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α-FAtE: A new predictive score of response to atezolizumab plus bevacizumab for unresectable hepatocellular carcinoma

Federico Rossari[1,2] | Toshifumi Tada[3] | Goki Suda[4] | Shigeo Shimose[5] | Masatoshi Kudo[6] | Changhoon Yoo[7] | Jaekyung Cheon[8] | Fabian Finkelmeier[9] | Ho Yeong Lim[10] | José Presa[11] | Gianluca Masi[12,13] | Francesca Bergamo[14] | Elisabeth Amadeo[1] | Francesco Vitiello[1] | Takashi Kumada[15] | Naoya Sakamoto[4] | Hideki Iwamoto[5] | Tomoko Aoki[6] | Hong Jae Chon[8] | Vera Himmelsbach[9] | Massimo Iavarone[16] | Giuseppe Cabibbo[17] | Margarida Montes[11] | Francesco Giuseppe Foschi[18] | Caterina Vivaldi[12,13] | Caterina Soldà[14] | Takuya Sho[4] | Takashi Niizeki[5] | Naoshi Nishida[6] | Christoph Steup[9] | Masashi Hirooka[19] | Kazuya Kariyama[20] | Joji Tani[21] | Masanori Atsukawa[22] | Koichi Takaguchi[23] | Ei Itobayashi[24] | Shinya Fukunishi[25] | Kunihiko Tsuji[26] | Toru Ishikawa[27] | Kazuto Tajiri[28] | Hironori Ochi[29] | Satoshi Yasuda[30] | Hidenori Toyoda[30] | Chikara Ogawa[31] | Takashi Nishimura[32] | Takeshi Hatanaka[33] | Satoru Kakizaki[34] | Noritomo Shimada[35] | Kazuhito Kawata[36] | Atsushi Hiraoka[37] | Fujimasa Tada[37] | Hideko Ohama[37] | Kazuhiro Nouso[20] | Asahiro Morishita[21] | Akemi Tsutsui[23] | Takuya Nagano[23] | Norio Itokawa[22] | Tomomi Okubo[22] | Michitaka Imai[27] | Hisashi Kosaka[38] | Atsushi Naganuma[39] | Yohei Koizumi[19] | Shinichiro Nakamura[3] | Masaki Kaibori[38] | Hiroko Iijima[32] | Yoichi Hiasa[19] | Mara Persano[40] | Valentina Burgio[1] | Fabio Piscaglia[41] | Mario Scartozzi[40] | Stefano Cascinu[1] | Andrea Casadei-Gardini[1] | Margherita Rimini[1]

Correspondence
Andrea Casadei-Gardini, Università Vita-Salute San Raffaele, San Raffaele Hospital-IRCCS, via Olgettina 60 20132, Milano, Italy.
Email: casadeigardini.andrea@hsr.it

Abstract

Atezolizumab plus bevacizumab (AB) and lenvatinib can be alternatively used as first-line systemic treatment of unresectable hepatocellular carcinoma (HCC). However, no direct comparison of the two regimens has been performed in randomized clinical trials, making the identification of baseline differential predictors of response of major relevance to tailor the best therapeutic option to each patient. Baseline clinical and laboratory characteristics of real-world AB-treated HCC patients were analyzed in uni- and multivariate analyses to find potential prognostic factors of overall

Andrea Casadei-Gardini and Margherita Rimini should be considered co-last authors.

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survival (OS). Significant variables were incorporated in a composite score (α-FAtE) and it was tested for specificity and sensitivity in receiver operating characteristic (ROC) curve and in multivariate analysis for OS. The score was applied in uni- and multivariate analyses for OS of a comparable lenvatinib-treated HCC population. Finally, comparison between treatments was performed in patients with low and high α-FAtE scores and predictivity estimated by interaction analysis. Time-to-progression (TTP) was a secondary endpoint. OS of AB-treated HCC patients was statistically longer in those with α-fetoprotein <400 ng/mL (HR 0.62, $p = .0407$), alkaline phosphatase (ALP) <125 IU/L (HR 0.52, $p = .0189$) and eosinophil count ≥70/μL (HR 0.46, $p = .0013$). The α-FAtE score was generated by the sum of single points attributed to each variable among the above reported. In ROC curve analysis, superior sensitivity and specificity were achieved by the score compared to individual variables (AUC 0.794, $p < .02$). Patients with high score had longer OS (HR 0.44, $p = .0009$) and TTP (HR 0.34, $p < .0001$) compared to low score if treated with AB, but not with lenvatinib. Overall, AB was superior to lenvatinib in high score patients (HR 0.55, $p = .0043$) and inferior in low score ones (HR 1.75, $p = .0227$). At interaction test, low α-FAtE score resulted as negative predictive factor of response to AB ($p = .0004$). In conclusion, α-FAtE is a novel prognostic and predictive score of response to first-line AB for HCC patients that, if validated in prospective studies, could drive therapeutic choice between lenvatinib and AB.

KEYWORDS
alpha-fetoprotein, atezolizumab plus bevacizumab, eosinophils, HCC, lenvatinib

What's new?

Hepatocellular cancer (HCC) varies considerably in its etiology, biology, and clinical characteristics. For unresectable HCC, first-line therapies include the multikinase inhibitor lenvatinib and the combination therapy of atezolizumab plus bevacizumab (AB). Here, the authors establish a prognostic score, called α-FAtE, that can predict response to first-line AB. The score incorporates blood-based biomarkers reflecting immunological activity, liver function, and disease aggressiveness, and if validated, could be useful to help determine whether lenvatinib or AB will be more effective for an HCC patient.

1 | INTRODUCTION

The therapeutic scenario for unresectable hepatocellular carcinoma (HCC) has changed during recent years with the clinical advent of multikinase inhibitors (MKIs)[1] and monoclonal antibodies targeting biological processes instrumental to tumor growth, that is neoangiogenesis, by tackling the vascular-endothelial growth factor (VEGF)[2] or its receptors (VEGFR1/2),[3] and immune evasion, by blocking immune checkpoint molecules (such as programmed death ligand 1 PD-L1 and Cytotoxic T-Lymphocyte Antigen 4 CTLA-4).[4]

In spite of the growing available therapeutic repertoire, HCC treatment remains challenging due to its complex and variegated biology, etiopathogenesis, anatomical localization and clinical characteristics of the patient that contribute to treatment feasibility and outcome.[5]

When HCC patients are ineligible for locoregional approaches, the standard first-line systemic therapy has been represented by the MKI sorafenib for the last decade.[6,7]

More recently, the REFLECT trial and several real-world studies showed that the second-generation MKI lenvatinib was not inferior to sorafenib in terms of overall survival (OS) and superior in terms of time-to-progression (TTP).[8]

Furthermore, the IMbrave150 trial demonstrated prolonged OS and TTP in the trial arm treated with the combination of the anti-PD-L1 atezolizumab plus the anti-VEGF bevacizumab compared to the arm treated with sorafenib, gaining approval as first-line systemic treatment.[9] More recently, the exclusive immunotherapy combination of the anti-PD-L1 durvalumab and the anti-CTLA-4 tremelimumab with the STRIDE regimen was shown to be superior to sorafenib in the HIMALAYA trial,[10] highlighting the therapeutic potential of immune-based approaches for this disease setting.

