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ORIGINAL RESEARCH

Serum IGF-1 Scores and Clinical Outcomes in the Phase III IMbrave150 Study of Atezolizumab Plus Bevacizumab versus Sorafenib in Patients with Unresectable Hepatocellular Carcinoma

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Purpose: Child-Turcotte-Pugh class A (CTP-A) in unresectable hepatocellular carcinoma (HCC) is the standard criterion for active therapy and clinical trial enrollment. We hypothesized that insulin-like growth factor-1 (IGF-1) derived scores may provide improved survival prediction over CTP classification. This study aimed to evaluate the potential prognostic and predictive effects of IGF-1 derived scores in the phase III IMbrave150 study.

Patients and Methods: Baseline and on-treatment serum IGF-1 levels from 371 patients were subjected to central analysis. Patients' IGF-1 score (1/2/3) and IGF-CTP score (A/B/C) were determined based on pre-specified cutoffs. Outcomes were analyzed by baseline and by on-treatment changes of the IGF-1 and IGF-CTP scores within and between the two treatment arms. The interaction between these scores and outcomes was assessed using univariate and multivariate analyses.

Results: Baseline IGF-CTP score (A vs B/C) showed prognostic significance for OS in both the atezolizumab-bevacizumab (hazard ratio [HR], 0.33; 95% confidence interval [CI], 0.20–0.56; $P<0.001$) and sorafenib (HR, 0.32; 95% CI, 0.16–0.65; $P=0.002$) arms. Baseline IGF-1 score (1 vs 2/3) also showed prognostic significance for OS in both the atezolizumab-bevacizumab (HR, 0.33; 95% CI, 0.20–0.55; $P<0.001$) and sorafenib (HR, 0.48; 95% CI, 0.26–0.89; $P=0.02$) arms. HRs for PFS were consistent with those for OS. No significant predictive effects were observed for either score between the two arms. Kinetic analysis revealed that patients with increased IGF-1 score (1-> 2/3) at 3 weeks post treatment had shorter OS than patients with stable IGF-1 score of 1 in both the atezolizumab-bevacizumab (HR, 3.70; 95% CI, 1.56–8.77; $P=0.003$) and sorafenib (HR, 5.83; 95% CI, 1.88–18.12; $P=0.0023$) arms.

Conclusion: Baseline and kinetic change of IGF-CTP and IGF-1 scores are independent prognostic factors for patients with unresectable HCC treated with atezolizumab-bevacizumab or sorafenib. These novel scores may provide improved patient stratification in future HCC clinical trials. IMbrave150 ClincialTrials.gov number, NCT03434379.

Keywords: IGF-CTP score, prognostic biomarker, immunotherapy, HCC

Introduction

For decades, the Child-Turcotte-Pugh (CTP) scoring system has been used to assess hepatic reserve for determining the prognosis of patients with cirrhosis.[1,2] It is also the standard used to stratify patients with hepatocellular carcinoma (HCC), and CTP Class A scores are the standard selection criterion for patient enrollment in HCC clinical trials[3,4] and for active therapy in routine practice.

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The original CTP scores are calculated by assigning points 1–3 to three objective serum measurements (albumin, bilirubin and prothrombin (PT) prolongation time) and two subjective variables (encephalopathy and ascites). Our team developed a new system for scoring hepatic reserve by replacing the two subjective parameters in the CTP score, encephalopathy and ascites, with the serum insulin-like growth factor-1 (IGF-1) level.[5] IGF-1 is a polypeptide hormone produced in response to growth hormone.[6] The majority of circulating IGF-1 is synthesized by the liver; therefore, the level of circulating IGF-1 reflects the synthetic function of the liver.[7] Lower circulating IGF-1 levels have been correlated with advanced clinicopathologic parameters and poor overall survival (OS) in patients with HCC.[8] This new scoring system, the IGF-CTP classification system, was validated as a means to assess hepatic reserve in different cohorts of patients with HCC and showed promising but inconclusive results regarding the prediction of OS and patient stratification compared with the CTP scoring system.[5,9–12] Notably, these studies were not randomized and had relatively few patients; therefore, they were underpowered to test the superiority of IGF-CTP.

In the Phase III open-label IMbrave150 trial (NCT03434379), CTP Class A patients with unresectable HCC received the anti–programmed death-ligand 1 antibody atezolizumab plus the anti–vascular endothelial growth factor antibody bevacizumab or received sorafenib.[13] The median progression-free survival (PFS) was 6.8 months (95% confidence interval [CI], 5.7–8.3) in the atezolizumab plus bevacizumab (atezolizumab-bevacizumab) group and 4.3 months (95% CI, 4.0–5.6) in the sorafenib group (hazard ratio [HR], 0.59; 95% CI, 0.47–0.76) in the IMbrave150 study. The median OS was not established (NE) and 13.2 months (95% CI, 10.4-NE) in the respective groups (HR, 0.58; 95% CI, 0.42–0.79).[13] On the basis of these findings, the combination therapy became the new standard care for systemic treatment-naive patients with unresectable HCC.[14] Our hypothesis was that prognosis of patients with CTP-A may be further stratified by IGF-1 and IGF-CTP scores. Here, we describe exploratory analyses of outcomes in the phase III IMbrave150 study based on IGF-1 and IGF-CTP scores at baseline and their kinetic changes during treatment.

Patients and Methods

Study Design, Patients, and Sample Collection

The design and methods of the IMbrave150 trial were described previously.[13] Briefly, 501 patients were randomized at a 2:1 ratio to receive either intravenous atezolizumab (1200 mg) plus bevacizumab (15 mg/kg) every 3 weeks or oral sorafenib (400 mg) twice daily until unacceptable toxicity or loss of clinical benefit. Key inclusion criteria were locally advanced, metastatic or unresectable HCC, no prior systemic therapy, Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, and CTP Class A score. The primary endpoints were OS and PFS (assessed by Response Evaluation Criteria in Solid Tumors version 1.1 by an independent review facility). The protocol was approved by the ethics committee or institutional review board of each participating center, written informed consent was obtained from all patients, and the study was conducted in accordance with International Conference on Harmonisation guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. The first IRB approval for IMbrave150 was granted on 19 December 2017 from the City of Hope National Medical Center, Duarte, CA, USA (IRB No. 20172734; Western Institutional Review Board, Inc. Puyallup, WA, USA), in addition to multiple other EC/IRB approvals obtained across all participating sites in the different countries of enrollment. As part of the study, serum samples were collected from all patients (except those enrolled in China) at baseline (on day 1 of cycle 1), during treatment (on day 1 of cycles 2 and 4), and at disease progression. All authors had access to study data and approved the final manuscript.

Serum IGF-1 Level Assessment

Serum IGF-1 levels were measured at the end of the study using an Elecsys IGF-1 enzyme-linked immunoassay (Roche Diagnostics, Indianapolis, IN, USA) with a detection range of 7 to 1600 ng/mL following applicable government regulations and local guidelines for quality control.

