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A Phase II Study of Cixutumumab (IMC-A12, NSC742460) in Advanced Hepatocellular Carcinoma

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Abstract

Background and Aims—IGF-IR is implicated in hepatic carcinogenesis. This and preliminary evidence of biological activity of anti-IGF-1R monoclonal antibody cixutumumab in phase I trials prompted this phase II study.

Methods—Patients with advanced HCC, Child-Pugh A-B8, received cixutumumab 6 mg/kg weekly, in a Simon two-stage design study, with the primary endpoints being 4-month PFS and RECIST-defined response rate. Tissue and circulating markers plus different HCC scoring systems were evaluated for correlation with PFS and OS.

Results—As a result of pre-specified futility criteria, only stage 1 was accrued: N= 24: median age 67.5 years (range 49–83), KPS 80% (70–90%), 20 males (83%), 9 stage III (37%)/15 stage IV (63%), 18 Child-Pugh A (75%), 11 HBV (46%) /10 HCV (42%)/11 alcoholic cirrhosis (46%)/2 NASH (8%), 11 (46%) diabetic. Median number of doses: 7 (range 1–140). Grade 3/4 toxicities > 10% included: diabetes, elevated liver function tests, hyponatremia, and lymphopenia. Four-month PFS was 30% (95% CI 13–48), and there were no objective responses. Median overall survival was 8 months (95% CI 5.8– 14). IGF-R1 staining did not correlate with outcome. Elevated IGFBP-1 correlated with improved PFS (1.2 [95% CI 1–1.4]; p 0.009) and OS (1.2 [95% CI 1.1–1.4]; p 0.003).

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Conflicts of interest: Ghassan K Abou-Alfa, Jennifer Ma, and Leonard B Saltz: Research grant support from ImClone; Leslie Abad: Employment: ImClone

Conclusions—Cixutumumab monotherapy did not have clinically meaningful activity in this unselected HCC population. Grade 3–4 hyperglycemia occurred in 46% of patients. Elevated IGFBP-1 correlated with improved PFS and OS.

INTRODUCTION

Cixutumumab is a fully human IgG1 monoclonal antibody that binds with high specificity to IGF-R1 [1]. IGF-1 binding activates the tyrosine kinase domain of IGF-R1 [2]. Phosphotyrosine residues in turn activate the MAP kinase proliferation pathway and the Akt survival pathway [3]. Cixutumumab effectively blocks ligand-induced phosphorylation, resulting in growth inhibition and apoptosis of tumor cells in a human tumor xenograft model [4]. It also reduces the number of IGF-R1 receptors expressed on the surface of tumor cells through receptor internalization and degradation. Being an IgG class 1 immunoglobulin, cixutumumab also has the potential to mediate immune effector functions, such as antibody-dependent complement-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

The dysregulated autocrine or paracrine production of IGF-1 and IGF-2, as well as overexpression of IGF-IR, has been implicated in human hepatic carcinogenesis [5–9]. IGF-2 is overexpressed in 16–40% HCC cells, and LOH or reduction of IGF-2R expression has been reported in 80% of HCC in a series of HCC patients [5]. Recent data have shown IGF-2 overexpression to be most noticeable in the histologically advanced tumors [9]. Blockade of IGF-1R activity with an IGF-1R inhibitor or anti-IGF-1R monoclonal antibody was shown to induce growth inhibition, apoptosis, and cell cycle arrest in preclinical models of HCC [10–12].

Most patients with HCC either present with or ultimately develop advanced disease [13]. Despite the reported 2.8 month median improvement in survival using sorafenib [14], there remains a clear continued need for new drugs or a combination of to help improve outcome. Thus we performed a phase II study evaluated cixutumumab in patients with advanced HCC.

PATIENTS AND METHODS

This was a single-institutional, open label study sponsored by the CTEP/NCI phase II N01 institutional grant. Cixutumumab was provided through the Clinical Trial Agreement between CTEP/NCI and ImClone/Lilly. The Institutional Review Board (IRB) of Memorial Sloan Kettering Cancer Center reviewed the protocol. Informed consent was obtained from each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. The study was registered with [www.clinicaltrials](http://www.clinicaltrials.gov) identifier NCT00639509.

