigational arm) or paclitaxel and carboplatin alone (control arm), stratified by previous adjuvant chemotherapy, sex, and histology (squamous-cell *v* combined large-cell or adenosquamous cancer).

The primary end point was overall survival (OS), which was defined as time from randomization to death as a result of any cause. Secondary end points included PFS, ORR, and safety. The association between serum IGF-1 levels and OS was a preplanned exploratory objective.

All patients received carboplatin (area under the concentration-time curve, 6 mg · min/mL) and paclitaxel (200 mg/m^2) intravenously on day 1 once every 3 weeks for up to six cycles. In the investigational arm, patients also received figitumumab 20 mg/kg intravenously on day 1 of each 3-week cycle, for up to 17 cycles (approximately 1 year of treatment).

On the investigational arm, if paclitaxel and/or carboplatin were discontinued early, patients could continue single-agent figitumumab (once every 3 weeks) until disease progression or intolerance. Additional cycles were permitted in patients exhibiting response, based on agreement between the study sponsor and investigator. If figitumumab was discontinued, paclitaxel and carboplatin were continued for a maximum of six cycles until disease progression or intolerance. Standard supportive therapies were instituted in both arms. Guidelines for managing emergent hyperglycemia were provided, including immediate treatment, protocol-defined figitumumab-dosage modification, and continued oral glucose-lowering therapy if hyperglycemia was expected to continue.

Study Procedures

Tumor assessment was performed at baseline and every 6 weeks until radiologic disease progression or initiation of subsequent anticancer therapy using Response Evaluation Criteria in Solid Tumors version 1.0.[10] Adverse events were graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Clinical assessments, including hematology and serum chemistry, were performed at baseline, on day 1 of cycle 1 (all measurements), days 8 and 15 of cycle 1 (hematology only), on day 1 of each subsequent cycle, and at the end of treatment. Levels of $HbA1_c$ were measured at baseline, before cycle 4, and at the end of treatment.

Serum samples were collected within 2 hours before chemotherapy and/or figitumumab infusion at cycles 1 and 4 and at the end of treatment. Total IGF-1 levels were determined by immunochemiluminometric assay at MDS Pharma Services (now LabCorp; Mississauga, Ontario, Canada). An independent Data Safety Monitoring Committee (DSMC) monitored safety and efficacy.

Statistical Analysis

With one-sided .025 level testing and 90% power, 820 patients were needed to detect a 30% improvement for figitumumab plus chemotherapy over the median 10-month survival rate seen with paclitaxel plus carboplatin therapy (hazard ratio [HR], 0.77); 649 events were expected at full follow-up. The primary assessment was a log-rank test stratified by factors used in randomization. The analysis set included all randomly assigned patients on an intent-to-treat basis. Two-sided *P* values were determined.

Two interim analyses were planned after approximately one third and two thirds of the anticipated number of events had occurred. A Lan-DeMets spending function approach with O'Brien-Fleming stopping bounds (Appendix Table A1 [online-only]) was used to reject the null hypothesis (efficacy boundary) and the alternative hypothesis (futility boundary). Statistical analyses were conducted by Pfizer.

RESULTS

Patients and Treatment Exposure

Between April 2008 and September 2009, 681 patients from 163 sites in 25 countries were randomly assigned and 671 received treatment (figitumumab group, 338; control group, 333; Fig 1). Demographic and baseline characteristics were well balanced between treatment arms (Table 1). Patients' median age was 62 years. Most of the patients were men and most had stage IV disease. Patients in the figitumumab and control arms received a median of four and five cycles of chemotherapy, respectively (Table 2); 33% and 44%, respectively, completed six cycles of paclitaxel, and 34% and 46% completed six cycles of carboplatin. Figitumumab-treated patients received a median of four figitumumab cycles; 109 (32%) of 338 figitumumab-treated patients received four to six cycles, seven (2%) of 338 patients received 17 cycles, and four (1%) of 338 received more than 20 cycles. A total of 124 (37%) of 338 patients received figitumumab after completing or discontinuing chemotherapy (median of two maintenance cycles). Of these, 87 (26%) of 338 patients received figitumumab maintenance after six cycles (maintenance therapy could start earlier than cycle 6).

On DSMC advice, enrollment was suspended in September 2009 because of a higher number of serious adverse events (SAEs) and deaths in the figitumumab arm. The study was permanently closed to new accrual in December 2009, after the first interim analysis indicated that the addition of figitumumab was highly unlikely to meet the primary end point of improving OS over chemotherapy alone. Follow-up for OS continued until March 2011. The overall median follow-up time was 23.1 months (Table 3).