However, no direct comparison between lenvatinib and atezolizumab plus bevacizumab (AB) has been evaluated in randomized clinical trials. Nevertheless, some real-world studies are providing new insights toward a more accurate clinical choice between the two treatments.[11–15] Kim and colleagues highlighted no statistically significant differences between lenvatinib and AB neither in terms of efficacy (evaluated as OS and TTP) nor tolerability (assessed as incidence of adverse events of any grade).[13] Our group recently confirmed this finding in a broad multicenter retrospective analysis of HCC patients receiving either lenvatinib or AB as first line treatment.[15] However, in the same study we also gathered preliminary evidence about putative etiology impact on response and survival under different treatments, in particular favoring lenvatinib for non-viral etiologies, especially non-alcoholic fatty liver disease (NAFLD) or steatohepatitis (NASH), and AB for viral etiology, especially in case of hepatitis B virus (HBV) infection.[14,15] Although confirmation in prospective trials will be pivotal to consolidate the findings, this observation lays the premises for the possible impact of biological differences in response to either lenvatinib and/or AB. Besides etiopathogenesis, also the patient immunological background, the disease burden and the residual liver function may underlie biological differences that could account for different sensitivity to treatments.[5,16] Basal blood counts and chemistry represent easily and widely accessible parameters that reflect the above disease and clinical aspects. Moreover, given the ancillary nature of histopathological diagnosis for HCC,[17] blood tests can be more consistently evaluated in all patients elected for systemic treatment and potentially return novel prognostic or predictive factor of response to different regimens.

In the present study we aim at assessing the impact on OS of basal immunological, disease and liver function parameters in blood exploiting real-world data from HCC patients treated with AB, and then interrogating a lenvatinib-treated cohort to evaluate the portability or singularity of the putative prognostic and/or predictive factors identified, possibly generating a composite index with superior specificity and sensitivity.

2 | MATERIALS AND METHODS

2.1 | Study population

A total of 543 patients treated with AB ($n = 204$, 37.6%) or lenvatinib ($n = 339$, 62.4%) as first-line systemic therapy for advanced-stage HCC (Barcelona Clinic Liver Cancer stage C, BCLC-C) or intermediate HCC (BCLC-B) who were ineligible for first- or re-treatment with surgical or locoregional therapies were included in the study population. Between May 2015 and April 2022, the overall cohort included Western and Eastern populations from 42 centers in five countries (Italy, Germany, Portugal, Japan and the Republic of Korea), with data for analysis collected retrospectively. Patients who were eligible had their HCC diagnoses confirmed histologically or clinically according to international guidelines, and none had previously received systemic therapy. The use of either treatment followed the same inclusion criteria as the registration trials.

2.2 | Treatments and definitions

All patients were treated with lenvatinib, until AB approval. After AB approval, the choice between the two therapies was left to physician in-charge with discretion. Lenvatinib was administered as described in the REFLECT trial (12 mg if baseline bodyweight was ≥60 kg or 8 mg if baseline body weight was <60 kg, given once daily orally).[8] AB was administered as described in the IMbrave150 trial (1200 mg of atezolizumab plus 15 mg per kilogram of body weight of bevacizumab intravenously every 3 weeks).[11]

Treatment interruptions and dose reductions were allowed to manage adverse events (AEs) as local practice. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. Patients were followed every 2–3 months with multiphasic scanning techniques. Tumor assessment was carried out regardless of dose interruption until radiological disease progression or imaging had become clinically irrelevant. When progression was diagnosed, the adoption of any subsequent anticancer medication depended on the local physician decision.

2.3 | Statistical analysis

Categorical variables were reported as the number of cases and percentage, continuous variables were expressed as median and 95% confidence interval (C.I.). OS was computed as the interval between the date of therapy start until the date of death for any reason. TTP was defined as the time from the start date of studied treatment to the date of progression or last follow-up whichever occurred first. OS and TTP were reported as median values expressed in months, with 95% C.I. Survival curves were estimated using the product-limit method of Kaplan–Meier. The role of stratification factors was analyzed using log-rank tests applying the Bonferroni's correction when more than two factors were evaluated.

Hazard ratios (HRs) in multivariate analysis of baseline characteristics were calculated using the Cox proportional-hazards regression model.

Differences in baseline characteristics between groups were estimated with Mann-Whitney test, Fisher exact test or Chi square test, as specified in Table 1.

Continuous variables were dichotomized using receiver operating characteristic (ROC) curves applying the survival either above or below the mean OS as classification variable to identify a possibly prognostic cutoff value based on the Youden's index in case of area under the curve (AUC) > 0.5 and $p < .05$, unless a cutoff value with a prognostic role was already been described. About the latter case, cutoff for albumin was set at 3.5 g/dL and α-fetoprotein (AFP) at 400 ng/mL according to references 18–20 and 21–23, respectively.

Interaction test was performed as Cox proportional-hazards regression model to calculate predictivity of the α-FAtE score (0–1 vs. 2–3) on treatment (AB vs. lenvatinib) outcome evaluated as OS.

Statistical significance threshold was set at $p < .05$.

TABLE 1 Baseline characteristics of the study populations.

Variable	Atezolizumab + bevacizumab ($n = 204$)	Lenvatinib ($n = 339$)	*p*-value	Test
Clinical				
Sex			.2958	Fisher
Male	163 (79.9%)	284 (83.8%)		
Female	41 (20.1%)	55 (16.2%)		
Age	66 (64, 68)	67 (65, 68)	.3764	Mann–Whitney
Etiology			.2775	Chi-squared
HCV	42 (20.6%)	93 (27.4%)		
HBV	82 (40.2%)	134 (39.5%)		
NASH/NAFLD	30 (14.7%)	40 (11.8%)		
Other	50 (24.5%)	72 (21.2%)		
Previous surgery	59 (28.9%)	89 (26.3%)	.5506	Fisher
Previous RF	57 (27.9%)	76 (22.4%)	.1507	Fisher
Previous TACE	94 (46.1%)	179 (52.8%)	.1330	Fisher
Child-Pugh			.3031	Fisher
A	186 (91.2%)	318 (93.8%)		
B	18 (8.8%)	21 (6.2%)		
BCLC			**<.0001**	Fisher
B	71 (34.8%)	61 (18.0%)		
C	133 (65.2%)	278 (82.0%)		
ECOG PS			**<.0001**	Chi-squared
0	120 (58.8%)	287 (84.7%)		
1	82 (40.2%)	52 (15.3%)		
2	2 (1.0%)	0 (0.0%)		
Neutrophils (/μL)	3129 (2807, 3420)	3265 (2989, 3460)	.2999	Mann–Whitney
Lymphocytes (/μL)	1221 (1103, 1300)	1190 (1119, 1299)	.9908	Mann–Whitney
Lymphocytes (cutoff)	$n = 203$pts	$n = 333$pts	1.000	Fisher
<950/μL	68 (33.5%)	111 (33.3%)		
≥950/μL	135 (66.5%)	222 (66.7%)		
NLR	2.688 (2.489, 3.021)	2.749 (2.610, 2.961)	.6074	Mann–Whitney
NLR (cutoff)	$n = 203$pts	$n = 312$pts	1.000	Fisher
<3	114 (56.2%)	175 (56.1%)		
>3	89 (43.8%)	137 (43.9%)		
Platelets (/μL)	148 000 (138 000, 163 480)	134 000 (130 000, 138 000)	**.0229**	Mann–Whitney
Eosinophils (/μL)	110 (99.6, 128.5)	121 (110.0, 136.3)	.1652	Mann–Whitney
Eosinophils (cutoff)		$n = 335$pts	.9199	Fisher
≥70/μL	151 (74.0%)	246 (73.4%)		
<70/μL	53 (26.0%)	89 (26.6%)		
Albumin (g/dL)	3.8 (3.7, 3.9)	3.9 (3.8, 4)	.1183	Mann–Whitney
Albumin (cutoff)	$n = 199$pts	$n = 337$pts	1.000	Fisher
≥3.5 g/dL	158 (79.4%)	268 (79.5%)		
<3.5 g/dL	41 (20.6%)	69 (20.5%)		
Bilirubin (mg/dL)	0.8 (0.7, 0.9)	0.8 (0.7, 0.8)	.6667	Mann–Whitney
Bilirubin (cutoff)		$n = 337$pts	.7753	Fisher
>1 mg/dL	63 (30.9%)	109 (32.3%)		
≤1 mg/dL	141 (69.1%)	228 (67.7%)		

