Original Article
Combination of CRAFITY score with Alpha-fetoprotein response predicts a favorable outcome of atezolizumab plus bevacizumab for unresectable hepatocellular carcinoma

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Abstract: Immune checkpoint inhibitors (ICIs) with atezolizumab plus bevacizumab are promising agents for unresectable hepatocellular carcinoma (HCC). We tried to guide the treatment based on recent developed CRAFITY score combining with on-treatment AFP response. Eighty-nine patients who received atezolizumab plus bevacizumab regardless of as a first-line therapy or not for unresectable HCC were enrolled for analyses. Radiologic evaluation was based on modified Response Evaluation Criteria in Solid Tumors (mRECIST). The objective response rate (ORR) and disease control rate (DCR) were 25.0% and 65.5%, respectively. Multivariate analysis showed that low CRAFITY score (AFP<100 ng/ml or CRP<10 mg/l) and satisfactory AFP response at 6 weeks (≥75% decrease or ≤10% increase from baseline) were independent factors determining good overall survival (OS) (hazard ratio [HR]=0.143, P=0.002 & HR=0.337, P=0.031), progression-free survival (PFS) (HR=0.419, P=0.022 & HR=0.429, P=0.025) and good responder (odds ratio [OR]=1.763, P=0.044 & OR=3.881, P=0.011). Patients were further divided into three classes by combination of CRAFITY score and AFP response at 6 weeks [The CAR (CRAFITY score and AFP-Response) classification)]: low CRAFITY score with satisfactory AFP response at 6 weeks (class I), either high CRAFITY score or unsatisfactory AFP response at 6 weeks (class II) and high CRAFITY score together with unsatisfactory AFP response at 6 weeks (class III). ORR was 35.0%, 18.2%, and 0% in class I, II and III patients, respectively (overall P=0.034). Patients in the class I had the best OS and PFS, followed by class II and class III (median OS: not reached vs. 11.1 vs. 4.3 months, log-rank P<0.001; median PFS: 7.9 vs. 6.6 vs. 2.6 months, log-rank P=0.001). Combination CRAFITY score and AFP response at 6 weeks with AUROC predicts OS and tumor response to be 0.809 and 0.798, respectively, better than either CRAFITY score (0.771 & 0.750) or AFP response at 6 weeks (0.725 & 0.680) alone. In conclusions, the CAR classification which combining CRAFITY score and AFP response at 6 weeks provides a practical guidance for atezolizumab plus bevacizumab therapy in unresectable HCC patients.

Keywords: CAR classification, hepatocellular carcinoma, atezolizumab plus bevacizumab, prognosis

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide [1] that patients are often diagnosed at an advanced stage without the opportunity to receive curative treatments [2, 3]. The atezolizumab plus bevacizumab combination therapy was approved in 2020 as the first immune-combined therapy for HCC and demonstrated better overall survival (OS), progression-free survival (PFS) as well as response rate than sorafenib [4, 5], that is now replacing the previously recommended therapy and widely used worldwide.

Alpha-fetoprotein (AFP) is widely used not only for the diagnosis of HCC but also as adjunctive

diagnostic tests to evaluate treatment effect in several studies. A decline of AFP level after therapy is associated with therapeutic efficacy and prognosis in patients treated with systemic chemotherapy [6-8], antiangiogenic therapy [9] and molecular-targeted therapy [10, 11]. Early changes in AFP within 4 weeks is also useful for predicting the efficacy of immune checkpoint inhibitor (ICI) [12-14]. However, the correlation between changes in AFP level at which definite timepoint during treatment and the therapeutic efficacy of atezolizumab plus bevacizumab is still not clear. Recently, data from group A of the phase 1b GO30140 trial had been recently reported by Zhu et al [15] demonstrated that, compared with baseline AFP levels, a decrease in AFP levels of 75% or greater or increases of 10% or less at 6 weeks was significantly associated with OS and response versus those without AFP change from baseline. On the other hand, a new CRAFITY score composed of baseline AFP≥100 ng/ml and C-reactive protein (CRP) ≥1 mg/dl level (0 point: AFP<100 ng/ml and CRP<10 mg/l, 1 point: either AFP≥100 ng/ml or CRP≥10 mg/l, or 2 points: AFP≥100 ng/ml and CRP≥10 mg/l) is developed and validated to predict likelihood of immunotherapy success as well as improved survival in patients with advanced HCC who received ICI [16].

In the present study, we tried to investigate the outcome of atezolizumab plus bevacizumab based on baseline CRAFITY score combining with on-treatment AFP response at 6 weeks after the initiation of therapy to early estimate the prognosis and guide the therapy for unresectable HCC patients.

Patients and methods

Patient recruitment

A total of 116 unresectable HCC patients who received atezolizumab plus bevacizumab as first or beyond a first-line systemic therapy because their tumor burden fulfilled with Barcelona Clinic Liver Cancer (BCLC) stage C or not suitable for locoregional therapy in BCLC stage B from September 2020 to January 2022 were retrospectively enrolled. Patients who received only one cycle due to poor liver function, economic problem, lost to follow-up, had ICI as an adjuvant therapy after curative ablation, and had double malignancies were all excluded.

Finally, 89 patients were included for analysis (Supplementary Figure 1). All patients received atezolizumab 1,200 mg and bevacizumab 5-7.5 mg/kg intravenously every 3 weeks according to the Patient Support Program (PSP) in Taiwan. Adverse events (AEs) were evaluated based on the Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE; version 5.0).