IGF-1 and IGF-CTP Scores

The original CTP scores are calculated by assigning points 1–3 to three objective serum measurements (albumin, bilirubin and prothrombin (PT) prolongation time) and two subjective variables (encephalopathy and ascites). For

serum albumin levels, >3.5, 2.8–3.5 and <2.8 g/dL are assigned as CTP points 1, 2 and 3, respectively. For bilirubin, <2, 2–3 and >3 mg/dL are considered as points 1, 2 and 3, respectively. And for PT time, <4, 4–6 and >6 seconds are assigned points 1, 2 and 3, respectively. For encephalopathy, point 1 means no encephalopathy is observed, point 2 means mid-level (grade 1–2) encephalopathy and point 3 corresponds to severe (grade 3–4) encephalopathy. Points 1, 2 and 3 for ascites are assigned to patients without ascites, with mid or moderate amount of ascites and with severe and refractory ascites, respectively. The minimum total score of the above-mentioned 5 variables is 5 and the maximum score is 15. Total points of 5 and 6 are considered CTP class A, of 7–9 points are class B and of points 10–15 are considered class C.

IGF-1 and IGF-CTP scores were determined based on the pre-specified cutoffs that were empirically optimized and reported previously.[5] Briefly, circulating IGF-1 levels were classified as high (>50 ng/mL; Point 1), normal (26–50 ng/mL; Point 2), or low (<26 ng/mL; Point 3). For IGF-CTP scores, the two subjective variables in the original CTP score are replaced with IGF-1 points. So, IGF-CTP scores are calculated by adding points from albumin, bilirubin, PT time and IGF-1. Scores of 4 or 5 areconsidered as IGF-CTP class A, scores of 6 or 7 are considered as IGF-CTP class B and scores of >7 are considered as IGF-CTP class C.

Statistical Analysis

Statistical analyses were performed using R, version 4.0.2 (The R Project for Statistical Computing, r-project.org). The prognostic value of serum IGF-1 and IGF-CTP scores was assessed in each treatment arm using both PFS and OS. Univariate and multivariate analyses were used to assess the predictive value of IGF-1 and IGF-CTP scores for OS and PFS. Associations between uncensored continuous variables were tested using Pearson correlation. Univariate comparisons of discrete values were tested with the Fisher's exact test. Univariate comparisons of continuous values between categories were performed with the Student *t* test on data, log-transformed if appropriate to normalize as judged by visual inspection and prior knowledge (eg, serum protein concentration measurements). Kaplan–Meier methodology was used to estimate survival. Hazard ratio estimates and their 95% CIs and *P* values were determined by using stratified Cox proportional hazards modeling and the log-likelihood test. The proportionality assumption was validated by confirming that there was not a significant correlation between event time and Schoenfeld residual. Multivariate analyses were adjusted for known prognostic factors such as sex, etiology, serum α-fetoprotein level >400 or ≤400 ng/mL, presence of macro- or microvascular invasion or extrahepatic spread, high tumor burden (tumor occupying >50% of the liver), and portal vein tumor thrombus status. *P*-values of 0.05 or less were considered statistically significant.

Results

Patients' Characteristics

As of the date of clinical data cutoff (August 2019), the median follow-up time was 8.6 months (8.9 months for the atezolizumab-bevacizumab arm and 8.1 months for the sorafenib arm). The biomarker-evaluable (BEP) populations included 371 patients (256 from the atezolizumab-bevacizumab arm and 115 from the sorafenib arm) of the 501 patients in the intention-to-treat (ITT) populations. In both treatment arms, the BEP and ITT populations had similar OS (Supplementary Figure 1A and 1B) and PFS (Supplementary Figure 1C and 1D). For the BEP, patients' IGF-1 score (1/2/3) and IGF-CTP score (A/B/C) were determined based on the pre-specified cutoffs that were empirically optimized and reported previously.[5] Although all patients enrolled in IMBrave150 were CTP Class A with an exception of one patient with CTP Class B, reclassification of the BEP patients with the IGF-CTP scores identified 306 patients with IGF-CTP Class A, and 65 patients with IGF-CTP Class B/C (Table 1). Patients' baseline characteristics by IGF-CTP class (Table 1) and IGF-1 levels (Table 2) were found to be comparable by univariate testing, as described in the Patients and Methods section.

Association of Baseline Serum IGF-1 Levels and Clinicopathological Features

In this pre-specified retrospective analysis, we investigated the association of baseline circulating IGF-1 and clinicopathological features. Consistent with previous findings,[7] serum IGF-1 levels were significantly associated with the synthetic function of the liver, showing positive correlation with serum albumin level, a marker of hepatic function

Table 1 Patient Characteristics at Baseline by IGF-CTP Classes

	IGF-CTP A		IGF-CTP B/C	
	Atezo + Bev	**Sorafenib**	**Atezo + Bev**	**Sorafenib**
	(n=212)	**(n=94)**	**(n=44)**	**(n=21)**
Median age (IQR), years	65.0 (14.0)	66.5 (10.8)	65.0 (11.5)	70.0 (17.0)
Male, n (%)	171 (80.7)	77 (81.9)	35 (79.5)	17 (81.0)
Race, n (%)				
Asian	114 (53.8)	57 (60.6)	14 (31.8)	8 (38.1)
Black or African American	3 (1.4)	2 (2.1)	2 (4.5)	0 (0)
Unknown	13 (6.1)	5 (5.3)	4 (9.1)	5 (23.8)
White	82 (38.7)	29 (30.9)	24 (54.5)	8 (38.1)
American Indian or Alaska native	0 (0)	1 (1.1)	0 (0)	0 (0)
Ethnicity, n (%)				
Hispanic or Latino	4 (1.9)	4 (4.3)	2 (4.5)	0 (0)
Not Hispanic or Latino	192 (90.6)	86 (91.5)	38 (86.4)	15 (71.4)
Not stated	7 (3.3)	1 (1.1)	1 (2.3)	3 (14.3)
Unknown	9 (4.2)	3 (3.2)	3 (6.8)	3 (14.3)
Geographic region, n (%)				
Asia excluding Japan	70 (33.0)	34 (36.2)	3 (6.8)	6 (28.6)
Rest of world	142 (67.0)	60 (63.8)	41 (93.2)	15 (71.4)
BCLC stage, n (%)				
Stage A1	3 (1.4)	1 (1.1)	1 (2.3)	0 (0)
Stage A4	2 (0.9)	2 (2.1)	1 (2.3)	0 (0)
Stage B	31 (14.6)	17 (18.1)	7 (15.9)	2 (9.5)
Stage C	176 (83.0)	74 (78.7)	35 (79.5)	19 (90.5)
ECOG performance status score, n (%)				
0	137 (64.6)	66 (70.2)	27 (61.4)	8 (38.1)
1	75 (35.4)	28 (29.8)	17 (38.6)	13 (61.9)
Presence of MVI/EHS, n (%)	162 (76.4)	68 (72.3)	33 (75.0)	16 (76.2)
Child-Pugh score, n (%)				
A5	158 (74.5)	79 (84.0)	17 (38.6)	7 (33.3)
A6	52 (24.5)	15 (16.0)	27 (61.4)	14 (66.7)
Etiology, n (%)				
Hepatitis B	90 (42.5)	41 (43.6)	13 (29.5)	8 (38.1)
Hepatitis C	52 (24.5)	18 (19.1)	10 (22.7)	6 (28.6)

(*Continued*)

Table 1 (Continued).