TABLE 1 (Continued)

Variable	Atezolizumab + bevacizumab ($n = 204$)	Lenvatinib ($n = 339$)	*p*-value	Test
ALBI	−3.33 (−3.42, −3.21)	−3.41 (−3.46, −3.34)	.1482	Mann–Whitney
ALBI grade	$n = 199$pts	$n = 335$pts	.7561	Fisher
Grade 1	181 (91.0%)	306 (91.3%)		
Grade 2	19 (9.0%)	29 (8.7%)		
Creatinine (mg/dL)	0.77 (0.75, 0.82)	0.84 (0.82, 0.87)	.1361	Mann–Whitney
AST (IU/L)	44.15 (40.00, 53.50)	39.00 (36.00, 44.00)	**.0288**	Mann–Whitney
AST (cutoff)		$n = 337$pts	.1567	Fisher
>65 IU/L	60 (29.4%)	80 (23.7%)		
≤65 IU/L	144 (70.6%)	257 (76.3%)		
ALT (IU/L)	31.00 (27.00, 35.00)	33.00 (30.00, 36.00)	.1526	Mann–Whitney
ALT (cutoff)			.1715	Fisher
>40 IU/L	70 (34.3%)	137 (40.4%)		
≤40 IU/L	134 (65.7%)	202 (59.6%)		
ALP (IU/L)	132.0 (116.9, 146.0)	164.0 (144.7, 196.0)	**.0002**	Mann–Whitney
ALP (cutoff)	$n = 153$pts	$n = 325$pts	**.0154**	Fisher
>125 IU/L	82 (53.6%)	213 (65.5%)		
≤125 IU/L	71 (46.4%)	112 (34.5%)		
Tumor				
Portal vein thrombosis	71 (34.8%)	116 (34.2%)	.9258	Fisher
AFP (ng/mL)	60.5 (33.2, 90.9)	140.7 (66.8, 229.7)	.2603	Mann–Whitney
AFP (cutoff)	$n = 199$pts		.0807	Fisher
≥400 ng/mL	66 (33.2%)	139 (41.0%)		
<400 ng/mL	133 (66.8%)	200 (59.0%)		
Extrahepatic disease	82 (40.2%)	197 (58.1%)	**<.0001**	Fisher

Note: Continuous data are reported as medians and 95% confidence interval (C.I.); categorical variables are reported as absolute counts and relative percentages within the total. When continuous variables had statistically significant AUC >0.5 at ROC analysis, cutoff where introduced to dichotomize them (see Methods). When data were not available for the entire study population for a certain variable, the numerosity of collected data is reported. Comparison for each variable between atezolizumab plus bevacizumab and lenvatinib were performed with the indicated test. Legend: AFP, alphafetoprotein; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; HBV, hepatitis B virus; HCV, hepatitis C virus; NASH/NAFLD, non-alcoholic steatohepatitis/fatty liver disease; NLR, neutrophil-to-lymphocyte ratio; pts, patients: RF, radiofrequency; TACE, transarterial chemoembolization.

A MedCalc package (MedCalc version 16.8.4) was used for statistical analysis.

3 | RESULTS

3.1 | Patients' characteristics

Data from $n = 204$ HCC patients treated with AB and $n = 339$ ones treated with lenvatinib as first-line systemic therapy were analyzed. In the AB group, the median follow-up time was 15.2 months (95% confidence interval C.I. 12.5–42.0 months), the median TTP 6.9 (95% C.I. 5.8–9.6 months) and the median OS 17.0 months (95% C.I. 14.3–23.9 months). In the lenvatinib group, the median follow-up time was 11.5 months (95% C.I. 9.8–13.3 months), the median TTP 5.0 (95% C.I. 4.5–46.5 months) and the median OS 13.3 months (95% C.I. 11.4–51.6 months).

Baseline clinical and laboratory characteristics of patients treated with AB or lenvatinib are depicted in Table 1.

3.2 | Prognostic factors of survival in HCC patients treated with atezolizumab plus bevacizumab

At univariate analysis, the risk of death of HCC patients treated with first-line AB (Figure 1) was reduced in Child-Pugh A patients compared to B ones (HR 0.08, 95% C.I. 0.03–0.24; $p < .0001$), in case of lymphocyte count ≥950/μL (HR 0.51, 95% C.I. 0.30–0.85; $p = .0094$), NLR <3 (HR 0.56, 95% C.I. 0.36–0.89; $p = .0147$), eosinophil count ≥70/μL (HR 0.32, 95% C.I. 0.18–0.57; $p < .0001$), AFP <400 ng/mL (HR 0.50, 95% C.I. 0.30–0.81; $p = .0050$), albumin ≥3.5 g/dL (HR 0.30, 95% C.I. 0.16–0.54; $p = .0001$), ALBI score 1 (HR 0.29, 95% C.I. 0.12–0.68; $p = .0048$), AST <65 IU/L (HR 0.40, 95% C.I. 0.23–0.67; $p = .0006$), ALP ≤125 IU/L (HR 0.38, 95% C.I. 0.23–0.65; $p = .0003$) and absence of portal vein thrombosis (HR 0.49, 95% C.I. 0.30–0.80; $p = .0045$). Of these, eosinophil count, ALP and AFP were confirmed as prognostic markers of OS in HCC patients treated with AB at multivariate analysis ($p = .0021$, $p = .0250$ and $p = .0492$, respectively;