Diagnosis of hepatocellular carcinoma and follow-up protocol

HCC was diagnosed according to the European Association for the Study of the Liver/ European Organization for Research and Treatment of Cancer (EASL/EORTC) diagnostic guidelines [2]. Radiological antitumor responses were evaluated by two independent radiologists according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [17] and modified RECIST (mRECIST) [18]. Objective response rate (ORR) was assessed as complete response (CR) plus partial response (PR) and disease control rate (DCR) was assessed as ORR plus stable disease (SD). Image study with dynamic computerized tomography (CT) or Magnetic Resonance Imaging (MRI) were monitored every 9-12 weeks and serum AFP levels were measured every 3 weeks post therapy. Baseline AFP level was measured within 14 days before initiation of therapy.

Statistical analysis and definitions

Categorical variables between the two groups were calculated by Chi-square. Descriptive data with normal distribution are presented as mean ± standard deviation (SD), otherwise as median (interquartile range, IQR). The independent Student's test and Mann-Whitney U test were used to assess differences between groups in normal distributed and non-normal distributed groups separately. Stepwise Cox regression models were used to determine the predictors of OS and PFS. Logistic regression models were used to determine the predictors of tumor response. A two-tailed P value <0.05 was considered as statistically significant.

PFS was defined as the time from the date of the first atezolizumab plus bevacizumab administration until radiological disease progression or death, whichever came first. Patients were censored at the date of the last contact or data

Table 1. Baseline characteristics of enrolled patients

Variables	No. of patients (N=89)	%
Age (years-old)	61.3 (IQR 56.4-67.8)	100
Male gender	75	84.3
BW (kg)	66.3 (IQR 57.0-74.9)	100
Etiology		
HBV/HCV/NBNC	69/10/10	77.6/11.2/11.2
ECOG PS 0/1/2	35/49/5	39.3/55.1/5.6
Child-Pugh A/B	76/13	85.4/14.6
ALBI grade I/II/III*	34/50/1	40.0/58.8/1.2
Portal vein thrombosis	45	50.6
Vp3/4	26/16	57.8/35.6
Esophageal varices	22	24.7
Extra-hepatic metastasis	35	39.3
AFP (ng/ml)	354 (IQR 18-3596)	100
≥400	43	48.3
BCLC stage B/C	23/66	25.8/74.2
Tumor size, maximum (cm)	8.0 (IQR 4.3-11.0)	100
Beyond up-to-seven	76	85.4
Lines of systemic therapy		
1/≥2	49/40	55.1/44.9
Prior resection history	12	13.5
Prior locoregional therapy	54	60.7
TACE/RFA/HAIC/RT	48/18/4/11	88.9/33.3/7.4/20.4
Previous TKI therapy	33	37.1
Sorafenib/Regorafenib/Lenvatinib/cabozantinib	19/7/14/1	57.6/21.2/42.4/3.0
Observation period (months)	7.2 (IQR 4.0-11.0)	100
Treatment cycles	4 (IQR 3-6)	100
Mortality	29	32.6

Abbreviations: AFP, Alpha-fetoprotein; ALBI, Albumin-bilirubin index; BCLC, Barcelona Clinic Liver Cancer; BW, Body weight; ECOG, Eastern Cooperative Oncology Group; HAIC, Hepatic artery chemotherapy infusion; HBV, Hepatitis B virus; HCV, hepatitis C virus; NBNC, Non-hepatitis B and C virus; RFA, Radiofrequency ablation; RT, Radiotherapy; TACE, Transarterial chemoembolization; TKI, Tyrosine kinase inhibitor. *missing data.

cutoff for patients who were still alive without radiologically confirmed progression. OS was calculated from the start of atezolizumab plus bevacizumab until the date of death. Survival curves were calculated using the Kaplan-Meier method and compared using log-rank test. Receiver operating characteristic (ROC) curves were plotted with 1-specificity and sensitivity measured along the horizontal and vertical axes, respectively. Statistical analyses were performed using the SAS version 9.4 and SPSS software, version 20.0 (SPSS, Inc., Chicago, IL).

Results

Clinical characteristics of enrolled patients

A total of 89 patients were enrolled for analysis and the baseline characteristics are shown in

Table 1. The median age was 61.3 years old (IQR 56.4-67.8) and 75 (84.3%) patients were male gender. The major etiology was hepatitis B or C virus infection (88.9%). Child-Pugh class A liver function at the time of initiation of therapy was observed in 79 patients (88.8%). When regarding to tumor characteristics, the median target tumor size was 8.0 cm (IQR 4.3-11.0) and 85.4% patients was beyond the up-to-seven criteria (seven as the sum of the size of the largest tumor (in cm) and the number of tumors) [19] while BCLC stage B and C was 23 and 66 patients, respectively. Portal vein thrombosis was noted in 45 patients (50.6%) and thirty-five patients (39.3%) had extrahepatic metastasis, with the most common metastatic site being the lungs (n=21, 60.0%), followed by lymph nodes (n=15, 42.9%) and bone (n=10, 28.6%). The median AFP level was 354 ng/mL (IQR

Table 2. Tumor response

Variables	RECIST v1.1				mRECIST			
	Overall (n=89)	1st line (n=49)	≥2nd line (n=40)	P-value	Overall (n=89)	1st line (n=49)	≥2nd line (n=40)	P-value
Initial response								
Complete response	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	
Partial response	17 (20.2)	12 (26.7)	5 (12.8)		21 (25.0)	15 (33.3)	6 (15.4)	
Stable disease	38 (45.3)	18 (40.0)	20 (51.3)		34 (40.5)	15 (33.3)	19 (48.7)	
Progressive disease	29 (34.5)	15 (33.3)	14 (35.9)		29 (34.5)	15 (33.3)	14 (35.9)	
Not evaluable	5	4	1		5	4	1	
Objective response	17 (20.2)	12 (26.7)	5 (12.8)	0.115	21 (25.0)	15 (33.3)	6 (15.4)	0.058
Disease control rate	55 (65.5)	30 (66.7)	25 (64.1)	0.805	55 (65.5)	30 (66.7)	25 (64.1)	0.805

18-3596), and 48.3% of the patients had AFP levels ≥400 ng/mL at baseline. Fifty-three patients (59.6%) underwent esophagogastro-duodenoscopy before treatment, and esophageal varices were found in 22 patients (41.5%). Atezolizumab and bevacizumab were administered as 1st-line and beyond 1st-line treatments in 49 (55.1%) and 40 (44.9%) patients, respectively. The median treatment cycles were 4 (IQR 3-6) with median observation duration was 7.2 months.