	IGF-CTP A		IGF-CTP B/C	
	Atezo + Bev	**Sorafenib**	**Atezo + Bev**	**Sorafenib**
	(n=212)	**(n=94)**	**(n=44)**	**(n=21)**
Non-viral	70 (33.0)	35 (37.2)	21 (47.7)	7 (33.3)
High risk population, n (%)	34 (16.0)	18 (19.1)	16 (36.4)	9 (42.9)
AFP ≥ 400 ng per mL, n (%)	72 (34.0)	32 (34.0)	19 (43.2)	10 (47.6)
Varices present, n (%)	57 (26.9)	21 (22.3)	16 (36.4)	9 (42.9)
Tumor burden > 50%, n (%)	7 (3.3)	4 (4.3)	6 (13.6)	6 (28.6)
Portal venous tumor thrombus, n (%)				
N	106 (50.0)	47 (50.0)	13 (29.5)	5 (23.8)
VP1	18 (8.5)	10 (10.6)	2 (4.5)	2 (9.5)
VP2	31 (14.6)	13 (13.8)	9 (20.5)	4 (19.0)
VP3	33 (15.6)	13 (13.8)	9 (20.5)	4 (19.0)
VP4	24 (11.3)	11 (11.7)	11 (25.0)	6 (28.6)

Abbreviations: AFP, α-fetoprotein; Atezo, atezolizumab; BCLC, Barcelona Clinic Liver Cancer; Bev, bevacizumab; CTP, Child-Turcotte-Pugh; ECOG, Eastern Cooperative Oncology Group; EHS, extrahepatic spread; IGF, insulin-like growth factor-1; IQR, interquartile range; MVI, macrovascular invasion; N, no tumor thrombus in the portal vein; VP1, presence of a tumor thrombus distal to, but not in, the second-order branches of the portal vein; VP2, presence of a tumor thrombus in the second-order branches of the portal vein; VP3, presence of a tumor thrombus in the first-order branches of the portal vein; VP4, presence of a tumor thrombus in the main trunk of the portal vein or a portal vein branch contralateral to the primarily involved lobe (or both).

Table 2 Patient Characteristics at Baseline by IGF-1 Levels

	IGF-1 Point 1		IGF1 Point 2 or 3	
	Atezo + Bev	**Sorafenib**	**Atezo + Bev**	**Sorafenib**
	(n=172)	**(n=78)**	**(n=84)**	**(n=37)**
Median age (IQR), years	65.0 (14.0)	65.0 (11.8)	67.0 (12.0)	70.0 (9.00)
Male, n (%)	144 (83.7)	63 (80.8)	62 (73.8)	31 (83.8)
Race, n (%)				
Asian	94 (54.7)	49 (62.8)	34 (40.5)	16 (43.2)
Black or African American	3 (1.7)	1 (1.3)	2 (2.4)	1 (2.7)
Unknown	11 (6.4)	3 (3.8)	6 (7.1)	7 (18.9)
White	64 (37.2)	24 (30.8)	42 (50.0)	13 (35.1)
American Indian or Alaska native	0 (0)	1 (1.3)	0 (0)	0 (0)
Ethnicity, n (%)				
Hispanic or Latino	4 (2.3)	3 (3.8)	2 (2.4)	1 (2.7)
Not Hispanic or Latino	155 (90.1)	72 (92.3)	75 (89.3)	29 (78.4)
Not stated	7 (4.1)	0 (0)	1 (1.2)	4 (10.8)

(*Continued*)

Table 2 (Continued).

	IGF-1 Point 1		IGF1 Point 2 or 3	
	Atezo + Bev	**Sorafenib**	**Atezo + Bev**	**Sorafenib**
	(n=172)	**(n=78)**	**(n=84)**	**(n=37)**
Unknown	6 (3.5)	3 (3.8)	6 (7.1)	3 (8.1)
Geographic region, n (%)				
Asia excluding Japan	58 (33.7)	31 (39.7)	15 (17.9)	9 (24.3)
Rest of world	114 (66.3)	47 (60.3)	69 (82.1)	28 (75.7)
BCLC stage, n (%)				
Stage A1	2 (1.2)	1 (1.3)	2 (2.4)	0 (0)
Stage A4	1 (0.6)	1 (1.3)	2 (2.4)	1 (2.7)
Stage B	27 (15.7)	13 (16.7)	11 (13.1)	6 (16.2)
Stage C	142 (82.6)	63 (80.8)	69 (82.1)	30 (81.1)
ECOG performance status score, n (%)				
0	115 (66.9)	51 (65.4)	49 (58.3)	23 (62.2)
1	57 (33.1)	27 (34.6)	35 (41.7)	14 (37.8)
Presence of MVI/EHS, n (%)	132 (76.7)	57 (73.1)	63 (75.0)	27 (73.0)
Child-Pugh score, n (%)				
A5	130 (75.6)	64 (82.1)	45 (53.6)	22 (59.5)
A6	40 (23.3)	14 (17.9)	39 (46.4)	15 (40.5)
Etiology, n (%)				
Hepatitis B	78 (45.3)	36 (46.2)	25 (29.8)	13 (35.1)
Hepatitis C	42 (24.4)	14 (17.9)	20 (23.8)	10 (27.0)
Non-viral	52 (30.2)	28 (35.9)	39 (46.4)	14 (37.8)
High risk population, n (%)	27 (15.7)	16 (20.5)	23 (27.4)	11 (29.7)
AFP ≥ 400 ng per mL, n (%)	59 (34.3)	27 (34.6)	32 (38.1)	15 (40.5)
Varices present, n (%)	38 (22.1)	17 (21.8)	35 (41.7)	13 (35.1)
Tumor burden > 50%, n (%)	4 (2.3)	3 (3.8)	9 (10.7)	7 (18.9)
Portal venous tumor thrombus, n (%)				
N	87 (50.6)	37 (47.4)	32 (38.1)	15 (40.5)
VP1	16 (9.3)	9 (11.5)	4 (4.8)	3 (8.1)
VP2	24 (14.0)	10 (12.8)	16 (19.0)	7 (18.9)
VP3	25 (14.5)	11 (14.1)	17 (20.2)	6 (16.2)
VP4	20 (11.6)	11 (14.1)	15 (17.9)	6 (16.2)

