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ORIGINAL RESEARCH

Early PIVKA-II Response Predicts Treatment Efficacy of Immune Checkpoint Inhibitors in Patients with Advanced Hepatocellular Carcinoma

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Background and Aims: Early alpha-fetoprotein (AFP) response has been reported to predict the treatment efficacy of immune checkpoint inhibitors (ICIs) in patients with advanced hepatocellular carcinoma (HCC). We evaluated the predictive value of another HCC tumor marker, protein induced by vitamin K absence/antagonists-II (PIVKA-II).

Methods: We prospectively established a cohort of advanced HCC patients who received ICI treatment at two medical centers. Serum PIVKA-II levels were obtained before and within 4 weeks after treatment initiation. Any decline in serum PIVKA-II levels was defined as an early PIVKA-II response. Treatment response, overall survival (OS), and progression-free survival (PFS) were compared between patients with and without an early PIVKA-II response.

Results: In total, 67 patients were included; liver reserve was Child–Pugh class A in all patients and albumin–bilirubin grade 1 in 67.2% of the patients. An early PIVKA-II response, which was observed in 19 (28.4%) patients, was associated with a higher objective response rate (50.0% vs 16.4%, p = 0.002). Patients with an early PIVKA-II response had superior OS (median 34.3 vs 13.7 months, p = 0.015) and PFS (median 8.4 vs 4.0 months, p = 0.049) compared with those without a response. In multivariate analysis, an early PIVKA-II response remained an independent predictor for longer OS (p = 0.012) and PFS (p = 0.044). An early PIVKA-II response can complement an early AFP response in predicting prognosis.

Conclusion: An early PIVKA-II response is predictive of tumor response and superior survival outcomes in patients who received ICIs for advanced HCC.

Plain Language Summary: PIVKA-II is an emerging tumor marker for HCC, widely used in diagnosis and prognostic stratification. Early PIVKA-II response, defined as any decline of serum PIVKA-II level within 4 weeks after initiation of ICIs treatment, may predict treatment efficacy for patients with advanced HCC.

Keywords: immunotherapy, PD-L1 blockade, protein induced by vitamin K absence/antagonists-II, PIVKA-II, des-γ-carboxy prothrombin, DCP

Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent cancers worldwide and is especially common in East Asia, where viral hepatitis is endemic.[1] A substantial proportion of patients with HCC are diagnosed with incurable advanced disease or experience disease recurrence and progression after locoregional therapies.[2] Immune checkpoint inhibitors (ICI) combinations have shown superior survival benefits compared with multikinase inhibitors, such as sorafenib and lenvatinib, and are now the standard first-line therapies. Nevertheless, the overall response rate of systemic treatment remains modest at approximately 30% with combination immunotherapy, and 20%–40% of patients exhibited primary resistance.[3–6] Furthermore, approximately 30% to 40% of patients are unable to receive second-line treatment after

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failure of first-line therapy.[7,8] Thus, identifying timely and accurate predictive markers of HCC is vital to assisting physicians in determining treatment strategies.

Several pretreatment biomarkers can predict the efficacy of immunotherapy for certain cancers. For example, microsatellite instability can be used to predict the efficacy of immunotherapy on metastatic colorectal cancer,[9] whereas expression of programmed death-ligand 1 (PD-L1) can be used to predict the efficacy of immunotherapy on lung cancer, head and neck cancer, breast cancer, esophageal cancer, and gastric cancer.[10–13] However, these biomarkers are not useful in predicting the effectiveness of ICIs for patients with advanced HCC.[14] Few predictive biomarkers for the effectiveness of immunotherapy on HCC are available before treatment. The CRP and alpha-fetoprotein (AFP) in immunotherapy (CRAFITY) score were developed to predict treatment outcomes and was validated in 2 cohorts.[15] Though the pivotal studies evaluating CRAFITY score were conducted on patients of European descent, a retrospective study also demonstrated good predictive value of CRAFITY score for Japanese patients who received Atezolizumab plus bevacizumab treatment.[16] The score's predictive power for other immunotherapies for individuals from other geographic regions remains unclear.