Patients' Eligibility

Men and women >18 years of age, of any racial or ethnic background with advanced-stage, histologically confirmed, unresectable locally advanced, or metastatic HCC with at least one measurable lesion by RECIST [15], who received no prior systemic therapy with the exception of sorafenib, were eligible. Unresectability was based on but not limited to, extent of disease, vascular involvement, liver function, performance status, and co-morbid conditions. Previous local therapy, e.g., hepatic artery embolization was allowed with evidence of progression of disease by RECIST criteria evident on protocol entry. Patients were required to have an Karnofsky performance status (KPS) of 70–100%; a Child-Pugh score of A5–B8; with adequate hematologic function (absolute neutrophil count 1,500/

mcL, Platelets 75,000/mcL, and PT/INR 1.7 times upper limit of normal); fasting serum glucose 125 mg/dL; adequate hepatic function (total bilirubin 2 mg/dL, and AST/ALT 93 units/L) and adequate renal function (creatinine <1.5 mg/dL or creatinine clearance 60 mL/min for patients with creatinine levels equal or above 1.5).

Diabetic patients were allowed to participate provided that their blood glucose is within normal range (fasting < 120 mg/dL or below upper limit of normal) and that they are on a stable dietary or therapeutic regimen for this condition. Patients with serious inter-current illnesses including known brain metastases and/or clinical encephalopathy, and/or known HIV infection were excluded. The study also excluded pregnant women and patients with other malignancies that might have affected patient's outcome.

Treatment Plan

Patients received single-agent cixutumumab 6 mg/Kg intravenously over one hour weekly. Treatment continued until progression of disease, unacceptable toxicity, or withdrawal of consent. Clinical evaluation occurred weekly for four weeks then every two weeks thereafter. Radiologic assessment was performed every 8 weeks.

Study Objectives

The primary endpoints of the study were four-month PFS, and best overall response using RECIST 1.0 criteria.

Progression-free survival was defined as the time from first date of first treatment on the study until such time as progressive disease (RECIST criteria) was confirmed or upon patient death if disease progression was not been evident at that time. The response was defined as the best response from the start of the treatment until disease progression/recurrence.

Secondary objectives included the evaluation of median OS and assessment of safety, tolerability, and adverse events using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Correlative Studies

IGF-1R expression by immunohistochemistry on pre-treatment biopsies was measured and evaluated for correlation with outcome endpoints. Ventana automation (Discovery XT platform-Ventana Medical Systems, Inc, Tucson, AZ) with standard streptavidin-biotin immunoperoxidase method and DAB detection system was used as a staining method, using IGF-1R antibody, clone G11, pre-diluted, rabbit monoclonal antibody from the same vendor. Antigen recovery was conducted using heat and CC1 conditioning solution. Positive tissue control used was previously tested positive colon cancer provided by the core research facility at Memorial Sloan-Kettering Cancer Center. The stains were scored based on the degree of staining relative to the total amount of tumor in the studied section, and were ranked based on a standard reference from 0 to 3+.

Similarly, levels of free IGF1, IGF2, IGFBP-1 and IGFBP -3 by ELISA (Beckman Coulter/DSL) on pre-treatment stored serum plus the IGF-1/IGFBP-1 and IGF-1/IGFBP-3 indices were evaluated for correlations with staging and clinical outcomes.

Statistical Analyses

Historical data shows the 4-month progression-free survival for placebo to be 42% and response rate 2%, from the double-blinded, randomized, phase III clinical trial of sorafenib versus placebo in patients with advanced HCC [12]. A Simon's optimal two-stage design

was used with the following assumptions: a 4-month PFS of 62% is considered acceptable while a 4-month PFS of 42% is not; and an overall response rate of more than 20% is of interest and a overall response rate less than 5% is not. Maximum trial size would be set at 50 evaluable patients, with 25 patients to be enrolled in the first stage. If no more than 11 patients (no more than 44%) were observed to be progression-free for at least 4 months and no more than 2 responses (no more than 8%) were observed, among the initial 25 patients, the study would be terminated early and declared negative. If the study continues and at least 26 patients (at least 52%) were observed to survive progression-free for at least 4 months, or at least 7 responses (at least 14%) were observed, among the 50 evaluable patients, cixutumumab would be considered worthy of further testing in HCC. Assuming that overall response rate and PFS are independent, the over-all type 1 error would be 0.10 and the probability of early termination is 0.57 for 5% true overall response rate and 42% true 4-month PFS. The type 1 error decreases very slightly and the probability of early termination increases towards 0.66 if overall response rate and PFS are positively correlated.