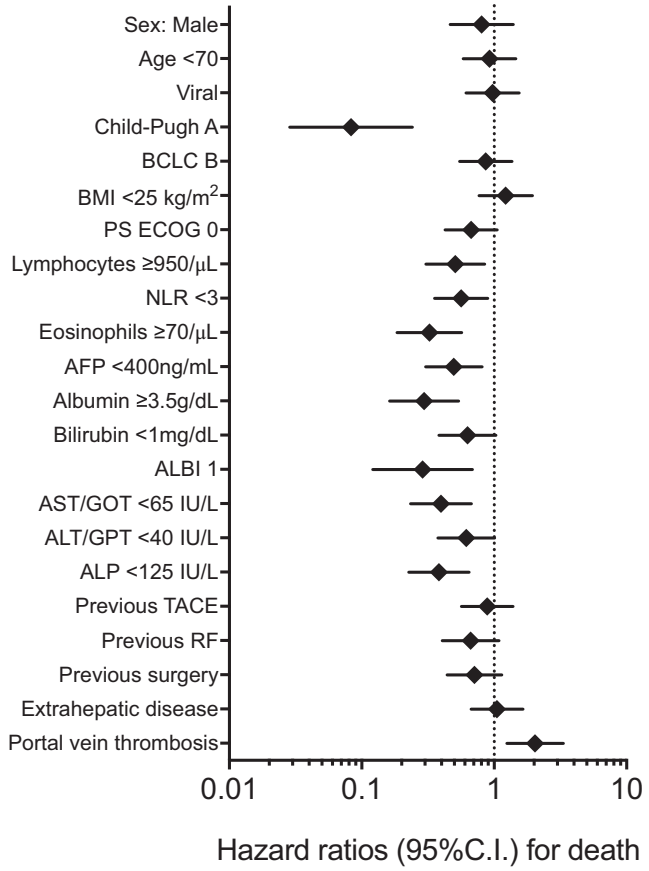

FIGURE 1 Risk and protective factors of death in atezolizumab plus bevacizumab-treated HCC patients. Forrest plot representing the hazard ratios of different baseline variables of HCC patients treated with atezolizumab plus bevacizumab on overall survival.

Table S1). We therefore reasoned to generate a combined prognostic score based on the latter three parameters, named α-FAtE (α-Fetoprotein, Alkaline phosphaTase, Eosinophils), resulting from the sum of individual points attributed as follow: AFP <400 ng/mL 1 point and ≥400 ng/mL 0 point; ALP ≤125 IU/L 1 point and >125 IU/L 0 point; eosinophil count ≥70/μL 1 point and <70/μL 0 point (Figure 2A).

By performing ROC curve comparison applying the survival either above or below the mean OS as classification variable, we found that AUC was 0.794 for α-FAtE score and significantly higher than individual AFP (AUC 0.649, $p = .0019$), ALP (AUC 0.706, $p = .0197$) and eosinophil count (AUC 0.669, $p = .0139$) (Figure 2B).

3.3 | α-FAtE score is a prognostic factor of survival for HCC patients treated with atezolizumab plus bevacizumab but not with lenvatinib

We performed Kaplan–Meier OS analysis of patients belonging to different α-FAtE classes treated with AB (Figure 2C) and found that score 3 patients out-survived all other score classes (median OS 22.5 months, 95% C.I. 18.9–22.5 months; vs. score 2 HR 0.52, 95% C.I. 0.29–0.94; $p = .0255$; vs. score 1 HR 0.23, 95% C.I. 0.11–0.46; $p < .0001$; vs. score 0 HR 0.11, 95% C.I. 0.03–0.46; $p < .0001$) and score 2 patients survived longer (median OS not reached) than score 1 (median OS 7.6 months, 95% C.I. 6.0–14.3 months; HR 0.44, 95% C.I. 0.22–0.89; $p = .0059$) and score 0 (median OS 3.9 months, 95% C.I. 1.4–8.8 months; HR 0.22, 95% C.I. 0.05–0.89; $p = .0005$) patients.

Youden's J statistic of α-FAtE ROC curve of OS (Figure 2B) identified cutoff score ≤ 1 having 83.3% specificity and 63% sensitivity. Thus, we grouped classes 0–1 and 2–3 patients and performed Kaplan–Meier analysis of OS (Figure 2D), finding significantly longer survival of score 2–3 patients (median OS 22.5 months, 95% C.I. 18.9–22.5 months) than class 0–1 (median OS 6.9 months, 95% C.I. 5.9–9.0 months; HR 0.22, 95% C.I. 0.12–0.40; $p < .0001$). We confirmed the prognostic role of grouped α-FAtE scores (2–3 vs. 0–1) of OS in HCC patients treated with AB at multivariate analysis (HR 0.48, 95% C.I. 0.29–0.79; Table S1). Moreover, we compared baseline characteristics of AB-treated patients having high score (2–3) and low score (0–1) (Table S2), and performed multivariate analysis incorporating all independent differing variables between the two groups (Table S3), further confirming the prognostic role of this novel score (HR 0.44, 95% C.I. 0.26–0.75, $p = .0025$).

Interestingly, patients with α-FAtE score 2–3 showed also prolonged TTP compared to score 0–1 (median TTP 11.8 months, 95% C.I. 6.9–20.7 months vs. 3.8 months, 95% C.I. 2.1–5.5 months; HR 0.34, 95% C.I. 0.21–0.55; $p < .0001$. Figure 2E).

We then investigated a lenvatinib-treated population of n = 339 HCC patients with similar baseline characteristics of that treated with AB, except for Barcelona Clinic Liver Cancer (BCLC) class, ECOG performance status, platelet count, ALP, α-FAtE score and extrahepatic disease (Table 1). At univariate analysis of OS, reduced risk of death was associated to BCLC class B compared to C (HR 0.58, 95% C.I. 0.40–0.85; $p = .0049$), previous surgery (HR 0.57, 95% C.I. 0.40–0.80; $p = .0014$), absence of portal vein thrombosis (HR 0.60, 95% C.I. 0.41–0.85; $p = .0040$), AFP <400 ng/mL (HR 0.52, 95% C.I. 0.37–0.73; $p = .0002$), bilirubin <1 mg/dL (HR 0.65, 95% C.I. 0.45–0.95; $p = .0262$) and absence of extrahepatic disease (HR 0.63, 95% C.I. 0.46–0.88; $p = .0065$), while, contrarily to the AB population, α-FAtE score ≥2 was not associated to reduced risk (HR 0.84, 95% C.I. 0.59–1.19; $p = .3199$; Figure 3A). At multivariate analysis, only AFP <400 ng/mL, previous surgery and absence of extrahepatic disease were confirmed as prognostic factors of OS in the lenvatinib-treated population (Table S1).