Overall therapeutic outcomes of atezolizumab plus bevacizumab

The median OS did not reach the median time during the observation period (Supplementary Figure 2A) while PFS were 5.7 months (Supplementary Figure 2B). The initial radiological therapeutic response to atezolizumab plus bevacizumab was shown in **Table 2**. Eighty-four patients received initial tumor image assessment results within 12 weeks after initiation of therapy and no patients achieved CR. The overall ORR and DCR were 20.2% (17/84), 65.5% (55/84) and 25.0% (21/84), 65.5% (55/84) when in assessment using RECIST v1.1 and mRECIST, respectively. There was no statistically significant difference in ORR between the first-line group and beyond 1st-line group whether assessment by RECIST (P=0.115) or mRECIST (P=0.058). Twenty-nine (32.6%) patients died and 51 patients (58.6%) had disease progression or died at the clinical data cut-off (March 1, 2022).

The predictor of OS, PFS and tumor response

The factors predicting the OS, PFS and response at first evaluation were examined separately.

Univariate analysis showed that ALBI grade, portal vein thrombosis, CRAFITY score and AFP response at 6 weeks were associated with OS whereas CRAFITY score and AFP response at 6 weeks were both associated with PFS and tumor response. Multivariate analysis all showed that CRAFITY score and AFP response at 6 weeks were significant and independent predictor of OS (HR=0.143, 95% CI: 0.042-0.481; P=0.002; HR=0.337, 95% CI: 0.108-0.850; P=0.031, respectively) (**Table 3**), PFS (HR=0.419, 95% CI: 0.199-0.884; P=0.022; HR=0.429, 95% CI: 0.205-0.898; P=0.025, respectively) (**Table 4**) and the early tumor response (OR=1.763, 95% CI: 1.387-8.037; P=0.044; OR=3.881, 95% CI: 1.732-20.57; P=0.011, respectively) (**Table 5**). Overall, patients encountered AFP response at 6 weeks had prolonged OS (median: not reached vs. 13.0 months, log-rank P=0.040), PFS (median: 7.9 vs. 4.3 months, log-rank P=0.016) as well as higher initial tumor response rate compared to those AFP non-responders (37.3 vs. 6.2%, P=0.002). On the other hand, patients with low CRAFIRY score also had prolonged OS (median: not reached vs. 7.2 months, log-rank P=0.001), PFS (median: 7.9 vs. 4.3 months, log-rank P=0.036) as well as better initial tumor response rate with target tumor size shrinkage or decreased tumor numbers (26.7 vs. 15.0%, P=0.049) compared to those high CRAFITY score among 53 patients with complete CRAFITY score.

The CAR (CRAFITY score and AFP-Response) classification predicts OS/PFS/tumor response

We then combined baseline CRAFITY score and on-treatment AFP response at 6 weeks and

Table 3. Cox's proportional hazards model for predictors of overall survival

Variables	Univariate			Multivariate		
	HR	95% CI	P-value	HR	95% CI	P-value
Age ≥65 y/o (vs. <65 y/o)	0.664	0.299-1.473	0.314			
Male (vs. female)	1.313	0.460-3.745	0.610			
ECOG 0 (vs. 1/2)	0.449	0.202-1.007	0.059			
Viral infection (vs. others)	0.669	0.257-1.742	0.411			
Child-Pugh grade A (vs. B)	0.518	0.223-1.206	0.127			
ALBI grade I (vs. II/III)	0.521	0.236-0.750	0.047	0.942	0.294-3.016	0.920
Portal vein thrombosis (vs. No)	2.365	1.160-4.825	0.018	1.397	0.455-4.286	0.559
Extrahepatic metastasis (vs. No)	1.114	0.558-2.225	0.759			
AFP≥400 ng/ml (vs. <400 ng/ml)	1.445	0.724-2.886	0.296			
BCLC stage B (vs. C)	0.474	0.195-1.151	0.099			
Beyond up-to-7 criteria (vs. within)	1.082	0.417-2.808	0.872			
First line (vs. second line or later)	1.454	0.725-2.917	0.292			
CRAFITY score low (vs. high)	0.144	0.046-0.454	0.001	0.143	0.042-0.481	0.002
≥75% AFP decrease or ≤10% AFP increase at 6 weeks (vs. No)	0.633	0.309-0.896	0.033	0.337	0.108-0.850	0.031
Prior loco-regional therapy (vs. No)	0.525	0.263-1.047	0.067			
IrAE (vs. No)	1.184	0.560-2.505	0.659			

Abbreviations: AFP, Alpha-fetoprotein; ALBI, Albumin-bilirubin index; BCLC, Barcelona Clinic Liver Cancer; CRAFITY, CRP and AFP in Immunotherapy; ECOG, Eastern Cooperative Oncology Group; IrAE, Immunotherapy related adverse events.