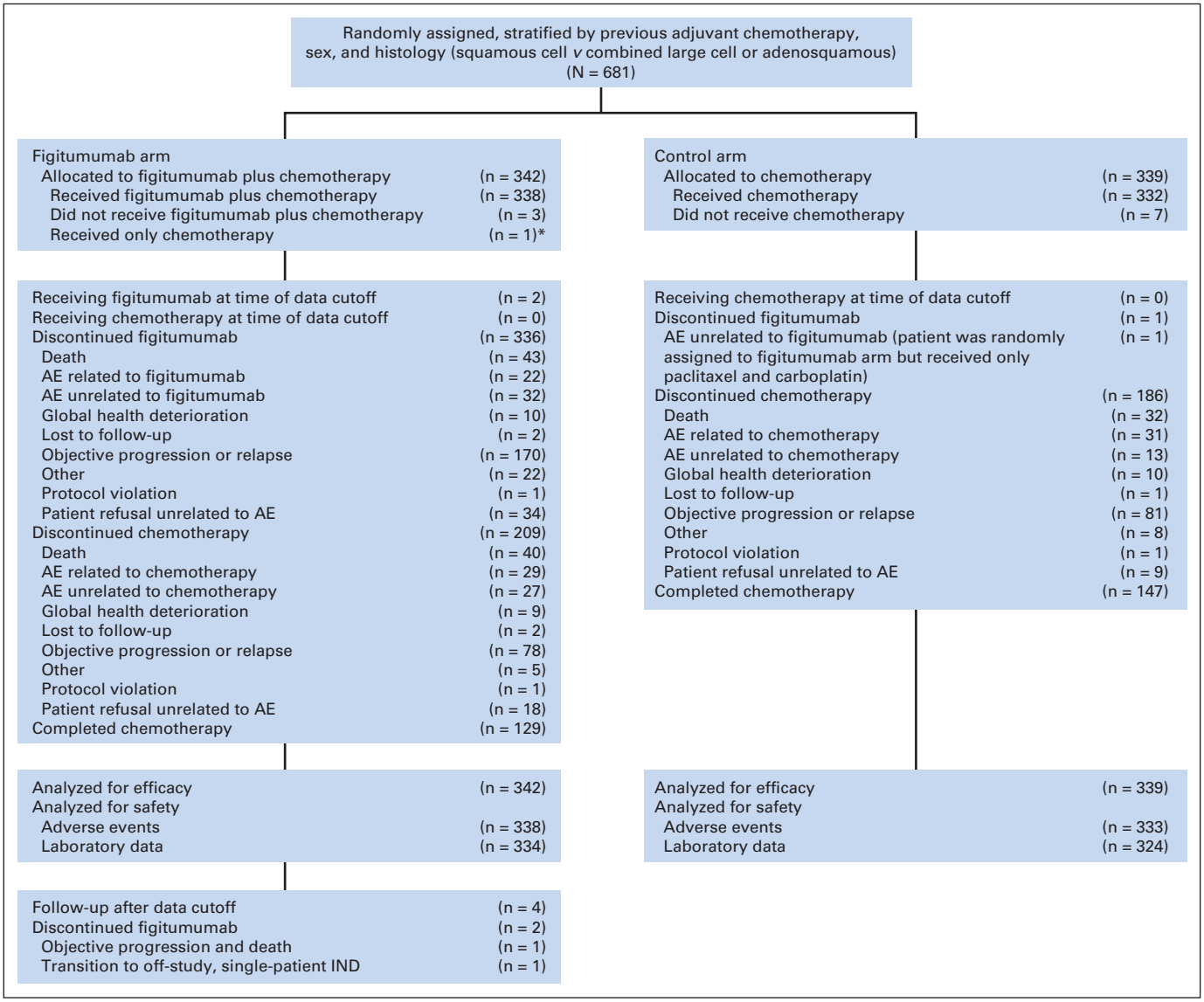

Fig 1. CONSORT diagram. (*) Patient analyzed in control arm for safety. AE, adverse events; IND, investigational new drug.

Efficacy

At the final analysis, 259 patients in the figitumumab arm and 251 in the control arm had died (Table 3). The median OS was 8.6 months (95% CI, 7.4 to 9.3) and 9.8 months (95% CI, 8.6 to 10.9), respectively (HR, 1.18; 95% CI, 0.99 to 1.40; $P = .06$; Fig 2A). Respective 1-year survival rates were 34% and 39%. The effect of figitumumab was similar across all subgroups based on demographic or other baseline characteristics (Fig 3).

Median PFS was 4.7 months for the figitumumab arm (95% CI, 4.2 to 5.4) and 4.6 months for the control arm (95% CI, 4.2 to 5.4; HR, 1.10; 95% CI, 0.93 to 1.32; $P = .27$; Fig 2B). Respective ORRs were 33% (95% CI, 28 to 38) and 35% (95% CI, 29 to 40; Table 3).

Safety

Alopecia and nausea were the most common treatment-emergent (all-causality) adverse events (AEs) of any grade and occurred in a similar number of patients in each arm (Table 4). Any-grade AEs that occurred more frequently in the figitumumab arm included hyperglycemia, diarrhea, decreased appetite, vomiting, and decreased weight. Grade 3/4 AEs that occurred more frequently in the figitumumab arm included hyperglycemia, decreased appetite, dehydration, diarrhea, fatigue, and nausea.

Treatment-emergent (all-causality) SAEs occurred in 66% of the figitumumab arm and 51% of the control arm ($P < .01$ by Fisher's exact test). Excluding disease progression, the most common SAEs were pneumonia (6% *v* 4%, respectively), dehydration (4% *v* 1%), asthenia (3% *v* 1%), and hyperglycemia (3% *v* < 1%). The SAEs were judged to have a reasonable possibility of being treatment-related in 22% and 12% of patients, respectively.