Using early posttreatment surrogate biomarkers, although unable to guide treatment decision beforehand, can reduce the duration of futile treatments and increase confidence that treatments are effective. In our earlier study, we demonstrated that an early AFP response within 4 weeks after initiation of targeted therapy or immunotherapy can effectively predict treatment response and survival benefits for patients with advanced HCC.[17,18] However, only approximately 35% of patients achieve an early AFP response, and this surrogate marker cannot be used in patients with normal AFP levels.[18] Together, these studies indicate that AFP response is useful but insufficient, thereby highlighting the need for additional biomarkers.

Protein induced by vitamin K absence/antagonists-II (PIVKA-II), also known as Des-γ-carboxy prothrombin, is primarily produced by HCC cells because of decreased carboxylation of the prothrombin precursor and is rarely found in normal hepatocytes.[19,20] PIVKA-II has been reported to be a useful marker for early detection and diagnosis of HCC; it can assist physicians in monitoring the disease after surgery or locoregional treatment and enable prognosis stratification in cases of advanced HCC.[21–28] PIVKA-II also complements AFP in HCC diagnosis and retains its diagnostic and prognostic value even in patients with normal AFP levels.[23,24,29–33] Despite these established diagnostic and prognostic roles, few studies have investigated PIVKA-II as a predictive marker for immunotherapy in HCC.[34,35] Moreover, the optimal cutoff point for PIVKA-II response remains unclear.[24,25] Therefore, the present study explored whether early posttreatment PIVKA-II changes could predict the treatment efficacy of ICIs for patients with advanced HCC and compared several cutoff points.

Materials and Methods

We prospectively established a patient cohort that received ICI as a treatment for advanced HCC at National Taiwan University Hospital (NTUH) and NTUH, Hsin-Chu Branch. We collected the serum of the patients within 7 days before treatment initiation, with the PIVKA-II and AFP levels in these samples considered the baseline levels. Serum was collected again at 2 to 4 weeks after initiation of ICIs, with these levels considered to be the posttreatment levels.

The inclusion criteria for this cohort were as follows: (1) Histopathologically or clinically diagnosed HCC; (2) advanced HCC, defined as Barcelona Clinic Liver Cancer (BCLC) stage C or deemed unsuitable for locoregional therapies; and (3) receipt of ICIs as any line of systemic treatment for advanced HCC from August 2015 to December 2022. Exclusion criteria were as follows: (1) liver function classified as Child-Pugh B or worse; (2) prior exposure to immunotherapy before enrollment into this study.

Serum PIVKA-II and AFP levels were measured using a microparticle enzyme immunoassay (Abbott Laboratories, Chicago, IL, USA) at the central laboratory of the Department of Laboratory Medicine, NTUH. An early PIVKA-II response was defined as any decline from the baseline level to the posttreatment level within 4 weeks. We then compared the overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) between groups. Other cutoff points for early PIVKA-II response that have been reported in the literature, such as a 20% or a 50% decline in PIVKA-II level within 4 weeks, were also tested. An early AFP response was defined following previously published

criteria[17,18] as a >20% decline in serum AFP levels within 4 weeks after treatment initiation compared with baseline levels. Only patients with abnormal baseline AFP levels could be evaluated for an early AFP response.

Statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA). For comparisons between patients with different PIVKA-II responses, the chi-square or Fisher's exact test was used for categorical variables, and independent *t* tests were used for continuous variables. The OS and PFS of the patients were estimated using the Kaplan–Meier method and compared using the Log rank test in univariate analysis. The Cox proportional hazards model was used in multivariate analysis to identify independent predictors of OS and PFS. Two-sided p values of ≤.05 were considered significant. The final follow-up date was July 31, 2023. Written informed consent was obtained from all individual participants included in the study.

Results

Between January 2015 and December 2022, 67 patients were enrolled in this study (Figure S1). Of these patients, 91% were men, and the median age was 63 years (Table 1). All patients had Child–Pugh class A liver reserve, and 45 (67.2%) had albumin–bilirubin (ALBI) grade 1. Macrovascular invasion (MVI) and extrahepatic spread (EHS) were observed in 26 (38.8%) and 50 (74.6%) patients, respectively (Table 1). More than half (58.1%) of the patients received ICIs as the first-line treatment for advanced HCC. The ICI regimens were mainly based on PD-1 blockade, including atezolizumab (n = 7, 10.4%), atezolizumab plus bevacizumab (with or without other investigational agents, n = 25, 37.3%),

Table 1 Characteristics of Patients Receiving Immune Checkpoint Inhibitors, Grouped by Early Protein Induced by Vitamin K Absence/Antagonists-II (PIVKA-II) Response