To further confirm the lack of prognostic value of the α-FAtE score in the lenvatinib-treated population, we performed ROC curve analysis of OS of the composite score and the individual variables it is composed of, finding that AFP provided the only statistically significant AUC >0.5 (AUC 0.615, $p = .0030$), with no significant difference in their comparison (Figure 3B). Moreover, score 2–3 patients showed similar OS to those with score 0–1 (median OS 14.8 months, 95% C.I. 11.4–51.6 months

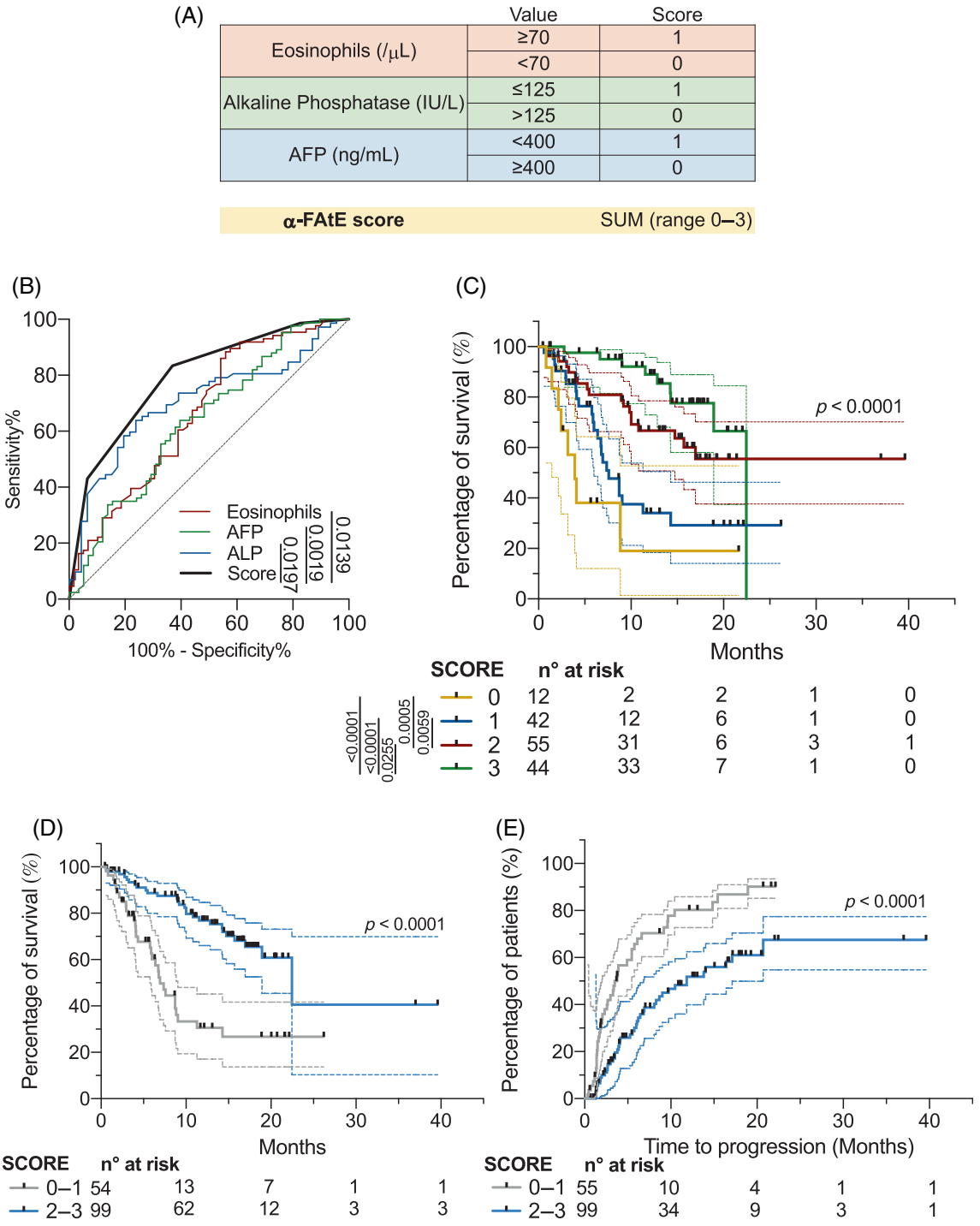

FIGURE 2 α-FAtE score as a novel prognostic factor of overall and time-to-progression of HCC patients treated with atezolizumab plus bevacizumab. (A) Graphical representation of α-FAtE score composition and calculation. (B) Receiver operating characteristic (ROC) curve of α-FAtE score and its constitutive parameters, that is, α-fetoprotein (AFP), alkaline phosphatase (ALP) and eosinophil count, on overall survival (OS) estimate of patients treated with atezolizumab plus bevacizumab (see Section 2; *p* values from DeLong *U*-statistics for area under the curve—AUC—comparison). (C) Kaplan–Meier survival curves of OS of atezolizumab plus bevacizumab-treated patients classified for α-FAtE score (*p* values from log-rank Mantel–Cox test with Bonferroni correction). (D) Kaplan–Meier survival curves of OS of atezolizumab plus bevacizumab-treated patients classified for α-FAtE score 0–1 versus 2–3 (*p* value from log-rank Mantel–Cox test). (E) Kaplan–Meier survival curves of time-to-progression (TTP) of atezolizumab plus bevacizumab-treated patients classified for α-FAtE score 0–1 versus 2–3 (*p* value from log-rank Mantel–Cox test). [Color figure can be viewed at wileyonlinelibrary.com]

vs. 13.0 months, 95% C.I. 10.0–19.6 months, respectively; HR 0.84, 95% C.I. 0.59–1.68; $p = .3199$. Figure 3C). Similar results were achieved when considering TTP, with score 2–3 patients showing a median TTP of 5.8 months, 95% C.I. 5.0–20.5 months, and score 0–1 patients 4.0 months, 95% C.I. 3.6–46.5 months (HR 0.79, 95% C.I. 0.61–1.02; $p = .0757$. Figure 3D).