Abbreviations: AFP, α-fetoprotein; Atezo, atezolizumab; BCLC, Barcelona Clinic Liver Cancer; Bev, bevacizumab; CTP, Child-Turcotte-Pugh; ECOG, Eastern Cooperative Oncology Group; EHS, extrahepatic spread; IGF, insulin-like growth factor-1; IQR, interquartile range; MVI, macrovascular invasion.

reserve, and negative correlation with biochemical markers of liver damage or dysfunction, including serum levels of bilirubin, alkaline phosphatase, alanine transaminase (ALT), and aspartate transaminase (AST) (Figure 1A). Low serum IGF-1 level was also associated with several unfavorable disease status factors, including high tumor burden, high risk status (defined by tumor invasion of the main portal vein and/or the portal vein branch contralateral to the primarily involved lobe [VP4], and/or bile duct invasion and/or tumor occupying ≥50% of the liver), and extent of portal vein thrombosis (Figure 1B–D). Patients whose etiology was either non-viral or hepatitis C virus (HCV)–driven HCC had significantly lower serum IGF-1 levels than those whose etiology was hepatitis B virus (HBV)–driven HCC (Figure 1E).

Prognostic and Predictive Effects of Baseline IGF-CTP Scores

To evaluate the prognostic effect of the IGF-CTP score in patients with HCC, we first investigated whether the IGF-CTP score was associated with the clinical outcomes in both treatment arms. Multivariate analysis (Table 3, Supplementary Figure 2) revealed that IGF-CTP score was an independent predictor of survival regardless of treatment. Patients with IGF-CTP Class A (IGF-CTP A) scores had significantly longer OS than those with IGF-CTP Class B or C (IGF-CTP B/C) scores in both the atezolizumab-bevacizumab arm (median OS, NE vs 7.2 months; HR, 0.33; 95% CI, 0.20–0.56; $P<0.001$) and the sorafenib arm (median OS, 15.1 vs 5.1 months; HR, 0.32; 95% CI, 0.16–0.65; $P=0.002$; Figure 2A). Similarly, patients with IGF-CTP A scores also had longer PFS than those with IGF-CTP B/C scores in the sorafenib arm

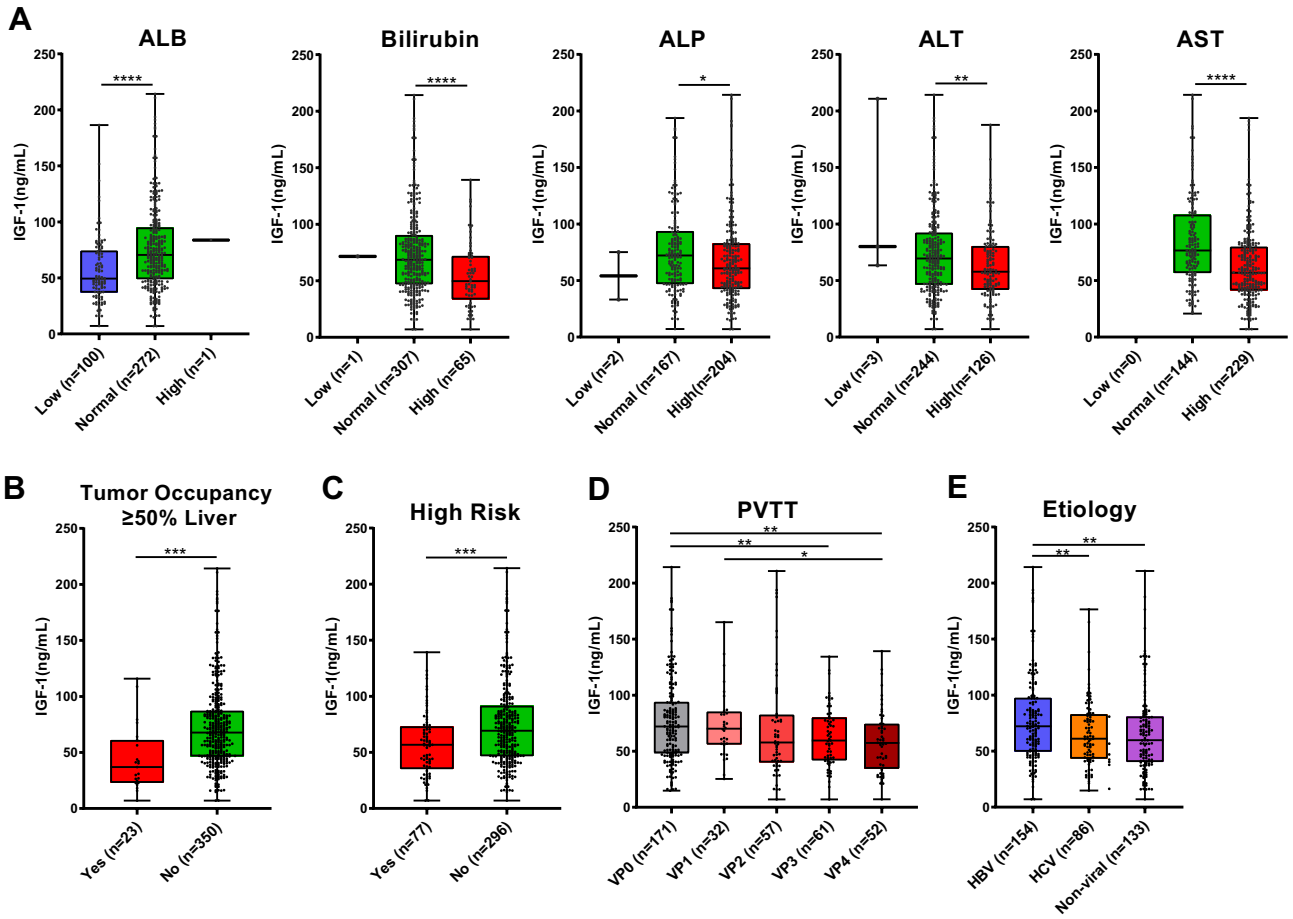

Figure 1 Association of serum insulin-like growth factor-1 (IGF-1) levels with clinicopathological features. Box plots show the associations between serum IGF-1 levels and (**A**) serum levels of albumin (ALB), bilirubin, alkaline phosphatase (ALP), alanine transaminase (ALT), and aspartate transaminase (AST); (**B**) tumor occupancy of ≥50% of liver; (**C**) high-risk status; (**D**) portal vein tumor thrombosis (PVTT); and (**E**) etiology. The upper and lower borders of each box represent maximum and minimum values, respectively, and the line inside each box represents the median of each data set. The points are test values of individual patients. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$. High risk was defined as tumor invasion into the main trunk of the portal vein and/or the portal vein branch contralateral to the primarily involved lobe (VP4), and/or bile duct invasion and/or tumor occupancy of ≥50% of liver.