Nonprogression grade 5 AEs occurred in 13% of the figitumumab arm and 10% of the control arm ($P = .22$). The most common grade 5 AEs in the figitumumab arm were pulmonary hemorrhage and pneumonia (2% each; Appendix Table A2). Grade 5 AEs were considered to be treatment-related in 5% of the

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Table 1. Baseline Patient Characteristics

Characteristic	Figitumumab Arm (n = 342) No. of Patients	%	Control Arm (n = 339) No. of Patients	%
Sex				
Male	261	76	260	77
Female	81	24	79	23
Age, years				
Median	62		62	
Range	30-90		36-83	
Ethnicity				
White	265	78	270	80
Asian	56	16	59	17
Black	9	3	4	1
Other	12	4	6	2
ECOG performance status				
0	113	33	115	34
1	226	66	217	64
Not reported	3	1	7	2
Current disease stage*				
Stage IIIB	39	11	39	12
Stage IV	302	88	300	88
Not reported	1	< 1	0	
Smoking status				
Never smoked	34	10	33	10
Current smoker	142	42	141	42
Former smoker	166	49	165	49
Histology				
Squamous cell	295	86	289	85
Large cell	28	8	26	8
Adenosquamous	15	4	19	6
Other	4	1	5	1
Prior treatments				
Surgery	72	21	61	18
Radiation	44	13	36	11
Adjuvant chemotherapy†	14	4	15	4

NOTE. Data are presented for all patients by randomized arm. The stratification factors (histology, sex, and adjuvant chemotherapy) are presented as collected in the case report forms rather than as collected by the randomization system.

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

*TNM Classification of Malignant Tumours (6th ed).[11]

†Systemic therapy included carboplatin/paclitaxel (n = 3), cisplatin/vinorelbine (n = 7), cisplatin/gemcitabine (n = 4), carboplatin/gemcitabine (n = 3), cisplatin/etoposide (n = 3), other regimens with carboplatin (n = 3), other regimens with cisplatin (n = 4), and other nonplatinum regimens (n = 2).

figitumumab arm and 1% of the control arm ($P < .01$). With figitumumab, these grade 5 AEs included hemoptysis, pneumonia, unknown cause reported only as death, septic shock, cardiorespiratory arrest, decrease of performance status, neutropenic sepsis, toxicity to various agents, renal failure, hemorrhage, and hypovolemic shock (≤ 1% each). In the control arm, the grade 5 AEs included unknown cause reported as death, pneumonia, septic shock, and dehydration (< 1% each).

Figitumumab was discontinued because of treatment-related AEs in 7% of patients, and chemotherapy was discontinued for this reason in 9% of patients in each arm.

Relationship of Total IGF-1 and HbA1$_c$ to Outcomes

For the exploratory analysis of outcomes based on baseline total IGF-1, a cutoff of 120 ng/mL was selected because it was associated with the largest observed differences in treatment effect above and below it. Baseline IGF-1 was not related to overall frequency or nature of AEs. However, grade 5 AEs were more common among figitumumab-treated patients with baseline IGF-1 levels less than 120 ng/mL (56%) than among those with baseline levels of 120 ng/mL or higher (38%) and those in the control arm (37% and 36% in the low and high IGF-1 groups, respectively). In the figitumumab arm, median OS for patients with low and high baseline IGF-1 was 7.0 months and 10.4 months, respectively; in the control arm it was 10.1 and 9.4 months, respectively (Appendix Fig A1). For patients with high IGF-1, there was no difference in OS between treatment groups (HR, 0.93; $P = .67$). For those patients with low IGF-1, OS was significantly shorter in the figitumumab arm (HR, 1.37; $P = .01$).

The rate of all-causality AEs did not vary markedly by baseline HbA1$_c$ status, but the rate of grade 3/4 AEs for patients with no grade 5 events was slightly lower in those with baseline levels less than 5.7% than in those with levels ≥ 5.7% (figitumumab arm, 30% *v* 36%; control arm, 33% *v* 35%). Median OS in patients with low baseline HbA1$_c$ was 8.7 months in the figitumumab arm and 10.2 months in the control arm (HR, 1.07; $P = .65$). The respective values in patients with high HbA1$_c$ were 8.2 and 9.7 months (HR, 1.26; $P = .05$).

DISCUSSION

This was the first randomized phase III study to test whether combining an IGF-1R inhibitor (figitumumab) with paclitaxel and carboplatin could improve OS versus chemotherapy alone as first-line treatment for advanced nonadenocarcinoma NSCLC. When this trial was initiated, IGF-1R was thought to play an important role in squamous cell histology NSCLC, an area of particular unmet need. Unexpectedly, adding figitumumab to chemotherapy proved deleterious. The DSMC closed the study because of therapeutic futility and increased SAEs, including treatment-related deaths, in the figitumumab arm. This outcome was disappointing given the originally reported phase II ORR of 54% for combination therapy compared with 42% for chemotherapy alone.[8]

The phase III study was designed and conducted in good faith based on the aforementioned phase II trial findings in treatment-naive advanced NSCLC. Following closure of the phase III trial, the phase II data were retracted after a reanalysis revealed a lower ORR in both treatment arms.[8] In addition, median PFS no longer trended in favor of figitumumab (4.5 months with figitumumab 20 mg/kg and 4.3 months with chemotherapy alone). The heightened toxicity of figitumumab in the phase III trial was not observed in the original phase I/II trials in NSCLC, which enrolled more than 150 patients in total. In our current study, the figitumumab combination failed to improve any efficacy end points over chemotherapy alone. Overall survival, the primary end point, was 8.6 months versus 9.8 months respectively. The ORR with figitumumab (33%) was similar to that observed in the phase II final analysis (37% in both the overall cohort [initially reported as 54%] and the nonadenocarcinoma cohort). Another advanced NSCLC trial, initiated after the phase III was underway, used the same treatment in combination with figitumumab and the ORR was 39%.[12]