N (%)	Total	Early PIVKA-II Response		*p* value
		Yes	No	
Total	67 (100)	19 (100)	48 (100)	
Median age (range)	63 (23–81)	63 (42–76)	62 (23–81)	0.939
Age > 70 years	8 (11.9)	3 (15.8)	5 (10.4)	0.678
Sex				1.000
Male	61 (91.0)	17 (89.5)	44 (91.7)	
Female	6 (9.0)	2 (10.5)	4 (8.3)	
Viral Hepatitis				
HBsAg positive	49 (73.1)	12 (63.2)	37 (77.1)	0.359
Anti-HCV positive	12 (17.9)	5 (26.3)	7 (14.6)	0.299
Neither above	7 (10.4)	2 (10.5)	5 (10.4)	
Tumor burden				
MVI	26 (38.8)	10 (52.6)	16 (33.3)	0.172
EHS	50 (74.6)	15 (78.9)	35 (72.9)	0.760
Both MVI and EHS	17 (25.4)	8 (42.1)	9 (18.8)	0.064
MVI or EHS	59 (77.6)	17 (89.5)	42 (87.5)	1.000
AFP ≥ 400 ng/mL	26 (38.8)	7 (36.8)	19 (39.6)	1.000
Baseline PIVKA-II (mAU/mL)				
Mean (SD)	5994.5 (13,561.1)	7797.0 (15,671.4)	5818.0 (13,597.9)	0.609
ALBI grade				0.389
1	45 (67.2)	11 (57.9)	34 (70.8)	
2	22 (32.8)	8 (42.1)	14 (29.2)	
Child-Pugh				
A	67 (100)	19 (100)	48 (100)	
B	0 (0)	0 (0)	0 (0)	

Abbreviations: AFP, alpha-fetoprotein; CLIP, Cancer of the Liver Italian Program; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; MVI, macrovascular invasion; EHS, extrahepatic spread; SD, standard deviation.

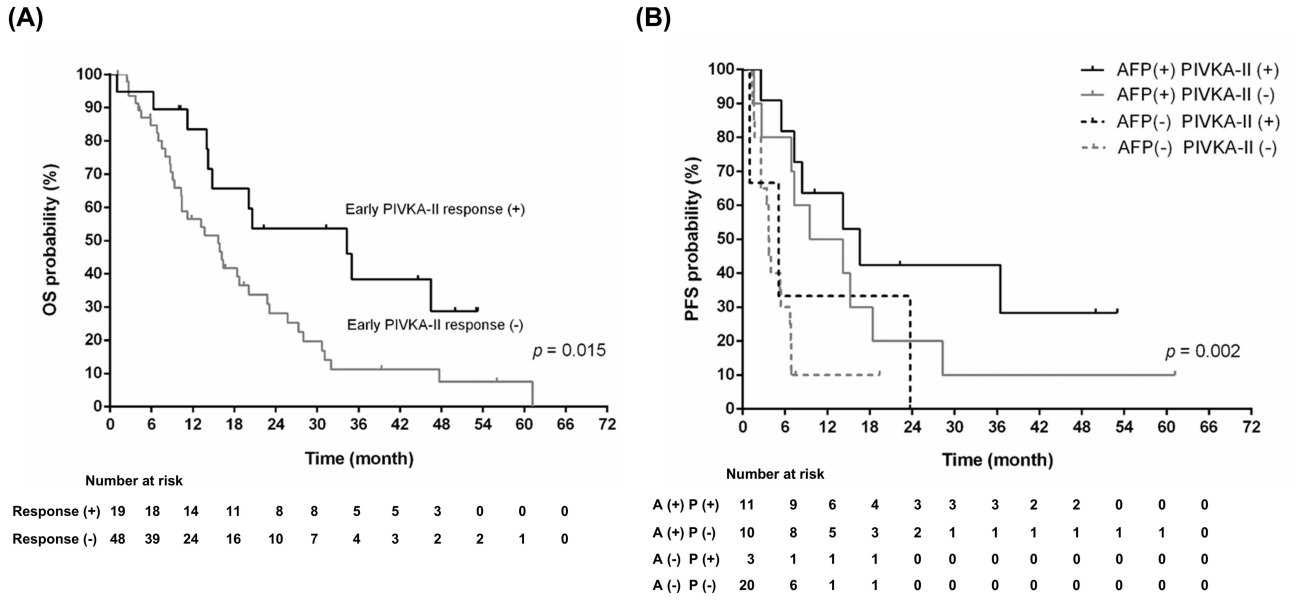

Figure 1 (**A**) Overall survival (OS) and (**B**) progression-free survival (PFS) of patients who received immune checkpoint inhibitors (ICIs) segmented into groups on the basis of whether they exhibited early protein induced by vitamin K absence/antagonists-II (PIVKA-II) response.