Table 3 Summary of Survival Models for IGF-1 and IGF-CTP Biomarkers

OS								
	Atezolizumab-bevacizumab				Sorafenib			
Variable	**Median, mo**	**HR**	**95% CI**	**P**	**Median, mo**	**HR**	**95% CI**	**P**
IGF-CTP Class								
IGF-CTP A	NE	-	-	-	15.1	-	-	-
IGF-CTP B/C	7.2	0.33	0.20–0.56	0.001	5.1	0.32	0.16–0.65	0.002
IGF-1 Score								
IGF-1 Point 1	NE	-	-	-	15.1	-	-	-
IGF-1 Point 2/3	10.3	0.33	0.20–0.55	0.001	7.5	0.48	0.26–0.89	0.02
IGF-CTP Change								
Deteriorated	8.6	-	-	-	13.3	-	-	-
Stable	NE	17.01	7.1–40.18	0.001	NE	1.4	0.52–3.81	0.51
IGF-1 Change								
Deteriorated	13	-	-	-	7.4	-	-	-
Stable	NE	3.7	1.56–8.77	0.003	NE	5.83	1.88–18.12	0.002
PFS								
	Atezolizumab-bevacizumab				Sorafenib			
Variable	**Median, mo**	**HR**	**95% CI**	**P**	**Median, mo**	**HR**	**95% CI**	**P**
IGF-CTP Class								
IGF-CTP A	7.8	-	-	-	4.5	-	-	-
IGF-CTP B/C	5.5	0.69	0.46–1.05	0.087	1.9	0.47	0.25–0.85	0.013
IGF-1 Score								
IGF-1 Point 1	9.5	-	-	-	4.3	-	-	-
IGF-1 Point 2/3	5.5	0.6	0.42–0.85	0.005	4.2	0.78	0.48–1.27	0.3
IGF-CTP Change								
Deteriorated	4.1	-	-	-	4.8	-	-	-
Stable	8.8	2.22	1.45–3.41	0.001	4	0.89	0.45–1.75	0.74
IGF-1 Change								
Deteriorated	5.3	-	-	-	4.1	-	-	-
Stable	7.7	1.49	0.94–2.36	0.09	4.2	1.14	0.62–2.1	0.66

Notes: IGF-CTP class and IGF-1 score were determined based on pre-specified cutoffs (Patients and Methods). HR was derived based on within-arm Cox Proportional Hazards modeling of IGF-1 and IGF-CTP biomarkers. 95% CI is the Wald Test confidence interval. *P* is the Wald Test P-value.

(median PFS, 4.5 vs 1.9 months; HR, 0.47; 95% CI, 0.25–0.85; P=0.013) and a similar trend (not statistically significant) in the atezolizumab-bevacizumab arm (median PFS, 7.8 vs 5.5 months; HR, 0.69; 95% CI, 0.46–1.05; P=0.087; Figure 2B). Overall survival multivariate modeling comparison of IGF-CTP to other clinical features showed that only overall tumor burden was more strongly prognostic, and metastatic status was substantially less so (Supplementary Figure 2).

Furthermore, we evaluated whether IGF-CTP score has a potential predictive effect between both arms. Multivariate analysis revealed that patients with IGF-CTP A or Class B or C score at baseline had similar survival benefits with atezolizumab-bevacizumab and sorafenib (Figure 2C and D).

Prognostic and Predictive Effects of Baseline IGF-1 Scores

Multivariate analysis (Table 3, Supplementary Figure 2) revealed that patients with baseline IGF-1 Point 1 had significantly longer OS than those with baseline Points 2 or 3 (Point 2/3) in both the atezolizumab-bevacizumab arm (median OS, NE vs 10.3 months; HR, 0.33; 95% CI, 0.20–0.55; P<0.001) and sorafenib arm (median OS, 15.1 vs 7.5