Subgroup analysis suggests that figitumumab safety and tolerability were poorer in patients with low baseline IGF-1 (< 120 ng/mL) compared with those with high IGF-1 (≥ 120 ng/mL), particularly

Table 2. Study Drug Exposure

Treatment Delivery	Figitumumab Arm (n = 338)						Control Arm (n = 333)*			
	Figitumumab		Paclitaxel		Carboplatin		Paclitaxel		Carboplatin	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Cycles started										
Median	4		4		4		5		5	
Range	1-52†		1-6		1-6		1-6		1-6	
Duration of treatment, weeks										
Median	12.1		10.2		10.2		12.3		12.6	
Range	0.1-161.3†		0.1-20.1		0.1-20.1		0.1-23		0.1-23	
Patients with at least one dose reduction	30	9	55	16	51	15	52	16	44	13
Patients with at least one dose delay	76	22	52	15	54	16	42	13	42	13

Abbreviation: IND, investigational new drug.
*Patients in the chemotherapy arm who received carboplatin, n = 332.
†Includes experience after data cutoff from the last ongoing patient, who transitioned to single patient IND in September 2012.

with respect to grade 5 AEs. Consequently, in the figitumumab arm, median OS was shorter in patients with low IGF-1 compared with those with high IGF-1 and was significantly shorter compared with control patients who had low IGF-1 (HR, 1.37, $P = .01$). Although additional studies are required, these data suggest that low baseline total IGF-1 may be a safety biomarker that identifies a subset of patients for whom IGF-1R inhibition is particularly harmful. In a phase I study of ganitumab, a human monoclonal antibody against IGF-1R, treatment transiently increased IGF-1.[13] Low baseline IGF-1 may indicate an inability to mount a compensatory increase in IGF-1 and greater likelihood of AEs.

Hyperglycemia of any grade occurred more frequently in the figitumumab arm than in the control arm (23% *v* 5%), as did grade 3/4 hyperglycemia (12% *v* 1%). Hyperglycemia was one of the most common SAEs, with greater frequency in the figitumumab arm than in the control arm. Hyperglycemia is likely a class effect stemming from impaired homeostatic control of glucose metabolism as a consequence of IGF-1R inhibition.[14] Hyperglycemia was rarely severe and was usually manageable with agents such as metformin, but could have contributed in subtle ways to increased toxicity in the figitumumab arm.

Baseline $HbA1_c$ was not a strong biosafety marker, although grade 3/4 AEs were slightly more common in patients with levels

Table 3. Efficacy Results

End Point	Figitumumab Arm (n = 342)		Control Arm (n = 339)		Hazard Ratio	*P*
	No. of Patients	%	No. of Patients	%		
Median follow-up time, months	23.3		22.8			
Overall survival (primary end point)						.06*
Patient deaths	259	76	251	74		
Median, months†	8.6		9.8		1.18‡	
95% CI	7.4 to 9.3		8.6 to 10.9		0.99 to 1.40	
One-year survival§		34		39		
Progression-free survival (investigator assessment)						.27*
Events	261	76	241	71		
Objective progression	206	60	197	58		
Death without objective progression	55	16	44	13		
Median, months†	4.7		4.6		1.10	
95% CI	4.2 to 5.4		4.2 to 5.4		0.93 to 1.32	
Best overall response (investigator assessment)¶						.68‖
Complete response	2	0.6	3	0.9		
Partial response	111	32	114	34		
Stable disease	126	37	120	35		
ORR		33		35		
95% exact CI		28 to 38		29 to 40		

Abbreviation: ORR, objective response rate.
*Two-sided stratified log-rank test.
†Brookmeyer and Crowley method.
‡Stratified Cox proportional hazards model *v* arm B.
§Kaplan-Meier method.
¶Confirmed no sooner than 4 weeks after initial observation.
‖Pearson χ^2 test.