durvalumab (n = 9, 13.4%), durvalumab plus tremelimumab (n = 4, 6.5%), nivolumab (n = 18, 26.9%), and tislelizumab (n = 4, 6.0%).

The initial mean PIVKA-II level was 5994.5 mAU/mL. Using our primary definition (any PIVKA-II decline within 4 weeks), early PIVKA-II response was observed in 19 (28.4%) patients. No significant differences in clinical factors were observed between patients with and without an early PIVKA-II response (Table 1). Patients with an early PIVKA-II response had longer OS (median 34.3 vs 13.7 months, $p = 0.015$; Figure 1A) and PFS (median 8.4 vs 4.0 months, $p = 0.049$; Figure 1B) than those without a response. The ORR was significantly higher in the patients with an early PIVKA-II response than in those without (52.6% vs 10.4%, $p = 0.001$; Table 2).

In the multivariate analysis adjusted for age, sex, viral hepatitis, ALBI grade, MVI, EHS, and initial AFP ≥ 400 ng/mL, early PIVKA-II response remained an independent predictive factor of longer OS (hazard ratio [HR] = 0.37, 95% CI = 0.17–0.80, $p = 0.012$) and longer PFS (HR = 0.51, 95% CI = 0.27–0.98, $p = 0.044$) (Table 3).

Table 2 Early Protein Induced by Vitamin K Absence/Antagonists-II (PIVKA-II) Response and Optimal Tumor Response

Early PIVKA-II Response Cutoff Point	Total (N)	Tumor Response According to RECIST 1.1		*p* value
		N	%	
Any decline				
Yes	19	10	52.6	0.001
No	48	5	10.4	
Decline > 20%				
Yes	12	6	50.0	0.002
No	55	9	16.4	
Decline > 50%				
Yes	8	4	50.0	0.068
No	59	11	18.6	

Table 3 Cox Proportional Hazards Models for Predictors of Overall Survival and Progression-Free Survival

Variable	OS			PFS		
	HR	95% CI	*p*	HR	95% CI	*p*
Early PIVKA-II response	0.37	0.17–0.80	0.012	0.51	0.27–0.98	0.044
Age > 70 years	1.84	0.65–5.20	0.253	2.26	0.86–5.96	0.100
Male	1.61	0.38–6.78	0.516	1.27	0.36–4.51	0.709
HBsAg (+)	0.82	0.31–2.17	0.685	1.09	0.47–2.54	0.834
Anti-HCV (+)	0.63	0.19–2.10	0.445	0.89	0.30–2.62	0.826
ALBI grade 2	1.14	0.57–2.26	0.710	0.72	0.39–1.33	0.294
MVI	2.62	1.38–4.96	0.003	1.78	1.01–3.14	0.045
EHS	1.36	0.63–2.92	0.435	1.08	0.56–2.06	0.819
AFP ≥ 400 ng/mL	0.79	0.41–1.53	0.485	1.08	0.61–1.92	0.800

Abbreviations: HR, hazard ratio; AFP, alpha fetoprotein; CI, confidence interval; EHS, extrahepatic spread; HBsAg, hepatitis B virus surface antigen; MVI, macrovascular invasion; PIVKA-II, protein induced by vitamin K absence/antagonist-II.

When an early PIVKA-II decline > 20% was used as the cutoff point, 12 patients (17.4%) were early responders. The ORR differed significantly between the 2 groups (50.0% vs 16.4%, $p = 0.002$; Table 2), but OS ($p = 0.428$, Figure S2A) and PFS ($p = 0.598$, Figure S2B) did not significantly differ between groups at this threshold. When an early PIVKA-II decline > 50% was used as the cutoff point, 8 patients (11.6%) were early responders. The ORR, OS, and PFS did not significantly differ between the 2 groups (Table 2; Figure S3A and B). These findings suggest that stricter cutoffs may miss clinically meaningful responders, reinforcing the utility of "any decline" as a practical definition.