Table 4. Cox's proportional hazards model for predictors of progression-free survival

Variables	Univariate			Multivariate		
	HR	95% CI	P-value	HR	95% CI	P-value
Age ≥65 y/o (vs. <65 y/o)	1.101	0.603-2.012	0.754			
Male (vs. female)	1.024	0.498-2.106	0.948			
ECOG 0 (vs. 1/2)	0.633	0.353-1.135	0.125			
Viral infection (vs. others)	0.903	0.385-2.119	0.814			
Child-Pugh grade A (vs. B)	0.709	0.344-1.460	0.351			
ALBI grade I (vs. II/III)	0.908	0.509-1.623	0.746			
Portal vein thrombosis (vs. No)	1.679	0.959-2.938	0.070			
Extrahepatic metastasis (vs. No)	1.173	0.671-2.051	0.575			
AFP≥400 ng/ml (vs. <400 ng/ml)	1.083	0.625-1.879	0.776			
BCLC stage B (vs. C)	0.651	0.334-1.270	0.208			
Beyond up-to-7 criteria (vs. within)	1.432	0.610-3.360	0.409			
First line (vs. second line or later)	1.012	0.584-1.756	0.965			
CRAFITY score low (vs. high)	0.463	0.223-0.959	0.038	0.419	0.199-0.884	0.022
≥75% AFP decrease or ≤10% AFP increase at 6 weeks (vs. No)	0.525	0.298-0.927	0.026	0.429	0.205-0.898	0.025
Prior loco-regional therapy (vs. No)	0.926	0.524-1.635	0.790			
IrAE (vs. No)	0.924	0.522-1.633	0.784			

Abbreviations: AFP, Alpha-fetoprotein; ALBI, Albumin-bilirubin index; BCLC, Barcelona Clinic Liver Cancer; CRAFITY, CRP and AFP in Immunotherapy; ECOG, Eastern Cooperative Oncology Group; IrAE, Immunotherapy related adverse events.

defined a novel CAR (CRAFITY score and AFP-Response) classification, which consisted of three classes: low CRAFITY score (AFP<100 ng/ml or CRP<10 mg/l) with satisfactory AFP response at 6 weeks (≥75% decrease or ≤10% increase from baseline) (class I), either high CRAFITY score (AFP≥100 ng/ml and CRP≥10 mg/l) or unsatisfactory AFP response at 6 weeks (<75% decrease or >10% increase from baseline) (class II) and high CRAFITY score and unsatisfactory AFP response at 6 weeks (class III) (**Figure 1**). Among 53 patients with complete CRAFITY score, there were 20 (37.7%), 22 (41.5%), and 11 (20.8%) patients in class I to III respectively according to the AFP response at 6 weeks (**Figure 1**). Patients in class I had the

Table 5. Logistic regression model for predictors of tumor responder

Variables	Univariate			Multivariate		
	OR	95% CI	P-value	OR	95% CI	P-value
Age ≥65 y/o (vs. <65 y/o)	0.407	0.146-1.129	0.084			
Male (vs. female)	0.400	0.112-1.432	0.159			
ECOG 0 (vs. 1/2)	2.050	0.754-5.577	0.160			
Viral infection (vs. others)	2.500	0.289-21.60	0.405			
Child-Pugh grade A (vs. B)	1.792	0.360-8.932	0.476			
ALBI grade I (vs. II/III)	1.423	0.522-3.882	0.491			
Portal vein thrombosis (vs. No)	0.525	0.191-1.442	0.211			
Extrahepatic metastasis (vs. No)	0.712	0.252-2.006	0.520			
AFP≥400 ng/ml (vs. <400 ng/ml)	0.475	0.172-1.308	0.150			
BCLC stage B (vs. C)	2.154	0.745-6.231	0.157			
Beyond up-to-7 criteria (vs. within)	0.618	0.166-2.309	0.474			
First line (vs. second line or later)	2.750	0.945-8.002	0.063			
CRAFITY score low (vs. high)	1.939	1.444-8.476	0.039	1.763	1.387-8.037	0.044
≥75% AFP decrease or ≤10% AFP increase at 6 weeks (vs. No)	9.194	1.969-42.93	0.005	3.881	1.732-20.57	0.011
Prior loco-regional therapy (vs. No)	1.581	0.583-4.290	0.368			
IrAE (vs. No)	1.316	0.466-3.716	0.604			

Abbreviations: AFP, Alpha-fetoprotein; ALBI, Albumin-bilirubin index; BCLC, Barcelona Clinic Liver Cancer; CRAFITY, CRP and AFP in Immunotherapy; ECOG, Eastern Cooperative Oncology Group; IrAE, Immunotherapy related adverse events.
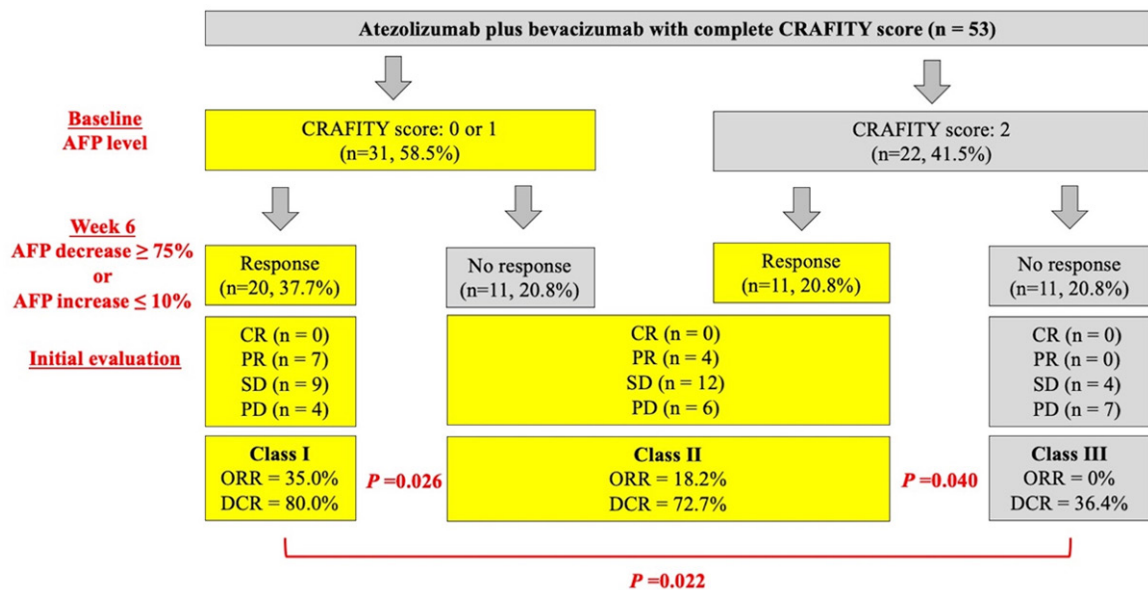