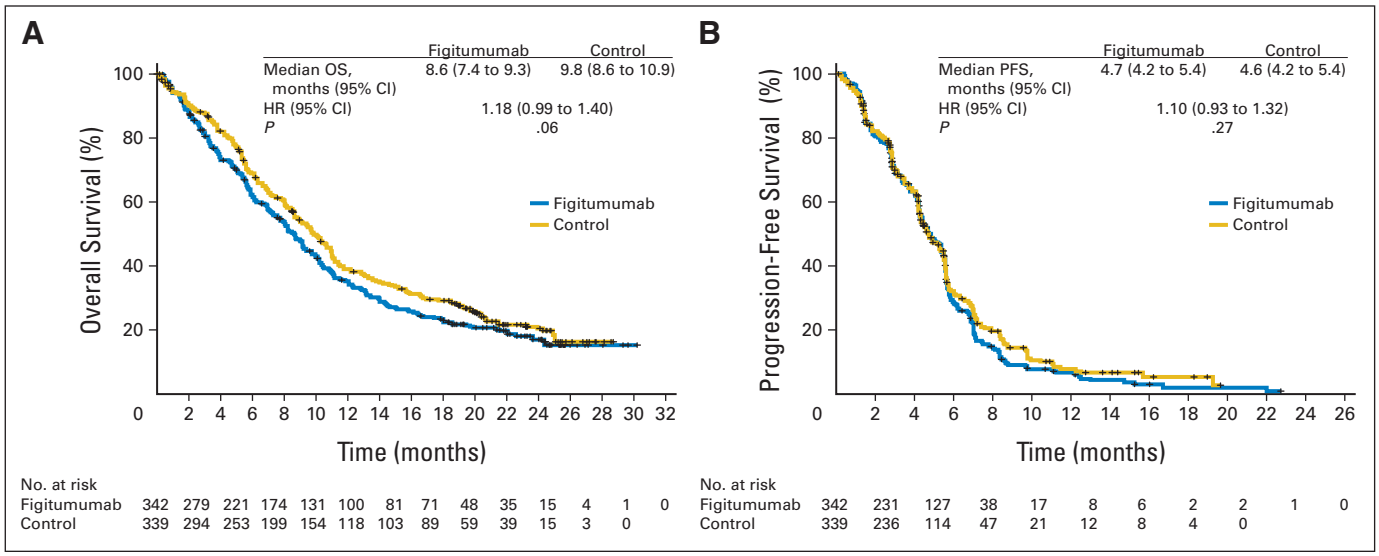

Fig 2. Kaplan-Meier estimates of (A) overall survival (OS) and (B) progression-free survival (PFS) in the randomly assigned population. HR, hazard ratio.

≥ 5.7% than in those with levels less than 5.7% in both treatment arms. Median OS was approximately 1.5 months shorter in the figitumumab arm than in the control arm, regardless of baseline $HbA1_c$ (HR: patients with low $HbA1_c$, 1.07; patients with high levels, 1.26).

Beyond the failure to demonstrate efficacy, a worrisome finding of this study was the relatively high frequency of treatment-related deaths associated with figitumumab (5%), an effect that was not detected in the phase II study. There are a number of potential reasons that may provide insight for future clinical trial design, dosing levels, and anticipation and management of toxicities, particularly where combination regimens are involved. First, only about half of the 98 patients randomly assigned to figitumumab in the phase II trial received the 20 mg/kg dose, a sample that might have been too small to detect safety signals. However, the incidence of grade 3/4 hyperglycemia was greater in the phase II study (20%) than in our current study (12%).[8] Second, there were inherent differences in the patient populations. For example, the phase III study enrolled patients with predominantly squamous cell histology and far more current smokers (42% *v* 13%) than the phase II study. Hence, the phase III patient population may have had more attendant comorbidities (latent or overt), which might have rendered them more vulnerable to toxicity or intercurrent grade 5 events. Third, the phase II trial was conducted almost exclusively at tertiary referral centers, which may have led to subtle differences in the types of patients enrolled and how they were managed. As several study centers in the phase III trial enrolled only a few patients each, the investigators may have initially lacked

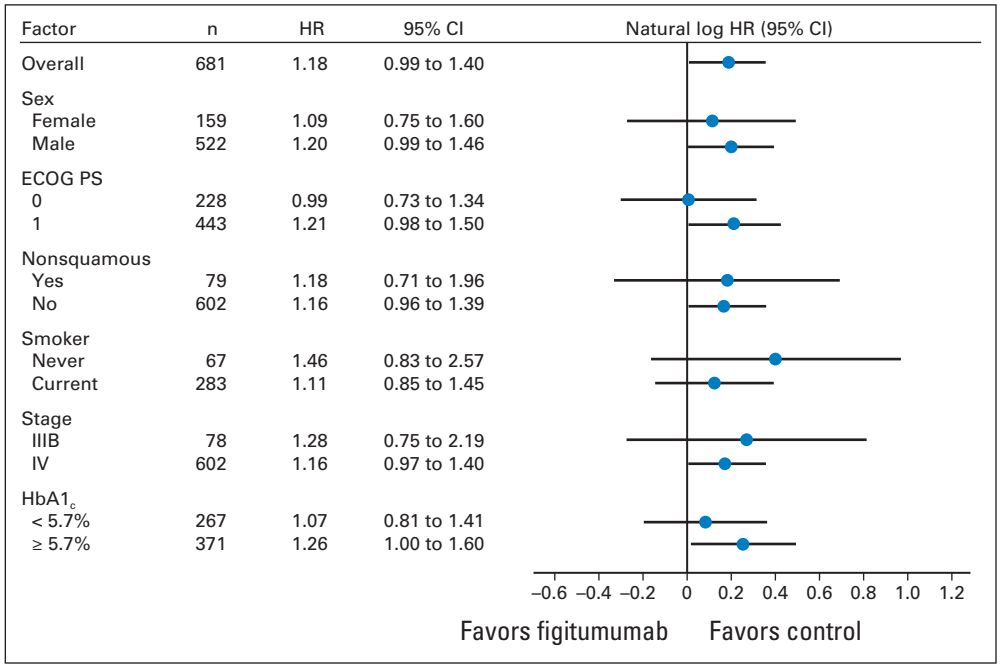

Fig 3. Forest plot of overall survival by selected baseline characteristics. ECOG PS, Eastern Cooperative Oncology Group performance status; $HbA1_c$, glycosylated hemoglobin; HR, hazard ratio.