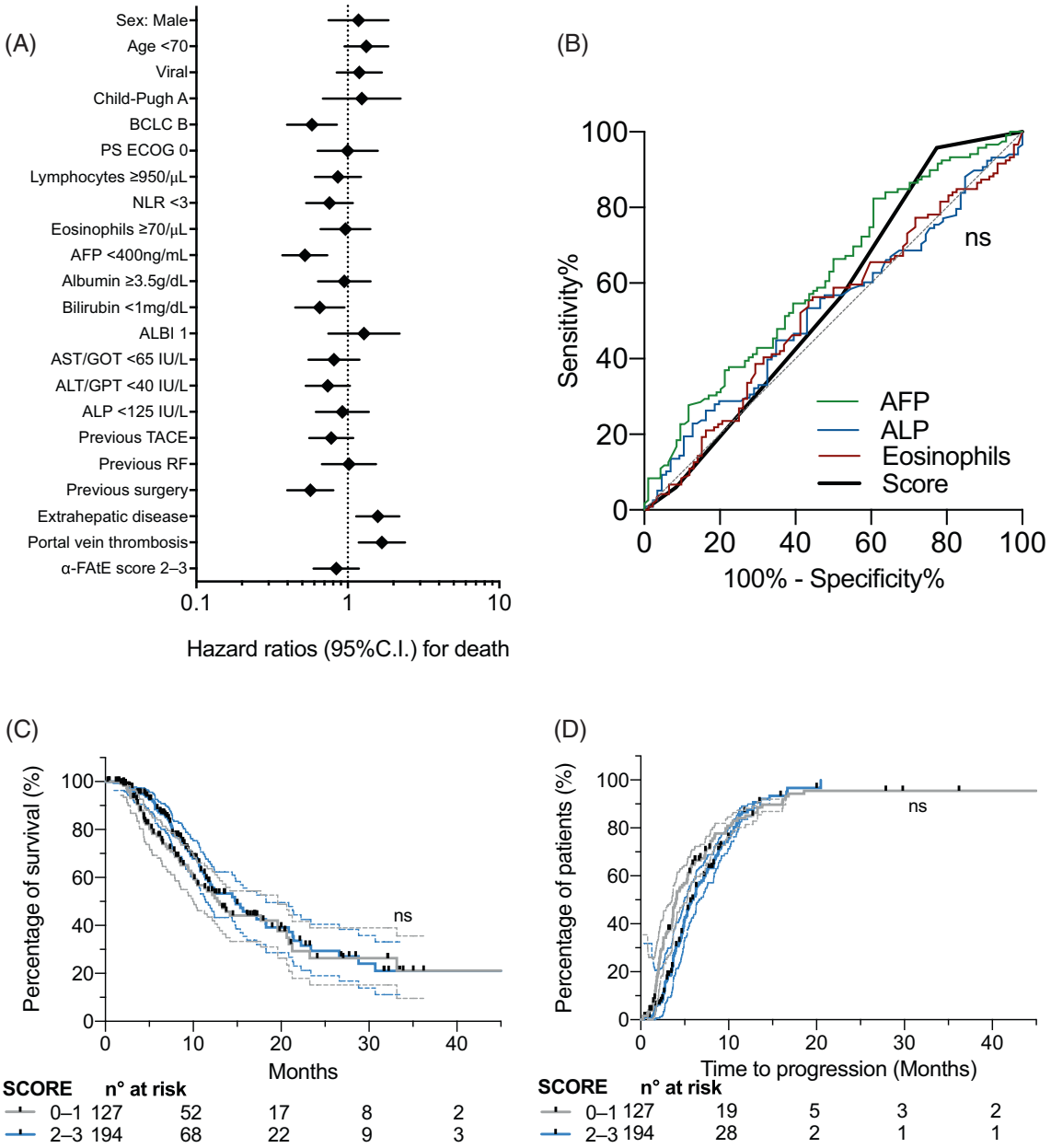

FIGURE 3 α-FAtE score is not prognostic in HCC patients treated with lenvatinib. (A) Forrest plot representing the hazard ratios of different baseline variables of HCC patients treated with lenvatinib on overall survival. (B) Receiver operating characteristic (ROC) curve of α-FAtE score and its constitutive parameters, that is, α-fetoprotein (AFP), alkaline phosphatase (ALP) and eosinophil count, on overall survival (OS) estimate of patients treated with lenvatinib (see Section 2; DeLong *U*-statistics for area under the curve—AUC—comparisons: all *p* values >.09). (C) Kaplan–Meier survival curves of OS of lenvatinib-treated patients classified for α-FAtE score 0–1 versus 2–3 (log-rank Mantel–Cox test, $p = .32$). (D) Kaplan–Meier survival curves of time-to-progression (TTP) of lenvatinib-treated patients classified for α-FAtE score 0–1 versus 2–3 (log-rank Mantel–Cox test, $p = .08$). [Color figure can be viewed at wileyonlinelibrary.com]

3.4 | α-FAtE score predicts response to atezolizumab plus bevacizumab and could drive therapeutic choice for HCC patients not eligible for locoregional approaches

Once established a prognostic role of the α-FAtE score for the AB-treated group of patients but not for the lenvatinib-treated one, we investigated preliminary evidence of its putative use to drive clinical decision in HCC patients eligible for systemic treatment.

In the overall population treated with either AB or lenvatinib, patients with low α-FAtE score (0–1) survived significantly longer when treated with lenvatinib (median OS 13.0 months, 95% C.I. 10.0–19.6 months) than AB (median OS 6.9 months, 95% C.I. 5.9–9.0 months; HR 0.57, 95% C.I. 0.35–0.92; $p = .0227$; Figure 4A). At multivariate analysis encompassing all the variables

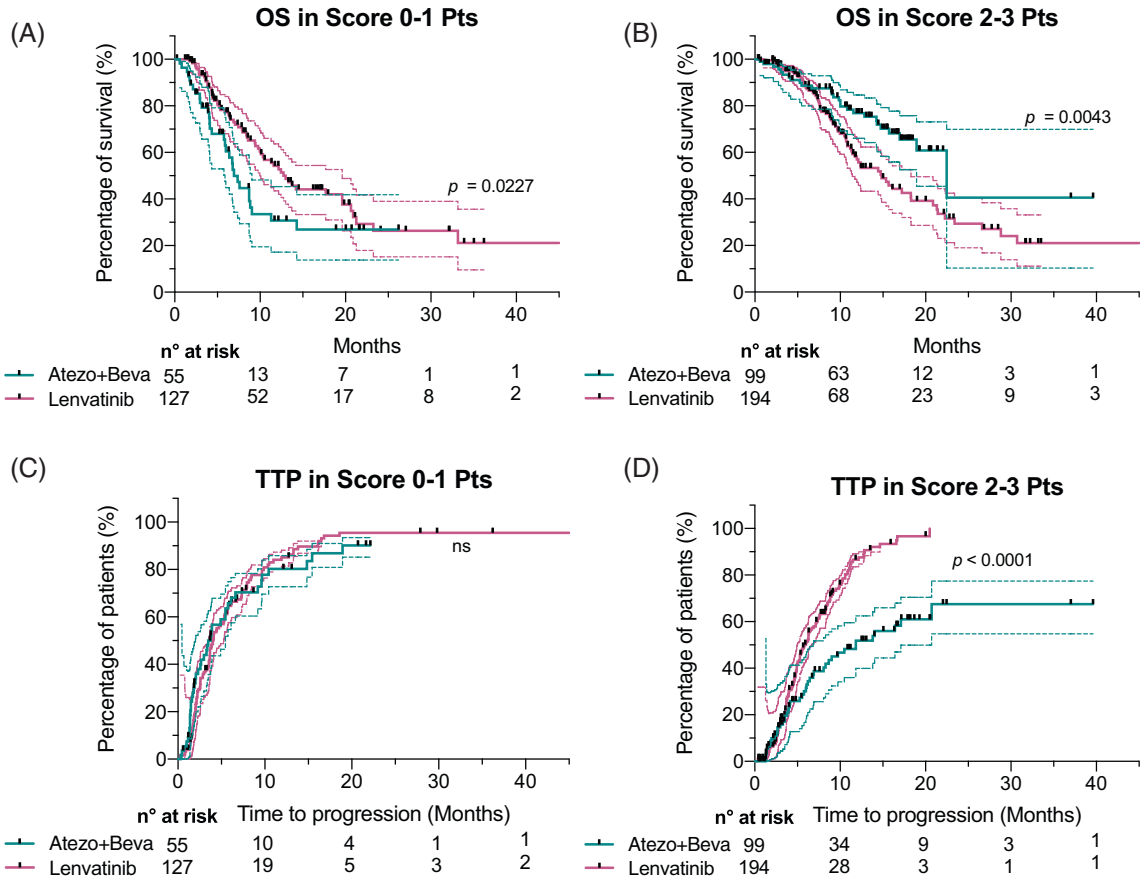

FIGURE 4 α-FAtE score can contribute to therapeutic choice in HCC patients eligible to systemic therapy. Kaplan–Meier survival curves of overall survival (A and B) and time-to-progression (C and D) of HCC patients with α-FAtE score 0–1 (A–C) or 2–3 (B–D) receiving either atezolizumab plus bevacizumab or lenvatinib as first-line systemic treatment (*p* values from log-rank Mantel–Cox tests). [Color figure can be viewed at wileyonlinelibrary.com]