Figure 1. Three classifications by the CAR classification. Class I: low CRAFITY score with satisfactory AFP response at 6 weeks; Class II: either high CRAFITY score or unsatisfactory AFP response at 6 weeks; Class III: neither low CRAFITY score nor satisfactory AFP response at 6 weeks. Abbreviations: AFP, Alpha-fetoprotein; CR, Complete response; PD, Progressive disease; PR, Partial response; SD, Stable disease.

best ORR and DCR, followed by class II, and III (35.0% vs. 18.2% vs. 0%; 80.0% vs. 72.7% vs. 36.4%; all P<0.05 between each group) as well as longer median OS compared to those in class II and III (median: not reached vs. 11.1 and 4.3 months, overall log-rank P<0.001, Figure 2A). Similarly, patients in class I also had longer PFS than those in class II and III (median: 7.9 vs. 6.6 and 2.6 months, overall log-rank P=0.001, **Figure 2B**). Combination CRAFITY score and AFP response at 6 weeks with AUROC predicts OS (**Figure 3A**), PFS (**Figure 3B**) and
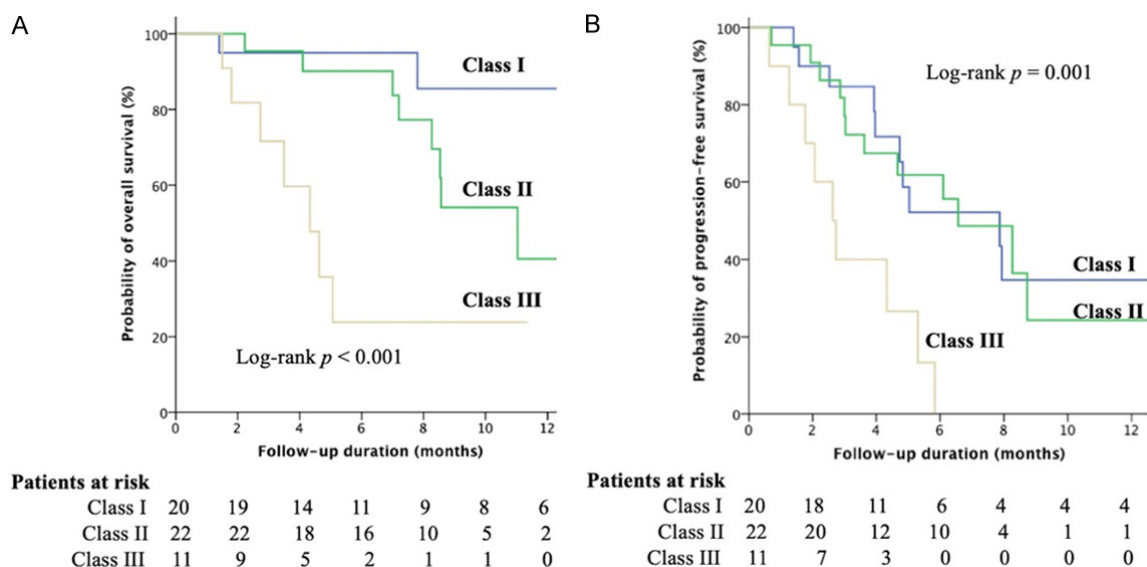
Figure 2. Kaplan-Meier curves. Comparison of (A) overall survival (OS) and (B) progression-free survival (PFS) among the patients stratified by the CAR classification. Patients in class I showed significantly the longest median OS and PFS among overall patients followed by class II and patients in class III had the worst outcome.

tumor response (**Figure 3C**) to be 0.809, 0.798 and 0.816, respectively, superior to either using CRAFITY score (0.771, 0.750 and 0.767) or AFP response at 6 weeks (0.725, 0.680 and 0.729) alone. Comparing the predictive value for OS with CRAFITY score and AFP response at 6 weeks, CAR classification had the best sensitivity (76.7% vs. 71.4% vs. 53.8%) and specificity (89.5% vs. 69.2% vs. 66.7%). For predicting PFS, CAR classification had the best sensitivity (71.0% vs. 50.0% vs. 50.0%) and specificity (95.2% vs. 71.4% vs. 75.0%) compared to either CRAFITY score or AFP response at 6 weeks. When regarding to tumor response, CAR classification also had superior sensitivity (100% vs. 72.7% vs. 90.5%) and specificity (62.5% vs. 43.6% vs. 48.4%) to either CRAFITY score and AFP response at 6 weeks alone (Supplementary Table 1).

Overall safety outcomes

The treatment related adverse events (AEs) are shown in Supplementary Table 2. The overall incident rate of AEs at any grade and over grade 3 were 61.0% (n=54) and 10.0% (n=9), respectively. The most frequent AE at any grade was hypertension (21%), followed by aspartate aminotransferase (AST) elevation (19%) or alanine aminotransferase (ALT) elevation (17%), fatigue (13%), anorexia (12%), proteinuria (10%), and

dermatitis (9%) in order. The most frequent AE over grade 3 was upper gastrointestinal bleeding (4%), followed by ALT elevation (2%) and hypertension (2%). Among the gastrointestinal bleeding events, three were variceal bleeding and the rest one was associated with ulcer.