Table 4. Most Common Treatment-Emergent (all-causality) Adverse Events for ≥ 10% of Patients (any grade) or > 5% of Patients (grade 3 or 4)

	Grade 3				Grade 4				Any Grade			
	Figitumumab Arm (n = 338)		Control Arm (n = 333)		Figitumumab Arm (n = 338)		Control Arm (n = 333)		Figitumumab Arm (n = 338)		Control Arm (n = 333)	
Adverse Event	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Any adverse event (< grade 5)	135	40	106	32	103	30	91	27	319	94	306	92
Alopecia	5	1	5	2	1	< 1	2	1	138	41	146	44
Nausea	12	4	2	1	0		0		133	39	103	31
Decreased appetite	23	7	7	2	0		0		130	38	75	23
Fatigue	19	6	11	3	2	1	2	1	112	33	86	26
Diarrhea	13	4	3	1	2	1	0		101	30	45	14
Anemia	15	4	20	6	4	1	0		95	28	88	26
Vomiting	9	3	3	1	0		0		85	25	47	14
Hyperglycemia	35	10	2	1	7	2	0		79	23	17	5
Neutropenia	20	6	31	9	45	13	33	10	77	23	78	23
Asthenia	23	7	15	5	4	1	1	< 1	75	22	61	18
Cough	5	1	4	1	0		0		66	20	60	18
Weight decreased	11	3	1	< 1	0		0		66	20	29	9
Peripheral neuropathy	13	4	14	4	0		2	1	62	18	57	17
Thrombocytopenia	17	5	15	5	10	3	5	2	61	18	52	16
Constipation	3	1	2	1	0		0		60	18	61	18
Dyspnea	8	2	15	5	4	1	3	1	60	18	68	20
Arthralgia	2	1	0		0		0		47	14	57	17
Peripheral sensory neuropathy	9	3	6	2	0		0		40	12	50	15
Dehydration	17	5	1	< 1	2	1	0		39	12	12	4
Myalgia	1	< 1	0		0		0		39	12	44	13
Dizziness	0		0		0		0		38	11	32	10
Hemoptysis	3	1	1	< 1	0		0		38	11	26	8
Headache	1	< 1	2	1	0		0		37	11	22	7
Pain in extremities	2	1	2	1	0		1	< 1	34	10	24	7
Paresthesia	1	< 1	1	< 1	0		0		29	9	35	11
Pyrexia	0		0		0		0		29	9	35	11
Leukopenia	8	2	14	4	4	1	4	1	19	6	34	10
Febrile neutropenia	3	1	12	4	3	1	6	2	7	2	18	5

NOTE. A total of 10 randomly assigned patients did not receive any study treatment and were not included in the safety analyses. One patient randomly assigned to the figitumumab arm received only paclitaxel and carboplatin and was included in the control arm in this analysis.

experience in managing figitumumab complications such as hyperglycemia and dehydration.

Furthermore, although patient and disease characteristics were well balanced between arms, we cannot exclude the possibility that minor baseline demographic imbalances in this study might have produced inconsistent results. Although figitumumab was combined with the same full-dose chemotherapy doublet as in the phase II study, lower doses of the doublet might have improved the tolerability of the combination. Finally, the difference in the incidence of treatment-related grade 5 AEs between the figitumumab and control arms (5% *v* 1%), may indicate that signaling through IGF-1R and its attendant pathways is critical in maintaining homeostasis, such that inhibition significantly disrupts the insulin receptor/IGF-1R/growth-hormone signaling axis. This concern may be heightened in patients with advanced squamous cell NSCLC, who often have multiple comorbidities and who constituted the vast majority of participants in this trial. Our experience highlights the potential discrepancies between phase II and phase III trials in both safety and efficacy, and underscores the importance of identifying a priori the patient population(s) most likely to benefit from therapy. However, as seen in our current study, inclusion of such a selected patient group (predominantly squamous cell NSCLC) does not guarantee improved safety or efficacy.

In conclusion, though the phase II trial suggested an ORR advantage for adding figitumumab to standard chemotherapy in advanced NSCLC, our current phase III study involving nonadenocarcinoma patients failed to show any benefit and unexpectedly suggested a possible detrimental effect. This may be a class effect and should be assessed in current and future trials examining IGF-1R inhibitors. Further clinical development of figitumumab is not being pursued.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception and design: Corey J. Langer, Tony Mok, Rebecca J. Benner, Judith R. Scranton, Anthony J. Olszanski, Jacek Jassem
Provision of study materials or patients: Corey J. Langer, Silvia Novello, Keunchil Park, Daniel D. Karp
Collection and assembly of data: Keunchil Park, Maciej Krzakowski, Tony Mok, Rebecca J. Benner, Judith R. Scranton, Anthony J. Olszanski
Data analysis and interpretation: Corey J. Langer, Silvia Novello, Keunchil Park, Daniel D. Karp, Tony Mok, Rebecca J. Benner, Judith R. Scranton, Anthony J. Olszanski, Jacek Jassem
Manuscript writing: All authors
Final approval of manuscript: All authors