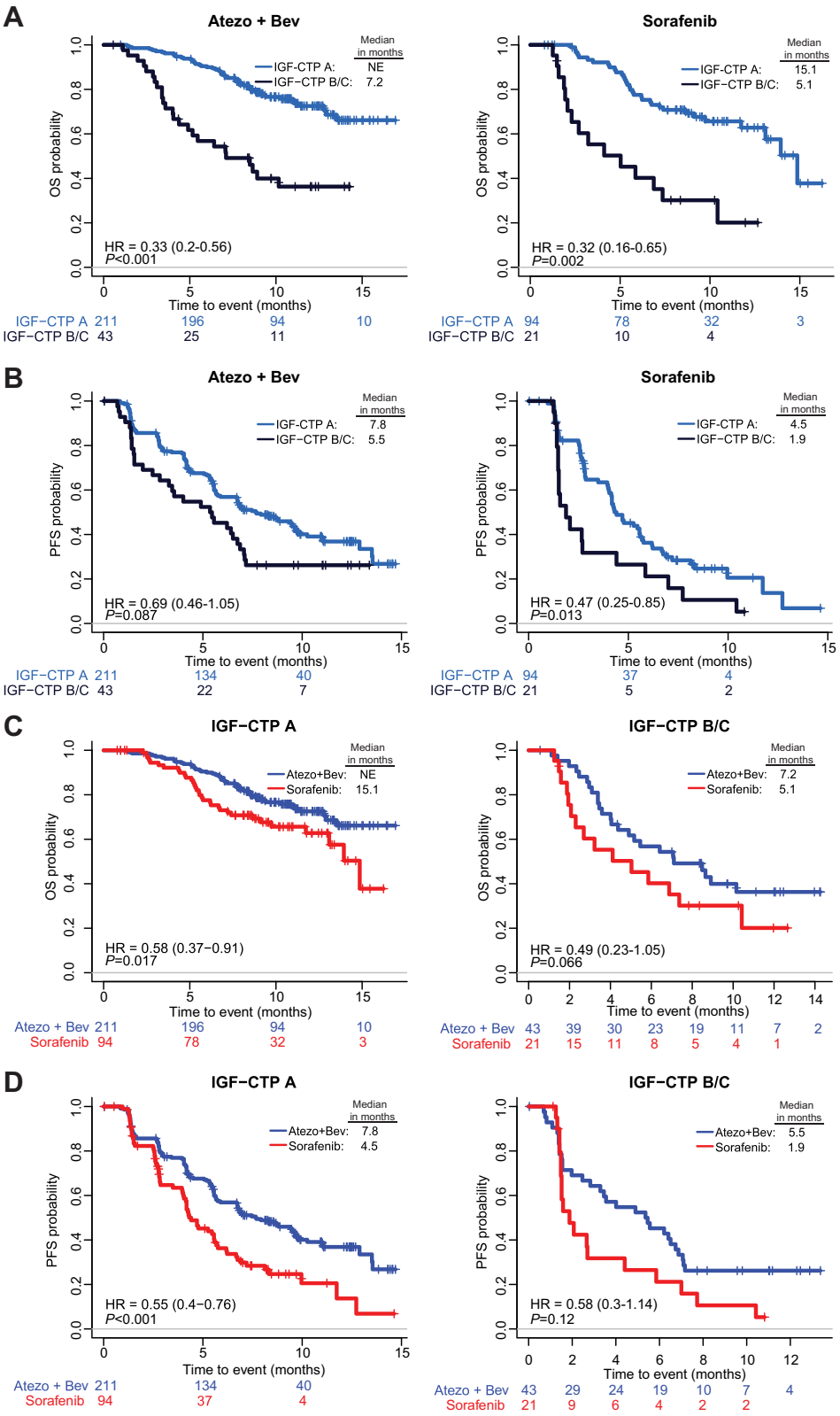

Figure 2 Prognostic and predictive effects of baseline IGF Child-Turcotte-Pugh (CTP) score. The prognostic effects of IGF-CTP scores are shown with Kaplan-Meier (KM) curves of OS (**A**) and PFS (**B**) stratified by IGF-CTP A vs B/C for patients within the atezolizumab-bevacizumab (Atezo+Bev) or sorafenib treatment arms. The predictive effect of IGF-CTP scores on Atezo+Bev benefit over sorafenib is shown with KM curves of OS (**C**) and PFS (**D**) stratified by treatment arms among patients with IGF-CTP A scores or with B/C scores. The HRs (95% CIs) and P values shown in each graph are adjusted for known prognostic factors described in the Patients and Methods section. NE, not established.

months; HR, 0.48; 95% CI, 0.26–0.89; *P*=0.02; Figure 3A). Similarly, in the atezolizumab-bevacizumab arm, patients with IGF-1 Point 1 had significantly longer PFS than those with Point 2 or 3 (Point 2/3) (median PFS, 9.5 vs 5.5 months; HR, 0.60; 95% CI, 0.42–0.85; *P*=0.005; Figure 3B). However, IGF-1 Point 1 did not show significant association with PFS in the sorafenib arm (median PFS, 4.3 vs 4.2 months; HR, 0.78, 95% CI, 0.48–1.27; *P*=0.3; Figure 3B). Similar to the IGF-CTP score, the IGF-1 score demonstrated no significant predictive effect for greater survival benefits with atezolizumab-bevacizumab vs sorafenib treatment (Figure 3C and 3D).

Kinetics of IGF-1 and IGF-CTP Scores and Their Association with Survival Outcomes

To understand the kinetics of IGF-1 and IGF-CTP scores, we longitudinally assessed patients' serum IGF-1 levels at baseline and after 1 cycle of treatment. Not all patients had the same IGF-1 and IGF-CTP scores during treatment as they did at baseline. Thirty-two patients in the atezolizumab-bevacizumab arm and 14 patients in the sorafenib arm had IGF-1 Point 1 at baseline but Points 2 or 3 after treatment. Patients with increases in IGF-1 score had shorter OS than patients with stable IGF-1 score of 1 in both the atezolizumab-bevacizumab arm (median OS, 13.0 months vs NE; HR, 3.70; 95% CI, 1.56–8.77; *P*=0.003) and sorafenib arm (median OS, 7.4 months vs NE; HR, 5.83; 95% CI, 1.88–18.12; *P*=0.0023; Figure 4A and B). Similarly, 34 patients in the atezolizumab-bevacizumab arm and 13 patients in the sorafenib arm had an IGF-CTP A score at baseline but a B/C score after treatment. In the atezolizumab-bevacizumab arm, patients whose IGF-CTP scores increased had poorer OS than those who remained in IGF-CTP A (median OS, 8.6 months vs NE; HR, 17.01; 95% CI, 7.1–40.18; *P*=0.001; Figure 4C). No definitive conclusion could be made in the sorafenib arm because the number of patients with deteriorated IGF-CTP was too limited (median OS, 13.3 months vs NE; HR, 1.4; 95% CI, 0.52–3.81; *P*=0.51; Figure 4D). Although not statistically significant, increases in IGF-1 or IGF-CTP scores showed a trend toward poorer PFS in both treatment arms (Supplementary Figure 3A–D).

Discussion

This biomarker analysis from the randomized Phase III IMbrave150 study demonstrated that both baseline and kinetic change of IGF-CTP and IGF-1 scores were independently prognostic of PFS and OS for patients with unresectable HCC treated with atezolizumab-bevacizumab or sorafenib. These findings also validated our hypothesis that the serum biomarker IGF-1 derived novel classification system might enable improved patient stratification over the original CTP classification system within CTP Class A.

Notably, despite the CTP Class A heterogeneity, patients with HCC with CTP Class A scores remain the classic population for enrollment in clinical trials and to receive active therapy in routine practice. Therefore, developing a more prognostic scoring system to refine patient stratification and equal randomization in trials is crucial to accurately interpret trial results and compare different arms of randomized trials. Therefore, the superiority of IGF-CTP and IGF-1 scores over original CTP score is clinically meaningful.

Others have suggested that serum IGF-1 level is a surrogate marker of functional liver reserve, as most IGF-1 is produced in the liver.[7,10] Patients with HCC have lower serum IGF-l levels than healthy controls.[15] Moreover, more advanced HCC parameters have been associated with lower serum IGF-1 levels.[8,12,16,17] In the present study, serum IGF-1 levels were associated with ALT, AST, alkaline phosphatase, bilirubin, and albumin levels, as well as tumor burden, risk status, portal vein thrombosis, and etiology. Kaseb et al similarly showed that IGF-1 level is associated with bilirubin level and tumor size and is most strongly correlated with AST level.[8] Huber et al showed that serum IGF-1 levels are associated with ALT, AST, bilirubin, albumin level, international normalized ratio, platelet count, and Model for End-Stage Liver Disease score.[11]

In our study, baseline IGF-1 level was an independent prognostic factor in both the atezolizumab-bevacizumab and sorafenib arms. Previous studies also showed that lower serum IGF-1 levels are associated with poorer survival among patients with HCC, although those studies used different cutoff values for serum IGF-1 levels.[8,11]

The IGF-CTP classification system was previously tested in US-based training and validation cohorts, and in both cohorts, the IGF-CTP system showed better stratification and survival prediction than the CTP system.[5] However, this single-center study was more heterogeneous in patient population and did not assess the IGF-CTP score's ability to predict specific treatment outcome. In the present study, patients in the IMbrave150 study, all of whom initially had CTP