Discussion

To the best of our knowledge, this is the first study not only to validate but also strengthen the CRAFITY score by proposing a novel CAR (CRAFITY score and AFP-Response) classification based on CRAFITY score and on-treatment AFP response at 6 weeks that predicts the outcome of unresectable HCC patients treated with atezolizumab plus bevacizumab. Accordingly, in contrast to patients with a high baseline CRACITY score with unsatisfactory AFP response at 6 weeks, patients with low CRAFITY score together with satisfactory AFP response at 6 weeks had the best tumor response and overall survival rate, even though patients who fulfilled only one criterion such as high CRAFITY score but satisfactory AFP response at 6 weeks still had a better outcome.

Despite the improvements of prognosis under current available ICIs [20-22], less than one-third of patients could achieve an ORR and median survival for patients with advanced-

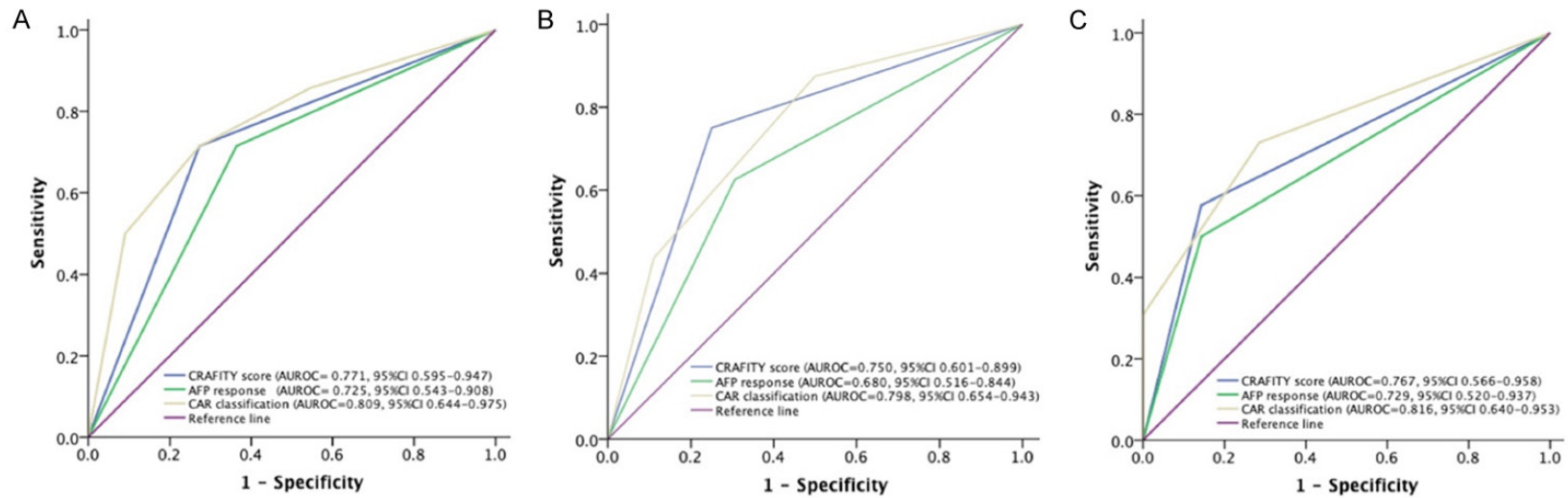# CAR classification determined prognosis of unresectable HCC patients

Figure 3. The risk prediction models of comparison among CAR classification, CRAFITY score and AFP response at 6 weeks with ROC curves for predicting (A) overall survival (OS) (B) progression-free survival (PFS) and (C) tumor response Combination CRAFITY score and AFP response at 6 weeks had the best discriminative ability in predicting OS, PFS and tumor response, superior to either using CRAFITY score or AFP response at 6 weeks alone.

stage HCC remains below two years. In clinical trials, it is common to perform imaging assessments every 6-8 weeks, however, such a high frequency of imaging assessments may be rare in clinical practice. Therefore, one of the most relevant unsolved problems is to identify a treatment response biomarker that can help select patients with a higher probability of response to ICIs. However, there are now still lack of reliable biomarkers to predict the outcome of HCC patients treated with ICI therapy [20-22]. Although programmed cell death ligand 1 (PD-L1) expression in immune or tumor cells has good correlation with tumor response for several other cancers [23, 24], the predictive quality of response targeting PD-L1 expression in hepatoma cells is restricted to certain variants [20, 25]. In addition to baseline AFP level [26, 27], on-treatment early AFP response decline within 4 week is reported to be associated with ORR and survival in patients who received 2 cycles nivolumab treatment administered every 2 weeks [13, 14]. Besides, some patients with delayed AFP response beyond 4 weeks were still beneficial from ICI therapy [14]. Therefore, it is a good rationale to define early AFP response at 6 weeks in patients who received 2 cycles atezolizumab plus bevacizumab administered every 3 weeks according to recent Japanese study [28]. In addition, Zhu et al [15] further demonstrated that reduction in AFP levels at 6 weeks with a AFP decrease ≥75% or increases ≤10% was significantly associated with OS and response versus those without AFP change from phase 1b trial. We further developed the CAR classification combining the pre-treatment AFP level and on-treatment AFP at 6 weeks to increase the sensitivity and specificity in the selection of patients and support decision-making in daily clinical practice. Patients were subdivided into 3 classes to assist physicians more precisely in identifying patients who are less likely to respond to atezolizumab plus bevacizumab treatment, and these patients may require more frequent imaging assessments or shift to other therapy as early as possible. The CAR classification greatly improved the discriminative ability of OS than using CRAFITY score alone in current study (AUROC: 0.81 vs. 0.77) and original study [16] (AUROC: 0.71). It is simple to use, low medical cost and no need for invasive histologic assessment.