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Appendix

Investigators. Charles A. Butts, MD, Daniele Marceau, MD, Christopher Charles Croot, MD, Shirish Madhav Gadgeel, MD, Mansoor Noorali Saleh, Lee C. Drinkard, MD, Haralambos E. Raftopoulos, MD, Isidoro Barneto Aranda, Luis Alfonso Gurpide Ayarra, Pilar Lopez Criado, Felipe Cardenal Alemany, Marta Lopez-Brea Piqueras, Amelia Insa Molla, Roy Timothy Webb, MD, Maciej Krzakowski, PhD, Kazimierz Roszkowski-Sliz, PhD, Janusz Rolski, MD, Tadeusz Tobiasz, MD, Petr Zatloukal, MD, Jitka Jakesova, MD, Martin Smakal, MD, Saime Ayse Kars, MD, PhD, Ismail Oguz Kara, MD, PhD, John Allan Ellerton, MD, Kurt Aigner, MD, Sabine Zoechbauer-Mueller, MD, PhD, Nashat Yousif Gabrail, MD, Hari Menon, MD, Anand Pathak, MD, Digambar Behera, MD, Charles Arthur Henderson, MD, Anthony Mark Landis, MD, Carlos Gil Moreira Ferreira, MD, Ulf Petrausch, MD, Daniel C. Betticher, PhD, Barna Szima, MD, Zsuzsanna Mark, MD, Zsolt Szekely Papai, MD, Attila Somfai, MD, Janos Strausz, MD, PhD, Adam Richard Broad, MD, Bogdan N. Kotiv, MD, Dmitriy P. Udovitsa, MD, Henrik Riska, MD, Matti Pietilainen, MD, Nathan Adam Pennell, William Graydon Harker, MD, Daniel David Karp, MD, Donald St Paul Gravenor, MD, Giorgio Vittorio Scagliotti, PhD, Francesco Grossi, MD, Davide Pastorelli, MD, Filippo De Marinis, PhD, Alain Catalin Mita, MD, Everett Emmett Vokes, MD, Jose Rodrigues Pereira, MD, Violina Taskova, MD, Constanta Velinova Timcheva, PhD, Krassimir Dimitrov Koynov, MD, Tatyana Vasileva Koynova, MD, Wieslaw Wiktor Jedrzejczak, PhD, Dae-Seog Heo, MD, Keunchil Park, MD, Heung Tae Kim, MD, Peter Berzinec, Pavol Demo, MD, Ewa Jankowska, MD, Michael T. Slaughter, MD, Tony S.K. Mok, PhD, Tsai Chun-Ming, Su Wu-Chou, MD, Meng-Chih Lin, MD, Chih-Hsin Yang, MD, Joseph Thomas Meschi, MD, Konstantinos Syrigos, PhD, George Fountzilas, PhD, Michael Vaslamatzis, MD, Stephen Lloyd Graziano, MD, Ping Fai So, MD, Frank Griesinger, MD, PhD, Martin Reck, MD, Martin Sebastian, MD, Sylvia Guetz, MD, Dennis Eli Slater, MD, Jean-Claude Guerin, Jean Yves Douillard, PhD, Claude El Kouri, MD, Herve Lena, MD, Patrick Merle, MD, Gerard Zalcman, PhD, Joerg Mezger, MD, PhD, Fabrice Paganin, MD, Christos Emmanouilides, MD, Sandip Abhay Shah, MD, Ganesha D. Vashishta, MD, Yaroslav Shparyk, MD, Nataliya L. Voytko, MD, Igor Mykolayovych Bondarenko, PhD, Vera Andreevna Gorbunova, PhD, Vasily I. Borisov, PhD, Oleksandr Yu. Popovych, PhD, Igor O. Vynnichenko, MD, Goetz H. Kloecker, MD, James Patrick Daugherty, MD, Janak K. Choksi, MD, Troy Hancil Guthrie Jr, MD, Sing Hung Lo, MD, Stephen Begbie, MD, Haluk Tezcan, MD, Susan Amy Sajer, MD, David William Zenk, MD, Samuel Spence McCachren Jr, MD, Stephen Daniel Myers, MD, Mark Ramsey Hutchins, MD, Richard Scott Siegel, Eric Powell Lester, MD, Tarek Eldawy Mohamed, MD, Erwin Lee Robin, MD, Nicholas Oswald Iannotti, MD, Ahmad Ali Tarhini, MD, Corey Jay Langer, MD, Steven Charles Buck, MD, CheolWon Suh, MD, Brian Nicholson Mathews, MD, David Holden Henry, MD, Manuel Francisco Gonzalez, MD, Juraj Beniak, MD, Robert Matthew Jotte, MD, Michaela Long Tsai, MD, William Connelly Waterfield, MD, David A. Van Echo, MD, Waseemullah Khan, MD, Gary E. Goodman, MD, John Ward McClean, MD, Ronald George Steis, MD, Konstantin Hristov Dragnev, MD, Lee M. Zehngebot, MD, Hector A. Velez Cortes, Stacey Kay Knox, MD, Sergey V. Orlov, MD, Mikhail V. Kopp, MD, Bruno Coudert, MD, Radj Gervais, MD, Robert Harold Gersh, MD, Michael Alan Savin, MD, Rama Koteswararoa Koya, MD, Marcus Alan Neubauer, MD, Alexander Illya Spira, MD, Jacek Jassem, PhD, Edward Thomas O'Brien, MD, Linda L. Ferris, MD, Richard C. Frank, MD, Beth Ann Hellerstedt, MD, Donald Anthony Richards, MD, Takeshi Horai, MD, Noboru Yamamoto, MD, Hiroshi Isobe, MD, Miyako Satouchi, MD, Shinji Atagi, MD, Isamu Okamoto, MD, Toshiyuki Sawa, MD, Hiroaki Okamoto, MD, Koji Takeda, MD, Tetsu Shinkai, MD, Richard Wilhelm Eek, MD, Valentina Ilieva Tzekova, PhD, Susan Fox, MD, Jan Novotny, MD, Maurice Perol, MD, Masaaki Kawahara, MD, Pilar Lopez Criado, Raul Manuel Marquez Vazquez, Susanna Stoll, MD, Alessandra Curioni, MD, Ismail Oguz Kara, PhD, Sinan Yavuz, MD, PhD, Tarek Mouris Mekhail, MD, Athanassios Argiris, MD, Brian Vincent Geister, MD, Samir Ezzeldin Witta, MD, Joseph Ward Leach, MD, and Nicholas James Robert, MD.