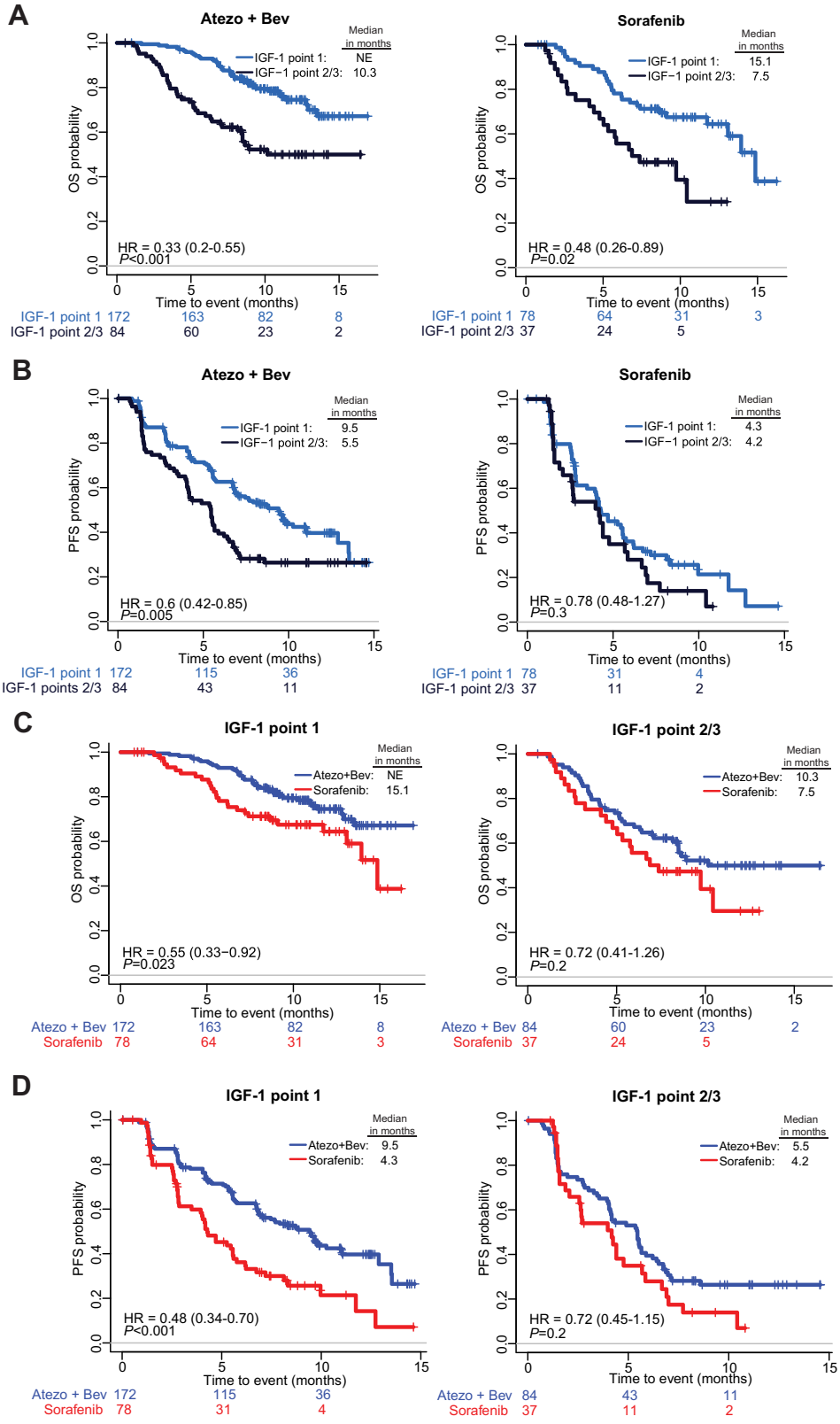

Figure 3 Prognostic and predictive effects of baseline IGF levels (Point 1 vs Point 2/3). The prognostic effects of IGF-1 levels are shown with KM curves of OS (**A**) and PFS (**B**) stratified by IGF-1 Point 1 vs Point 2/3 for patients within the Atezo+Bev or sorafenib arms. The predictive effect of IGF-1 levels on Atezo+Bev benefit over sorafenib is shown with KM curves of OS (**C**) and PFS (**D**) stratified by treatment arms within patients with Point 1 or with Point 2/3 IGF-1 levels. The HRs (95% CIs) and P values shown in each graph are adjusted for known prognostic factors described in the Patients and Methods section. NE, not established.