AFP is a glycoprotein expressed and secreted by hepatoma cells in approximately 70% of patients with HCC. Apart from the indicator of high tumor aggressiveness such as vascular invasion, AFP plays an important role in the promoting proliferation of human hepatoma cells including mediated by the binding of AFP receptors (AFPR), leading to the intracellular Ca^{2+} increases [29], then the intracellular CAMP correspondingly rises dependent on the CAMP-PKA pathway and the activation of PI3K/AKT signal pathway [30], the stimulation of oncogene protein, and the dysfunction of PTEN antioncogene protein. AFP could promote tumor invasion and metastasis via upregulating expression of metastasis related proteins, such as keratin 19 (K19), epithelial cell adhesion molecule (EpCAM), matrix metalloproteinase 2/9 (MMP2/9), and CXC chemokine receptor 4 (CXCR4) [31]. Besides, AFP promoted the expression of FasL and TRAIL in hepatoma cells and Fas and TRAILR in lymphocytes that induced the escape of hepatoma cells from the host's lymphocytes immune surveillance [32]. AFP also promote the tumor angiogenesis by increasing expression of vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor 2 (VEGFR-2) [33]. In summary, AFP promotes the proliferation and metastasis of tumor cells as well as prevents apoptosis and escaping of HCC from immune surveillance. Therefore, it is reasonable for AFP responders to have better outcome than those AFP non-responders.

High CRP levels have been associated with increased cancer risk and also poor clinical outcome in different malignancies including hepatoma [34]. Recently, it has been shown in small studies that high CRP level was associated with a poor outcome when treated with the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blocking antibody tremelimumab for patients with melanoma [35] and PD-1 immune checkpoint blockade in patients with advanced non-small-cell lung cancer [36], yet the role of CRP in modulating the antitumor immune response has not been explored in detail. More recent evidence [37] showed that CRP has a profound suppressive effect on adaptive immunity in patients with melanoma. Up to 40% of CD8 T cells bound and internalized CRP, and high levels of CRP diminished the proliferation of CD4+ and CD8+ T cells from patients with

melanoma, and it downregulated dendritic cell (DC) function and altered T-cell and DC phenotypes [38, 39]. In non-small cell lung cancer patients, high CRP was associated with PD-L1 positivity [40] that CRP may impair the efficacy of immunotherapy. More recently, tissue samples from the Checkmate040 Trial demonstrated an inflammatory 4-gene signature, including CD274, CD8A, LAG3, and STAT1, was associated with objective responses and OS among patients treated with Nivolumab [41]. This observation was not only highlighted the importance of inflammation in ICI treatment but also point out the possible role of CRP, a marker that strongly correlated with inflammation, in ICI treatment [42]. The recently developed CRAFITY score including baseline AFP and CRP level that provides a good predictor for the outcome of immunotherapy [16] re-emphasized the importance of CRP. In the present study, we combined both CRAFITY score and on-treatment AFP response to create the CAR score. The benefit of this scoring system is to include the inflammation related CRP and tumor-related AFP together with the tumor response (on-treatment AFP response). This reasoning is confirmed by the good predictive ability of CAR score as shown in this study.

However, this study still has several limitations. First, this is a retrospective study with a relative small sample size. Second, most patients (77.5%) were hepatitis B virus infection and the predictive model should be interpreted cautiously when applying to other populations. Third, bevacizumab was given with dosage 5-7.5 mg/kg under patient support program in Taiwan instead of 15 mg/kg followed by the IMbrave150 trial, a dosage at the upper limit of the dosage range used in other cancers. Data from previous trials of bevacizumab indicated that doses of 5 or 10 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks were well tolerated in patients with HCC, while pharmacokinetics (PK) analyses showed that 10 mg/kg every 2 weeks and 15 mg/kg every 3 weeks were comparable with respect to maximum, minimum and mean serum concentrations [43]. In previous phase II studies in HCC, different doses and schedules of bevacizumab showed evidence of activity, although this finding has not been validated in the phase III randomized trial setting [44, 45]. In current study, patients treated in the first-line although enrolled patients with Child-Pugh class B still had similar ORR compatible with IMbrave150 trial whether assessed by using RECIST (26.7% vs. 27.3%) or mRECIST (32.6% vs. 33.2%).

In conclusion, the novel CAR (CRAFITY score and AFP-Response) classification which combining CRAFITY score and AFP response at 6 weeks provides a practical guidance for atezolizumab plus bevacizumab therapy in unresectable HCC patients. Patients with low CRAFITY score concomitant with satisfactory AFP response at 6 weeks had the best disease control and survival rate, even though patients who fulfilled only one criterion such as high CRAFITY score but satisfactory AFP response at 6 weeks still had a good outcome. Patients with a high baseline CRACITY score with unsatisfactory AFP response at 6 weeks should shift early to other therapy if feasible. We still need a larger population to validate our recommendation.

Disclosure of conflict of interest

None.

Abbreviations

AEs, Adverse events; AFP, Alpha-fetoprotein; AST, Aminotransferase; ALT, Alanine aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CR, Complete response; CRAFITY, CRP and AFP in Immunotherapy; CRP, C-reactive protein; CT, Computerized tomography; CTLA-4, Cytotoxic T-lymphocyte-associated protein 4; DC, Dendritic cell; DCR, disease control rate; EASL/EORTC, European Association for the Study of the Liver/European Organization for Research and Treatment of Cancer; HCC, Hepatocellular carcinoma; ICI, Immune checkpoint inhibitor; IQR, Interquartile range; MRI, Magnetic Resonance Imaging; ORR, Objective response rate; OS, Overall survival; PD-L1,

Programmed cell death ligand 1; PR, Partial response; RECIST, Response Evaluation Criteria in Solid Tumors; ROC, Receiver operating characteristic; SD, Stable disease.