A total of 49 (73.1%) patients had elevated baseline AFP levels. After 5 patients whose posttreatment AFP levels were unavailable were excluded, we evaluated early AFP response in 44 patients. Of the 14 patients with an early PIVKA-II response, 11 (78.6%) also had an early AFP response (Table S1). Patients with an early PIVKA-II response were more likely to have an early AFP response, and vice versa ($p = 0.009$). Combining early PIVKA-II and AFP responses revealed significant differences in patient OS ($p = 0.014$, Figure 2A) and PFS ($p = 0.002$, Figure 2B). Patients with neither an early PIVKA-II nor an early AFP response exhibited the shortest OS (median 10.4 months) and PFS

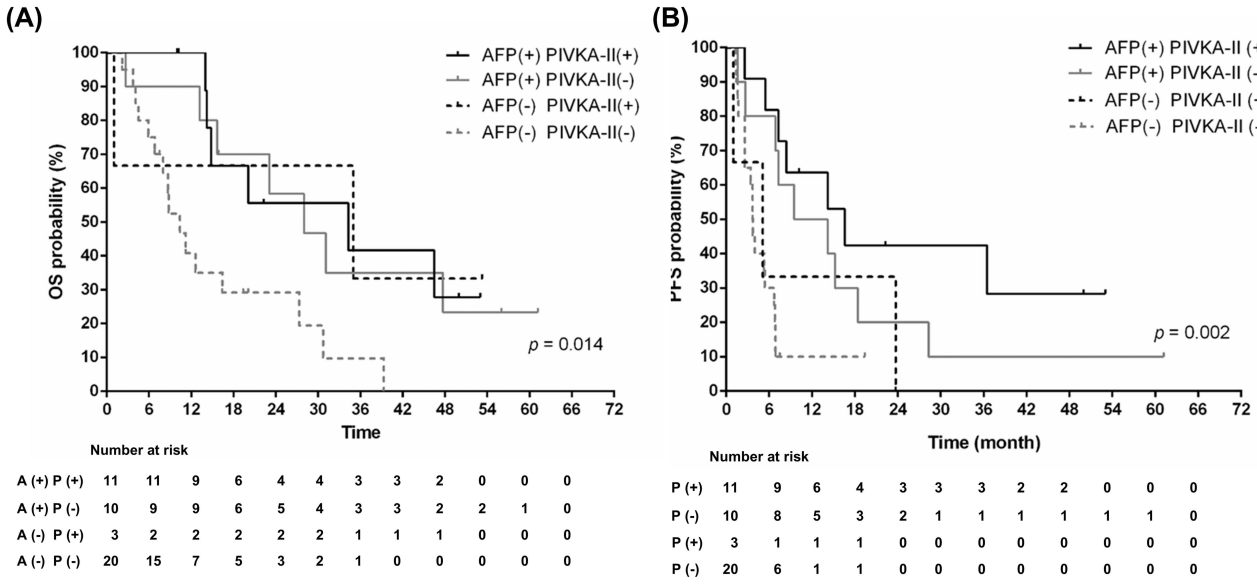

Figure 2 (**A**) Overall survival (OS) and (**B**) progression-free survival (PFS) of a subgroup of patients (n = 44) for whom both early protein induced by vitamin K absence/antagonist II (PIVKA-II) response and early alpha fetoprotein (AFP) response could be evaluated. PIVKA-II (+): presence of early PIVKA-II response. AFP (+): presence of early AFP response.

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(median 3.7 months). Patients with an early PIVKA-II and an early AFP response exhibited the longest PFS (median 16.6 months, Table S2).

Discussion

This study found that an early PIVKA-II response, defined as any decline in PIVKA-II levels within 4 weeks of treatment, was associated with improved efficacy of ICIs in advanced HCC. Although an early PIVKA-II response could not guide treatment selection before therapy, it can serve as an early surrogate marker. For example, for patients with no PIVKA-II reduction, imaging assessment can be performed earlier to prevent continuation of futile therapy. A timely shift to effective treatment can avoid unnecessary toxicities and help initiate salvage therapy before liver function deteriorates. It may also provide an opportunity for locoregional therapy in cases of local progression.[30]