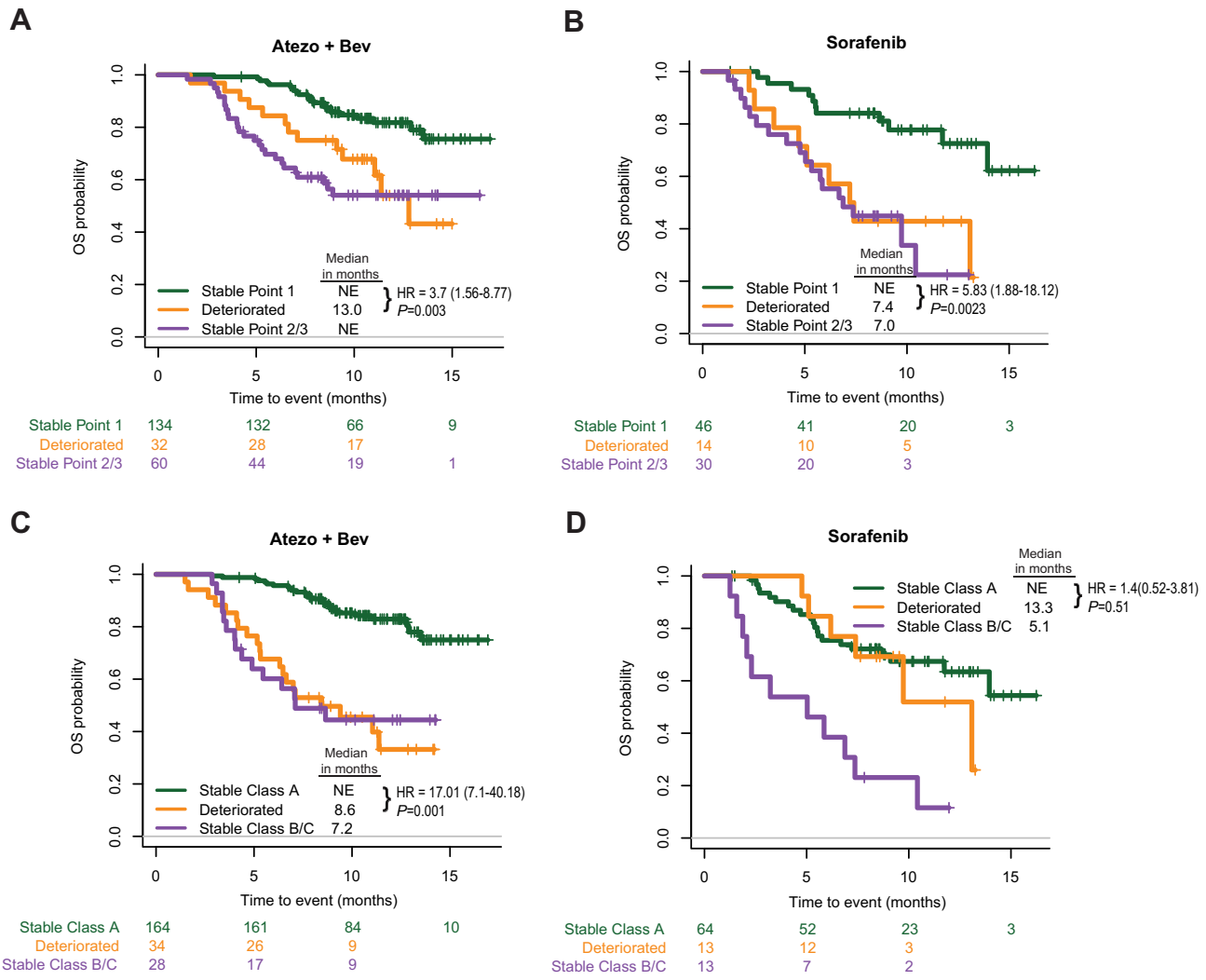

Figure 4 Association of kinetics of IGF-1 levels or IGF-CTP scores with survival outcomes. KM curves of OS stratified after 1 cycle of Atezo+Bev (**A**) or sorafenib (**B**) treatment IGF-1 levels stayed at Point 1 (Stable Point 1), decreased from Point 1 to Point 2/3 (Deteriorated) or stayed at Point 2/3 (Stable Point 2/3). KM curves of OS stratified after 1 cycle of Atezo+Bev (**C**) or sorafenib (**D**) treatment IGF-CTP classes stayed at A (Stable A), changed to B/C (Deteriorated) or stayed at B/C (Stable Class B/C).

Class A scores, were stratified according to IGF-CTP score. Regardless of treatment, patients with baseline IGF-CTP A scores had significantly longer OS than those with IGF-CTP B/C scores, and baseline IGF-CTP A was predictive of survival outcomes for patients treated with atezolizumab-bevacizumab vs sorafenib.

The present study improves upon other studies that evaluated the IGF-CTP classification system in different cohorts of patients with HCC. In one cohort with HCC and underlying HCV, 32.5% of patients with CTP Class A scores were reclassified as having IGF-CTP Class B scores, and these patients had significantly shorter OS than patients reclassified as having IGF-CTP A scores.[10] Similarly, patients with CTP Class B scores who were reclassified as having IGF-CTP A scores had better survival than patients reclassified as having IGF-CTP Class B scores. This study showed that the IGF-CTP classification system provides better survival prediction and patient stratification than the CTP classification system.[10] In another cohort of 393 patients with HCC, the prognostic value of IGF-CTP scores was higher than that of CTP scores.[12] However, this difference was not statistically significant, possibly because most patients (86%) had the same class score by either classification system. In addition, most patients (71.5%) had early- or intermediate-stage HCC (Barcelona Clinic Liver Cancer Stage 0-B), which may have independently affected survival, since patients with Barcelona Clinic Liver Cancer Stage 0-A disease might have received curative treatment such as surgery, transplant, or ablation. Importantly, the majority of the patients in the study (78.9%) had HBV as the primary etiology of the tumor.[12] In another large cohort of 216 patients with

HCC, 35.6% of patients were reclassified using the IGF-CTP classification system.[11] However, the two classification systems offered similar survival prediction. Unlike previous cohorts, most patients (44.4%) had underlying alcohol-induced liver disease. Finally, in a more recent cohort in which many patients (42.8%) had underlying HBV as the primary etiology of the tumor, 51.8% of the patients were reclassified; however, IGF-CTP scores did not predict OS better than the original CTP scores.[9] Collectively, the patients in these cohorts had heterogeneous demographics, underlying risk factors, HCC stages, and treatments that may have independently affected their survival. More importantly, these studies were retrospective and were not powered to detect significant differences in patient risk stratification and in predicting OS with the IGF-CTP and the original CTP scoring systems. However, all patients in the present study had unresectable HCC and CTP Class A scores at the time of trial enrollment, and the baseline characteristics of patients grouped by IGF-CTP score were generally well balanced. Of note, in this study, the most common cause of HCC was HBV (40.9%), followed by non-viral causes (35.8%) and HCV (23.1%), which covered all major underlying pathologies for HCC.

In the present study, no significant predictive effect was observed for IGF-CTP or IGF-1 point scores in terms of predicting OS and PFS benefits in the atezolizumab-bevacizumab arm compared with the sorafenib arm. This suggests that these scores are more suitable to serve as prognostic biomarkers rather than predictive biomarkers of response to combination therapy.

Limitations of our analysis include the retrospective nature of the IGF-CTP score calculation after completion of the IMbrave150 trial and lack of stratification based on baseline IGF-CTP score. This was also a post hoc subgroup analysis and was not powered to look at differences by IGF-CTP status. However, the analysis has several unique strengths, including the large number of patients, the randomized Phase III nature of the trial, and the hypothesis-driven type of analyses. Thus, the study results are clinically meaningful and informative to the HCC field, given that integrating baseline IGF-CTP score into future studies could validate its utility in equal stratification of patients in randomized studies and in guiding treatment decisions in routine practice.

In conclusion, this study is the first to investigate the prognostic and predictive values of IGF-1 and IGF-CTP scores in patients with unresectable HCC enrolled in a large, randomized trial. Our results demonstrated that IGF-CTP and IGF-1 classification predicted OS and PFS regardless of treatment and offered a potentially better patient stratification than CTP classification. Furthermore, serum IGF-1 level was correlated with several clinical features and was prognostic. The serum IGF-1 derived scoring system should be validated in large, prospective HCC clinical trials by including it as a stratification factor to test the prognostic and potentially predictive abilities in local and systemic therapy trials before its universal application. Importantly, serum IGF-1 level is a routine laboratory test that can be readily implemented clinically, even in low-resource settings. Thus, the eventual implementation of the serum biomarker IGF-1 derived scoring system will be an improvement over the status quo of relying solely on CTP Class A scores to select and stratify clinical trial candidates and treat patients in routine practice.

Data Sharing Statement

Serum IGF-1 data for the IMbrave150 trial will be deposited to the European Genome-Phenome Archive under accession number EGAS00001005519. Qualified researchers may request access to individual patient-level data through the clinical study data request platform at http://www.clinicalstudydatarequest.com. Further details on Roche's criteria for eligible studies are available at https://clinicalstudydatarequest.com/StudySponsors/Study-Sponsors-Roche.aspx. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see http://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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