Survival curves were estimated using the Kaplan-Meier methodology. Associations between the biomarkers and OS and PFS were assessed using univariate Cox regression models with the biomarkers treated as continuous predictors. Due to the small sample size only univariate analyses were conducted. The safety, tolerability, and adverse events were summarized using descriptive statistics. All analyses of outcome were based on an intent to treat. Patients who received at least one dose of cixutumumab were evaluable for toxicity.

RESULTS

Demographics

Between March 26, 2008 and January 13, 2009, 24 patients were enrolled at Memorial Sloan Kettering Cancer Centers. Nineteen patients were previously untreated and were offered sorafenib as standard of care but elected to join the clinical trial as first line treatment. Five patients had previously received sorafenib; 3 progressed and 2 could not tolerate it, one due to allergic reaction, and the other due to significant fatigue. Median age was 67.5 years (range 49–83), with KPS 80% (70–90%). There were twenty men (83%). Nine patients had AJCC stage III (37%), and 15 stage IV (63%) disease. Eighteen patients (75%) had Child-Pugh score A and 6 (25%) had a Child-Pugh score B. Eleven patients had hepatitis B (46%), 10 had hepatitis C (42%), 11 had alcoholic cirrhosis (46%), and 2 had non-alcoholic steatohepatitis (NASH) (8%) as their risk factor for HCC, with 10 having more than one etiology. Eleven patients (46%) were diabetic: 10 had grade 2 diabetes requiring oral agents, and one had grade 3 diabetes requiring insulin. Detailed demographics are shown in Table 1.

Treatment

A total of 396 doses of cixutumumab were given during the study. The median number of doses was 7 (range 1–140). The median dose was 6 mg/kg (range 5–6). Three patients required dose reduction to 5mg/Kg because of grade 3 diabetes, one grade 2 diabetes, and one because of grade 3 thrombocytopenia.

Safety and Tolerability

All 24 patients were evaluated for safety. Grade 3 and 4 toxicities which occurred in more than 10% of patients included, hyperglycemia (46%); hyponatremia (25%); elevated AST (25%); ALT (12%), alkaline phosphatase (12%), hyperbilirubinemia (12%), and lymphopenia (12%). Therapy was discontinued in two patients, due to ALT/AST elevation, and hyperglycemia. All adverse events are summarized in table 2.

The diabetes was of notable concern. Seventeen patients (71%) were on active therapy for diabetes throughout the study. Of 10 originally diabetic patients with grade 2 diabetes, 7 (70%) progressed to grade 3, which required adding insulin to their regimen. Six patients (25%) became diabetic while on study: 4 grade 2, and 2 grade 3. Patients who discontinued therapy required less therapy to control their diabetes.

One patient had grade 4 renal failure that was treated with aggressive hydration. Considering this patient's advanced disease status, a best supportive care approach was started and patient was not started on hemodialysis. This was the only treatment related mortality on the study.

Grade 1 koilonychia (thinning of the nail beds) was observed in one patient. While this adverse event did not prevent the patient from continuing therapy, it was followed carefully to ensure complete thinning of the nail beds did not recur (Figure 1). We plus others have previously reported this skin finding [16].

Four patients died within 30 days of discontinuing therapy. All four patients were on best supportive case at that time, and their death was correlated with progression of their disease.

Outcome

Of 24 evaluable patients, there were no responses by RECIST criteria. There were no objective responses. Seven patients (29%) had stable disease for at least 4 months, and 9 (37%) had progression of disease for a median of 2.7 months (range: 0.9–32.63 months). By 4 months, 17 patients have progressed or died. The 4-month PFS estimated by the Kaplan-Meier method was 30% (95% CI 13–48). The median overall survival was 8 months (95%CI 5.8–14). Kaplan-Meier curves depicting PFS and OS are shown in figures 2 and 3 respectively. A waterfall plot is depicted in figure 4.

Correlative Studies

All patients had serum and tumor tissues available for biomarker studies, except for one patient who was missing tumor tissue for IGF-1R staining.