PIVKA-II production is highly correlated with tumor activity, and the short half-life of PIVKA-II renders it a timely reflection of tumor burden.[24,36] We defined early PIVKA-II response as any PIVKA-II decline within 4 weeks after the initiation of immunotherapy. A retrospective study reported that an early PIVKA-II response has predictive value, with such a response defined as a >50% decline within 6 weeks after treatment initiation.[34] In that study, 53.2% of patients achieved a >50% PIVKA-II decline. By contrast, only 11.9% of the patients in the present study achieved a >50% decline in PIVKA-II levels within 4 weeks. This discrepancy in the percentage of patients who achieved a > 50% decline may be due to variations in the timing of posttreatment examinations; later assessments may result in greater reductions. The limited number of patients who achieved a >50% decline in the present study may explain why we could not establish an association of PIVKA-II with tumor response, PFS, or OS. In terms of early prediction, assessing PIVKA-II at 2 to 4 weeks may allow earlier insight into treatment efficacy than evaluation at 6 weeks. Taken together, these findings highlight the importance of defining both cutoff values and the timing of biomarker assessment when evaluating PIVKA-II as a predictor of immunotherapy efficacy.

Early AFP response is useful for predicting the efficacy of antiangiogenic treatment and ICIs in advanced HCC. Nevertheless, approximately 65% of patients with advanced HCC do not have an early AFP response.[18] Other predictive markers could potentially assist these patients. In the present study, we discovered that an early PIVKA-II response could help predict the treatment efficacy of ICIs in such patients. Patients with neither an early AFP response nor an early PIVKA-II response exhibited the shortest PFS and OS.

Other commonly used biomarkers in HCC, such as lens culinaris agglutinin-reactive fraction of AFP (AFP-L3) and neutrophil-to-lymphocyte ratio (NLR), have also been investigated as a marker to predict treatment response. AFP-L3 may provide added diagnostic value in combination with AFP and PIVKA-II, but evidence for its role in predicting ICI efficacy remains limited.[37,38] In a multicenter study, its predictive power for survival under atezolizumab–bevacizumab was weaker than that of AFP or PIVKA-II, and it mainly contributed as part of a composite biomarker panel.[39] In contrast, NLR has been more consistently associated with ICI outcomes: patients with high baseline NLR generally have inferior OS,[40] and recent analyses suggest that early dynamic changes in NLR (within 4–6 weeks of treatment) provide stronger and more reliable prediction of ORR, PFS, and OS.[41] This supports the broader concept that dynamic biomarker changes, including early PIVKA-II decline, may better capture treatment response than static measurements.

Our study has some limitations. First, our patients received a variety of ICI regimens primarily involving PD-1 blockades only. However, as we discovered in our study on early AFP response,[18] such surrogate biomarkers may be effective across various immunotherapy regimens. Second, no consensus has been reached regarding the upper normal limit of serum PIVKA-II levels.[23,24,42] In consideration of this, we enrolled all patients with available baseline and posttreatment PIVKA-II levels. Third, this study lacked a validation cohort to confirm the optimal cutoff point for the percentage decline in PIVKA-II. We tested multiple endpoints to determine the optimal cutoff point; nevertheless, further research is required to validate our findings.

In conclusion, the present study demonstrated that an early PIVKA-II response, defined as any decline in PIVKA-II levels within 4 weeks after treatment initiation, can predict tumor response, PFS, and OS in patients with advanced HCC treated with ICIs. An early PIVKA-II response can complement an early AFP response in predicting survival outcomes.

Abbreviations

AFP, Alpha-Fetoprotein; ALBI, Albumin–Bilirubin; EHS, Extrahepatic Spread; HCC, Hepatocellular Carcinoma; ICIs, Immune Checkpoint Inhibitors; MVI, Macrovascular Invasion; ORR, Objective Response Rate; OS, Overall Survival; PD-1, Programmed Cell Death Protein-1; PD-L1, Programmed Death-Ligand 1; PFS, Progression-Free Survival; PIVKA-II, Protein Induced by Vitamin K Absence/Antagonists-II.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are not publicly available due to patient privacy and ethical restriction but are available from the corresponding author on reasonable request.

Ethics Approval Statement

This study is approved by Institutional Review Board of National Taiwan University Hospital (111-221-E).

Consent to Participate

Written informed consent was obtained from all individual participants included in the study. The study was conducted in accordance with the Declaration of Helsinki and relevant institutional guidelines.

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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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Disclosure

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