Table A1. Boundaries for the Planned Interim Analyses and First Interim Analysis Results

Analysis	No. of Events	Efficacy Boundaries for Rejecting the Null Hypothesis		Futility Boundaries for Rejecting the Alternative Hypothesis	
		Z Score	Hazard Ratio*	*Z* Score	Hazard Ratio*
Plan for first interim analysis	216	3.710	0.603	−0.695	1.10
Plan for second interim analysis	433	2.511	0.785	1.003	0.908
Plan for final analysis	649	1.993	0.855		
Computed boundaries for actual first interim analysis	225	3.632	0.616	−0.595	1.083
Observed results for first interim analysis	225			−1.407†	1.209†

*Hazard ratio was computed from *z* score boundary assuming proportional hazards and approximating the SE using the No. of events. Decisions were based on the *z* score boundaries.
†Based on interim data.

Table A2. Grade 5 All-Causality Adverse Events, Excluding Disease Progression

Adverse Event	Figitumumab Arm (n = 338)		Control Arm (n = 333)	
	No. of Patients	%	No. of Patients	%
Total*	43	13	32	10
Pulmonary hemorrhage	7	2	4	1
Pneumonia	7	2	3	1
Cardiopulmonary failure	5	1	2	1
Sepsis	4	1	1	< 1
Death	3	1	3	1
Pulmonary embolism	1	< 1	3	1
Respiratory failure	2	1	1	< 1
Renal failure	2	1	1	< 1
Cerebrovascular accident	0		3	1
Gastrointestinal hemorrhage	0		2	1
Cardiovascular disorder	2	1	0	
Hemorrhage	2	1	0	
Sudden death	1	< 1	1	< 1
Performance status decreased	1	< 1	1	< 1
Arrhythmia	1	< 1	0	
Emphysema	1	< 1	0	
Hypovolemic shock	1	< 1	0	
Hypoxia	1	< 1	0	
Myocardial infarction	1	< 1	0	
Multiorgan failure	1	< 1	0	
Neutropenia	1	< 1	0	
Neutropenic sepsis	1	< 1	0	
Staphylococcal infection	1	< 1	0	
Toxicity to various agents	1	< 1	0	
Asphyxia	0		1	< 1
Cardiac failure	0		1	< 1
Dehydration	0		1	< 1
Dyspnea	0		1	< 1
Pulmonary edema	0		1	< 1
Suicide	0		1	< 1
Superior vena cava syndrome	0		1	< 1

*P = .22 by two-sided Fisher's exact test. Some patients had more than one grade 5 adverse event.

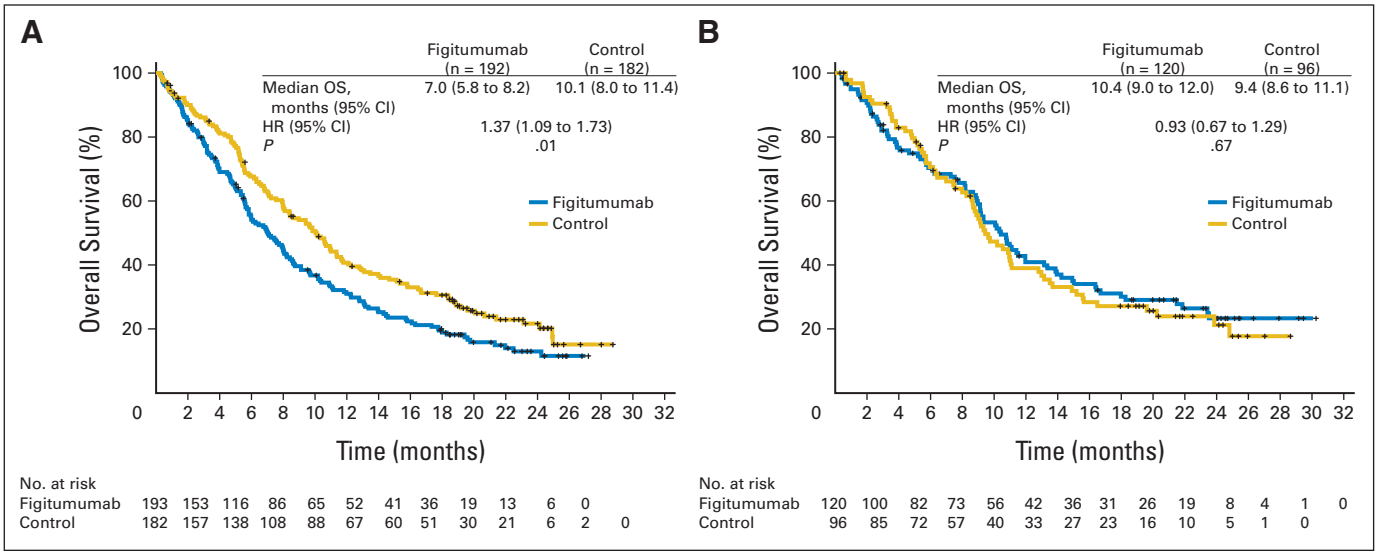

Fig A1. Kaplan-Meier estimates of overall survival (OS) in patients with (A) total baseline insulin-like growth factor 1 (IGF-1) less than 120 ng/mL or (B) total baseline IGF-1 ≥ 120 ng/mL. HR, hazard ratio.