Sixteen patients' tumors out of 24 (67%) did not stain for IGF-1R by immunohistochemistry. Five patients had tumors that stained 1+ (4 patients) or 2+ (one patient). Three were non evaluable. As there were no patients with 3+staining, the range was limited to 2+ with no statistical implications. There was no correlation between any level of staining (1+ and 2+) and PFS or OS, when compared to no staining (HR 1.092 (95% CI 0.353–3.377, $p=0.88$).

Serum marker ranges were as depicted in table 3. Elevated IGFBP-1 correlated with improved PFS (HR 1.2 [95%CI 1–1.4]; $p=0.009$) and OS (HR 1.2 [95%CI 1.1–1.4]; $p=0.003$). All other serum markers, free IGF1, IGF2, and IGFBP3, plus the IGF1/IGFBP-1 and IGF1/IGFBP3 indices did not show any correlation with PFS and OS (Table 4). Three markers correlated with stage III versus IV: IGF2 ($p=0.001$), IGFBP 1 ($p=0.04$), and IGFBP 3 ($p=0.003$), plus a strong correlation of IGF1/IGFBP3 index and stage [stage III ($n=9$), median of 0.00013 versus stage IV ($n=15$), median of 0.000072]-($p=0.007$). No such correlation was found with IGF1 ($p=0.46$) or the IGF1/IGFBP1 ($p=0.35$) index.

DISCUSSION

Despite the implication of IGF-1R in human hepatic carcinogenesis [5–9] and the preclinical data in HCC [10–12], cixutumumab monotherapy did not show evidence of clinically meaningful activity in this unselected group of HCC patients. The study presented herein

was halted at its first stage, as it failed to achieve the pre-specified indicators of activity using two different primary endpoints. The 4-month PFS of 30% was inferior to that of the placebo control arm of the sorafenib registration trial historical control of 42% [14]. This comparison is however limited by the unselected nature of the patients in this trial with 25% Child-Pugh B and 21% receiving therapy as second line after sorafenib failure. Furthermore, there were no objective responses by RECIST criteria and no indications of tumor shrinkage to any degree. The two primary endpoints used in this study have their limitations in HCC. In particular, a low response rate by conventional RECIST may not mean lack of clinically meaningful activity. Despite that, it is clear that the study is negative.

Hyperglycemia was the major toxicity encountered, with 62% of patients of patients on study requiring initiation or increase in active therapy for diabetes; 42% required an intensification of their diabetes regimen, and 21% became diabetic while on study. Most patients required the close follow-up of an endocrinologist. While one may argue that such a safety profile is manageable, obviously this can create serious inconvenience to patients, in a larger community scale. It is unclear if the metabolic aspects of HCC and its associated cirrhosis may have played a role the frequency with which diabetes was evident in a HCC population, especially that so far there has been no direct mechanistic proof of association between cixutumumab and diabetes. The frequency of this toxicity confirms that were administering a biologically active dose.

The toxicity concerns are central to our findings. Cirrhosis is a state of IGF1 deficiency and restoration of IGF1 levels beneficially influences not only liver function and fibrosis but also many of the extrahepatic manifestations of cirrhosis in animal models. In patients, administration of subtherapeutic doses of IGF1 improved liver function [17]. It is unclear if the IMC-A12 intervention in the reported in the study herein did influence any cirrhosis component base don the reported grade 3 and 4 liver function tests abnormalities. The one case of lethal renal failure and the 25% grade 3 and 4 hyponatremia are worth noting. IGF-1 exerts important effects on renal hemodynamics and renal sodium handling. Among cirrhotics, IGF1 correlated with renal blood flow while a negative correlation was found between IGF1-IGF-BP index and fractional sodium excretion and between IGF-BP1 and urinary sodium excretion. These findings suggest that IGF1 may be related to renal vasodilation and renal sodium retention in cirrhotic patients [18].