with significantly different distribution between lenvatinib and AB patients (see Table 1), lenvatinib maintained significant risk reduction of death compared to AB (HR 0.62, 95% C.I. 0.38–0.99; $p = .0470$; Table S4). Conversely, class 2–3 of α-FAtE score (high) achieved prolonged OS when treated with AB (median OS 22.5 months, 95% C.I. 18.9–22.5 months) compared to lenvatinib (median OS 14.8 months, 95% C.I. 11.4–51.6 months; HR 0.55, 95% C.I. 0.37–0.83; $p = .0043$; Figure 4B), maintaining also significant risk reduction at multivariate analysis (HR 0.50, 95% C.I. 0.29–0.86; $p = .0120$; Table S4). While the latter patients displayed also TTP advantage when treated with AB than lenvatinib (median TTP 11.8 months, 95% C.I. 6.9–20.7 months vs. 5.8 months, 95% C.I. 5.0–20.5 months; HR 0.44, 95% C.I. 0.33–0.60; $p < .0001$; Figure 4D), no differences in TTP were found in class 0–1 patients (AB: median TTP 3.8 months, 95% C.I. 2.1–5.5 months; lenvatinib: median TTP 4.0 months, 95% C.I. 3.6–46.5 months; HR 0.98, 95% C.I. 0.69–1.40; $p = .9178$; Figure 4C).

Finally, we demonstrated the negative predictive role of response to AB of the α-FAtE score by performing an interaction test between class 0–1 and 2–3 of the score and the treatment ($p = .0004$). These results provide first evidence of the need of different treatment indications for low α-FAtE score patients, to whom lenvatinib seems to confer prolonged OS, and those with high score, since AB accounts for both improved OS and TTP.

3.5 | α-FAtE and etiology: immunological factors could explain stronger prognostic value in viral HCC treated with atezolizumab plus bevacizumab

In our retrospective cohort, viral and non-viral etiologies were not associated to neither prolonged OS nor TPP regardless the systemic treatment received. Moreover, AB-treated patients, in which we have demonstrated the prognostic and predictive value of the α-FAtE score, displayed similar contribution of viral and non-viral etiologies in high-score versus low-score patients (Table S2), suggesting that the score is not biased by HCC etiologies. However, given that immunological factors, represented by eosinophils in the α-FAtE score, may play a stronger role in viral-related HCC compared to non-viral HCC,[24–27] we performed additional subgroup analyses to investigate potential implications of the prognostic score depending on HCC etiology and the treatment received (Figure 5). Interestingly, AB was superior to lenvatinib in viral HCC patients with high α-FAtE score

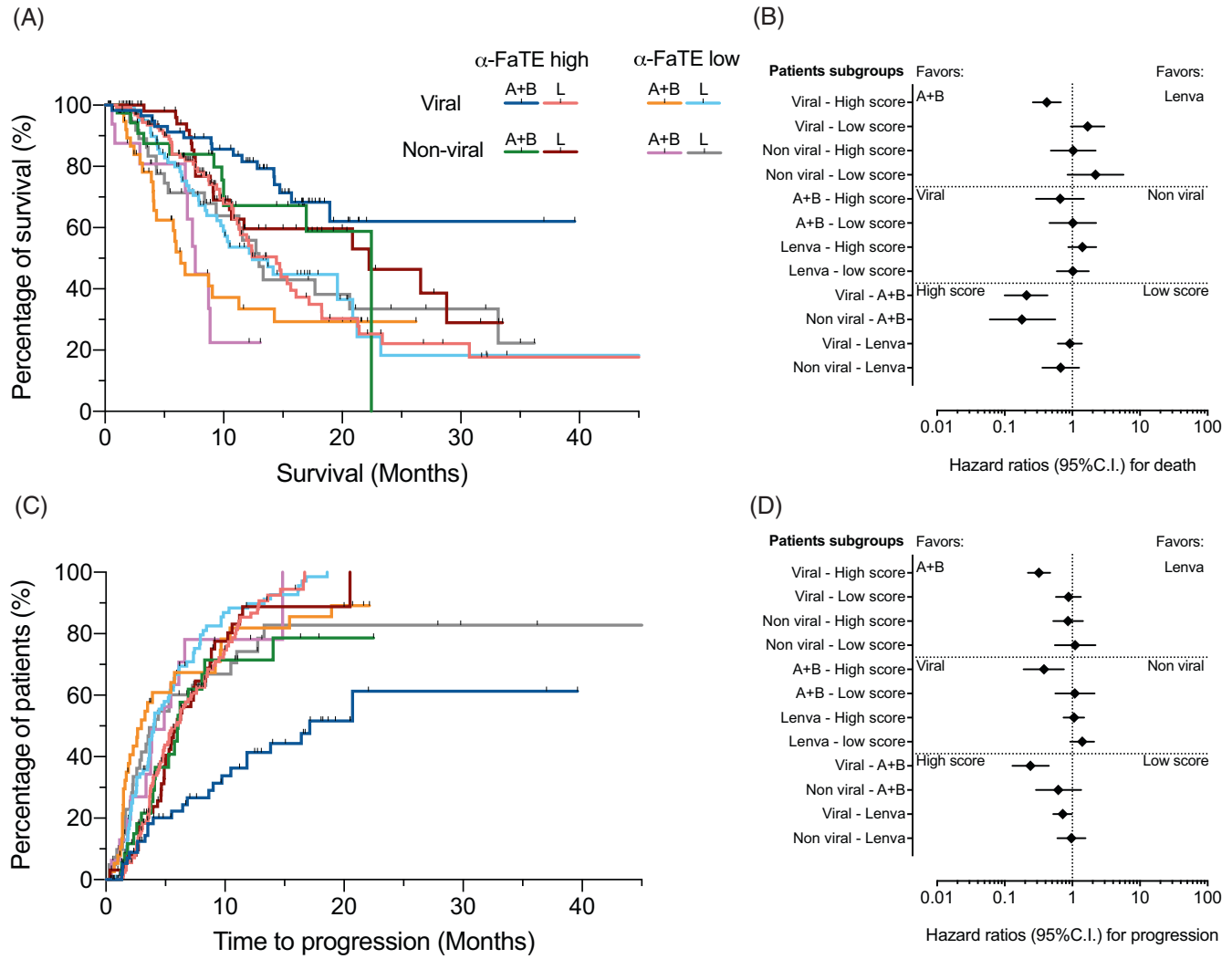

FIGURE 5 α-FAtE score, HCC etiology and treatment identify different prognostic classes. Kaplan–Meier survival curves of overall survival (A) and time-to-progression (C) of HCC patients grouped based on α-FAtE score 0–1 (low) or 2–3 (high), HCC etiology (viral and non-viral) and treatment (atezolizumab plus bevacizumab, A + B, and lenvatinib, L). Statistical comparisons are reported aside in forest plots representing the hazard ratios of the three variables in the different subgroups of patients in terms of overall survival (B) and time-to-progression (D) (log-rank Mantel–Cox test). [Color figure can be viewed at wileyonlinelibrary.com]

both in terms of OS (mOS not reached vs. 14.4 months, 95% C.I. 11.2–51.6 months; HR 0.42, 95% C.I. 0.26–0.68; $p = .0005$; Figure 5A,B) and TTP (mTTP 17.1, 95% C.I. 10.5–20.7 months vs. 5.8 months, 95% C.I. 4.8–16.7 months; HR 0.32, 95% C.I. 0.22–0.47; $p < .0001$; Figure 5C,D), and not in the other subgroups. Consistently, viral etiology was associated to a reduced risk of progression compared to non-viral one in HCC patients treated with AB and having high α-FAtE score (mTTP 17.1, 95% C.I. 10.5–20.7 months vs. 6.1 months, 95% C.I. 4.1–8.3 months; HR 0.38, 95% C.I. 0.19–0.75; $p = .005$; Figure 5C,D).