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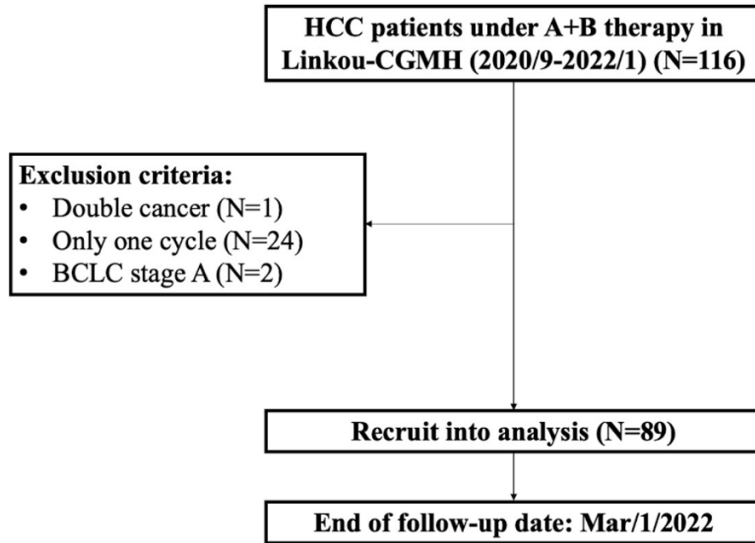
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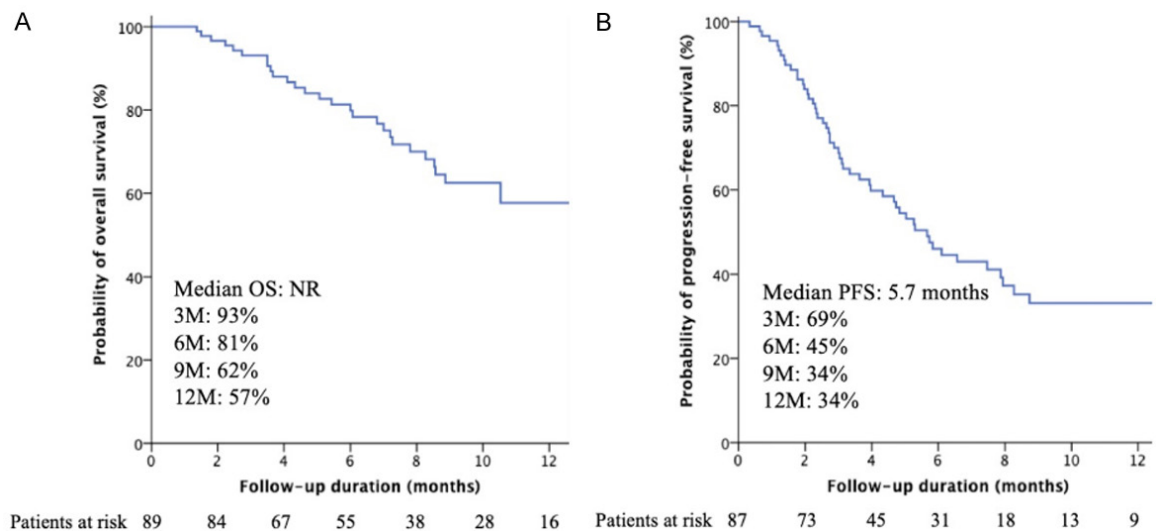
Supplementary Figure 2. Kaplan-Meier curves of overall patients. (A) Overall survival (OS) (B) progression-free survival (PFS).

Supplementary Table 1. Accuracy for prediction of OS, PFS and tumor response

	OS	PFS	Tumor response
Sensitivity			
CRAFITY score	71.4%	50.0%	72.7%
AFP response at 6 weeks	53.8%	50.0%	90.5%
CAR classification	76.7%	71.0%	100%
Specificity			
CRAFITY score	69.2%	71.4%	43.6%
AFP response at 6 weeks	66.7%	75.0%	48.4%
CAR classification	89.5%	95.2%	62.5%
PPV			
CRAFITY score	45.5%	71.4%	26.7%
AFP response at 6 weeks	41.2%	72.7%	37.3%
CAR classification	63.6%	90.0%	36.2%
NPV			
CRAFITY score	87.1%	50.0%	85.0%
AFP response at 6 weeks	76.9%	52.9%	93.8%
CAR classification	81.0%	57.6%	100%

Abbreviations: AFP, Alpha-fetoprotein; CAR, CRAFITY score and AFP-Response; CRAFITY, CRP and AFP in Immunotherapy; NPV, negative predictive value; PPV, positive predictive value.

Supplementary Table 2. Treatment-related adverse events due to Atezolizumab and bevacizumab

Adverse events	Any grade	Grade ≥3
Any adverse event	54 (61)	9 (10)
Hypertension	19 (21)	2 (2)
Aspartate aminotransferase increased	17 (19)	1 (1)
Alanine aminotransferase increased	15 (17)	2 (2)
Fatigue	12 (13)	0 (0)
Anorexia or nausea	11 (12)	1 (1)
Proteinuria	9 (10)	0 (0)
Dermatitis	8 (9)	1 (1)
Pyrexia	8 (9)	1 (1)
Diarrhea	7 (8)	0 (0)
Upper gastrointestinal bleeding	4 (4)	4 (4)
Muscle soreness	3 (3)	1 (1)
Hypothyroidism	3 (3)	0 (0)
Hoarseness	3 (3)	0 (0)
Platelet decrease	3 (3)	0 (0)
Blood bilirubin increased	2 (2)	0 (0)
Hyperthyroidism	2 (2)	0 (0)
Headache	2 (2)	0 (0)
Chills	2 (2)	0 (0)
Dizziness	2 (2)	0 (0)
Cough	2 (2)	0 (0)
Epistaxis	2 (2)	0 (0)
Oral ulcer	1 (1)	0 (0)
Infusion reaction	1 (1)	0 (0)
Alkaline phosphatase increase	1 (1)	0 (0)