We did not demonstrate a high expression of the target by immunohistochemistry, with 71% of samples staining negative for IGF-1R. No correlation was noted among those with positive IGF-1R and outcome. We found a correlation between IGF2, IGFBP 1 and IGFBP 3, and histologic grade. Similar to Tovar et al [9], this correlation was the most significant with IGF2 ($p=0.001$). These observations are however limited as assays were done on archival tissue, which may be remote from the tumors being treated. Add to this, the assays were not calibrated for the level of actual IGF-1R levels so the staining results should be interpreted with care. On the other hand, increased IGFBP 1 did correlate with improved PFS (1.2 [95%CI 1–1.4]; $p=0.009$) and OS (1.2 [95%CI 1.1–1.4]; $p=0.003$). This observation is similar in essence to that noted by Gualberto et al [19], except that herein the insulin levels were not measured at baseline and thus a corrective ratio based on insulin level will remain unknown. The other discrepancy is the lack of correlation between IGF-1R level and outcome, which was noted in this exploratory analysis of patients with non-small cell lung cancer treated with figitumumab. The bioactivity of IGF1 is influenced by its binding proteins (BP) of which IGF-BP3 favors retention in the capillary lumen while IGF-BP1 facilitates the transport to the target tissues. The IGF-1-IGF-BP indexes better reflect the accessibility of circulating IGF-1 to target cells. We however did not find any correlation between these indices and outcome.

So far efforts to improve outcome over sorafenib using single agent sunitinib [20], brivanib [21] and linifanib [22] have not succeeded. Concentrated efforts evaluating different combination of therapies are underway. These were also faced with discouraging results of the sorafenib plus erlotinib combination [23]. The erlotinib plus bevacizumab (www.clinicaltrials.gov, NCT00881751), and Alliance CALGB 80802 sorafenib plus doxorubicin (www.clinicaltrials.gov, NCT01015833) studies are still ongoing. Cixutumumab in combination with sorafenib is also being evaluated in HCC [24]. While no data is reported so far, the adverse events we have reported using single agent cixutumumab, would require exerting extreme prudence using this drug in combination with other therapies.

Our experience with cixutumumab in patients with advanced HCC has been disappointing. It is unclear if more restrictive eligibility criteria, i.e. Child-Pugh A and KPS of 80% only would have made a difference, although this seems unlikely.

While we await the results of the combination efforts of the role for cixutumumab in solid malignancies, the lack of patient selection markers for IGF-1R targeted therapy, and the degeneracy and parallel pathways within the IGF system or outside, may very well explain the lack of substantial benefit seen so far.

Acknowledgments

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List of abbreviations in the order of appearance

IgG1	Immunoglobulin 1
IGF-1R	Insulin growth factor 1 receptor
IGF-1	Insulin growth factor 1
MAP	Mitogen activated protein
ADCC	Antibody-dependent complement-mediated cytotoxicity
CDC	Complement-dependent cytotoxicity
IGF-2	Insulin growth factor 2
HCC	Hepatocellular carcinoma
LOH	Loss of heterozygosity
IGF-2R	Insulin growth factor 2 receptor
CTEP/NCI	Cancer Therapy Evaluation Program (CTEP)/ National Cancer Institute IRB, Institutional Review Board
RECIST	Response evaluation criteria in solid tumors
KPS	Karnofsky performance status
mcL	Cells per microliter
PT/INR	Prothrombin time/International normalized ratio
mg/dL	Milligram/deciliter
AST	Aspartate aminotransferase

ALT	Alanine aminotransferase
units/L	Units/Liter
mL/min	Milliliter per minute
HIV	Human immunodeficiency virus
Mg/Kg	milligram/kilogram
PFS	progression free survival
S	Overall survival
CTCAE	Common terminology criteria for adverse events
CC1	Cell conditioning 1
IGFBP 1	Insulin-like growth factor binding protein 1
IGFBP 3	Insulin-like growth factor binding protein 3
ELISA	Enzyme-linked immunosorbent assay
AJCC	American Joint Committee on Cancer
NASH	Non-alcoholic steatohepatitis
HR	Hazard ratio
CALGB	Cancer Leukemia Group B.

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Fig. 1.
Koilonychia grade 1 adverse event.

Fig. 2.
Kaplan-Meier curve depicting PFS

Fig. 3.
Kaplan-Meier curve depicting OS

Fig. 4.
Waterfall plot: Percent reduction in tumor measurements.

Table 1

Demographics (n=24)

	N	%
Median Age	67.5	
Sex		
Male	20	83
Female	4	17
Race		
White	16	67
Black	2	8
Asian	5	21
Other	1	4
Hepatitis Status		
B+/C+	5	21
B-/C-	8	33
B+/C-	6	25
B-/C+	5	21
Other Risk Factors		
Alcoholic Cirrhosis	11	46
Non-Alcohol Steatohepatitis	2	8
Performance Status (KPS)		
70%	2	8
80%	20	84
90%	2	8
HX of Diabetes	10 (+5 became diabetic)	42
Disease Stage		
III	9	37
IV	15	63
Child-Pugh Score		
A5	11	46
A6	7	29
B7	2	8
B8	4	17
Laboratory Findings	Median (Range)	
Baseline AST (Units/L)	65 (22–159)	
Baseline ALT (Units/L)	46 (13–167)	
Baseline Platelets (K/mcL)	191.5 (92–478)	
Baseline AFP (ng/mL)	52 (3–587203)	
Tumor Characteristics		

	N	%
Extrahepatic Spread	15	63
Vascular Invasion	11	46
Pathology Grading		
Well Differentiated	5	21
Mildly-Moderately Differentiated	1	4
Moderately Differentiated	6	25
Moderately-Poorly Differentiated	2	8
Poorly Differentiated	2	8
Unknown	8	33
Previous Treatment with Sorafenib	6	25

Table 2

All Adverse events n (%)

	Grade 1	Grade 2	Grade 3	Grade 4
Constitutional				
Nail changes (koilonychia)	1 (4)			
Nausea	4 (16)	1 (4)	1 (4)	
Pain - Abdomen NOS	2 (8)		1 (4)	
Pleural effusion (non-malig)				1 (4)
Vomiting	2 (8)	1 (4)	1 (4)	
Vision-blurred vision	2 (8)			
Gastrointestinal/Hepatology				
ALT	10 (41)	8 (33)	3 (12)	
AST	10 (41)	7 (29)	5 (21)	1 (4)
Albumin, low	8 (33)	15 (62)	1 (4)	
Alkaline phosphatase	7 (29)	7 (29)	3 (12)	
Ascites		1 (4)	2 (8)	
Bilirubin	9 (37)	9 (37)	2 (8)	1 (4)
Confusion			1 (4)	
Dehydration			1 (4)	
Diarrhea	7 (29)		1 (4)	
Hemorrhage, rectum			1 (4)	
Hemorrhage, esophageal (varices)			1 (4)	
Lipase			1 (4)	
Hematologic				
Lymphopenia			3 (12)	
Platelets	15 (62)	3 (12)	1 (4)	
Metabolic				
Glucose, high	8 (33)	5 (21)	11 (46)	
Phosphate, low	1 (4)	3 (12)	1 (4)	
Renal failure				1 (4)
Sodium, low (hyponatremia)	15 (62)		6 (25)	

Table 3

Serum markers ranges

Marker	Range (Median)
Free IGF-1	0.051 – 0.804 (0.335)
IGF II	340.8 – >2200 (811.5)
IGFBP-1	3.8 – > 160 (44.7)
IGFBP-3	739.6 – 8740.6 (2704.7)

Table 4

Univariate analysis on the biomarkers and PFS and OS

Biomarker	PFS			OS		
	HR	95% CI	p	HR	95% CI	p
Free IGF1	0.298	(0.022–4.106)	0.3657	0.815	(0.055–12.001)	0.8817
IGF2	0.920 ^a	(0.829–1.020)	0.1147	0.939 ^a	(0.836–1.055)	0.2890
IGFBP-1	1.194 ^b	(1.045–1.363)	0.0090	1.224 ^b	(1.071–1.398)	0.0030
IGFBP-3	0.785 ^c	(0.592–1.040)	0.0921	0.816 ^c	(0.597–1.116)	0.2024
IGF1/IGFBP1	0.975 ^d	(0.728–1.306)	0.865	1.005 ^d	(0.734–1.375)	0.976
IGF1/IGFBP3	1.571 ^e	(0.915–2.698)	0.101	1.283 ^e	(0.831–1.981)	0.261

^aHR of 100 unit increase in IGF2;^bHR of 10 unit increase in IGFBP-1;^cHR of 1000 unit increase in IGFBP-3;^dHR of 0.01 unite increase in ratio of free IGF1/IGFBP1;^eHR of 0.0001 unit increase in ratio of free IGF1/IGFBP3