Finally, the positive prognostic impact of high α-FAtE score in AB-treated patients was confirmed in both viral and non-viral subgroups in terms of OS (HR 0.21, 95% C.I. 0.10–0.43, $p < .0001$, and HR 0.18, 95% C.I. 0.06–0.56; $p = .0032$, respectively; Figure 5A,B), while only in viral patients in terms of TTP (HR 0.24, 95% C.I. 0.13–0.45; $p < .0001$).

Altogether these findings strengthen the association of AB treatment, viral etiology and α-FAtE score prognostic value, indicating a major role played by immunological cues as least common denominator.

4 | DISCUSSION

Here we showed the prognostic and predictive role of a novel composite score incorporating baseline blood AFP, ALP and eosinophils count, named α-FAtE, for OS of HCC patients treated with first-line AB, but not with lenvatinib. Interestingly, high-score patients (score 2 and 3) treated with AB displayed longer OS and TTP compared to both lenvatinib-treated patients and low-score patients (score 0 and 1) treated with AB. The latter group, instead, despite having similar TTP as low-score patients treated with lenvatinib, had significantly

shorter OS times. When considering only lenvatinib-treated patients, the α-FAtE score did not stratify for different prognosis.

Altogether, these results provide first evidence of a baseline parameter that could drive the treatment choice of HCC patients eligible to first-line systemic therapy. Importantly, no direct comparison of AB and lenvatinib has been carried out in randomized clinical trials, therefore making identification of predictive factors of response of first relevance to tailor the best therapeutic option to each patient, particularly considering the marked clinical heterogeneity of HCC.[5,12,16] Moreover, the α-FAtE score relies on easily accessible, non-invasive and routinely performed blood tests prior to treatment start, making its putative implementation into clinical practice straightforward.

On the biological standpoint, the three contributing factors to the α-FAtE score account for different clinical and disease characteristics.

Serum AFP is a well-established biomarker of HCC aggressiveness and prognosis, as well as biomarker of recurrence and/or therapeutic response during clinical follow-up.[21,28] Consistently, in the present work AFP values below 400 ng/mL were associated with reduced risk of death in both AB- and lenvatinib-treated patients at uni- and multivariate analysis, demonstrating that, on the opposite, more aggressive diseases expressing high levels of AFP tend to respond less to both systemic therapies and bear worse prognosis.

ALP is a liver enzyme commonly used in the clinics as indicator of cholestasis, and multiple evidence propose its prognostic role for HCC patients treated with both locoregional and systemic approaches.[29–31] However, in our cohort of patients ALP values above 125 IU/L were prognostic of worse outcome only for AB and not for lenvatinib treatment. The underlining biological reason of such a difference remains unknown, but it is possible that HCC distribution and pattern of growth may vary and imply different biliary canaliculi involvement.[5,16] While MKI may not be affected by such histology, immune cells may be excluded by such specific tissue sub-localization of tumor cells and tend to respond less to immunotherapy.

Eosinophils are an emergent cellular type increasingly investigated in the immunoncology field.[32] Recent evidence suggests important direct and indirect antitumor activities carried out by tumor-infiltrating eosinophils.[32] Eosinophils can be recruited into the tumor site and activated by multiple cytokines, such as interleukin (IL)-5, IL-33, Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), tumor necrosis factor (TNF)-α and interferon (IFN)-γ, to carry out eosinophil-mediated cytotoxicity after degranulation of antitumor molecules like granzymes and vessel normalization in the tumor site.[33,34] Furthermore, eosinophils seem to play a major role in NK and T cell activation in the tumor microenvironment, both by acting as antigen-presenting cells expressing co-stimulatory molecules and by releasing activating cytokines.[35–37] However, suppressive stimuli of the tumor microenvironment can also impact on eosinophils, which can express PD-L1 and other immune checkpoint molecules.[38] Indeed, growing evidence is also supporting the prognostic role of blood eosinophil count for immunotherapy with immune checkpoint blockers in different cancer types, such as breast,[38] lung[39] and renal[40] cancer, melanoma,[41] head and neck squamous cell carcinoma,[42] and Hodgkin lymphoma.[43] In the present work we provide first evidence of the prognostic value of eosinophil count, especially when incorporated into the α-FAtE score, for HCC patients treated with AB, but not lenvatinib. Speculatively, AB can synergize with eosinophils in both vessel normalization and immune response against the tumor, thus explaining the strong prognostic value in our setting. Furthermore, the strongest association of the score with reduced risk of death and progression was found in patients with viral HCC treated with AB, supporting the key relevance of immunological factors in this specific etiology and treatment subgroup that can be captured by the α-FAtE score.

On the other hand, lenvatinib is a MKI with both direct tumor cell inhibition activities and antiangiogenic functions, but lacks strong immunological mechanisms that may underlie the absence of eosinophils impact on outcome in this group of patients. Of note, we previously showed that eosinophils count is a prognostic factor of OS for HCC patients treated with the early-generation MKI sorafenib.[44] This apparently controversial difference between sorafenib and lenvatinib may be explained in part by the different cutoff retrieved by ROC curve analysis (50 vs. 70/μL, respectively) and in part by different affinities for tyrosine kinase receptors: for instance, while sorafenib may exert a weak antiangiogenic effect due to lower affinity for VEGFR therefore requiring eosinophils to achieve better antitumor activity, lenvatinib may inhibit angiogenesis more stringently regardless the presence of eosinophils due to its greater inhibitory function on VEFGR.[45]

Overall, the α-FAtE score incorporates three different biomarkers reflecting disease aggressiveness, liver status and immunological features representing a more accurate prognostic factor of OS than the constitutive individual variables for HCC patients treated with first-line AB treatment; importantly, we also demonstrated its negative predictive role of response to AB when <2.

Among the limitations of the present work, its retrospective nature may have affected the completeness of data and the uniformity of the study population, since selection bias may have occurred. For instance, baseline ALP values were available in $n = 153$ and $n = 325$ patients treated with AB and lenvatinib, respectively, limiting the sample size for α-FAtE score calculation. Moreover, the evaluation of TTP may suffer from reproducibility issues due to the multicentric and multinational nature of the work, since no centralized imaging review was included in the study protocol and the tumor assessment was made accordingly to the clinical protocol of each institute. Another possible drawback is the exclusive baseline evaluation of the α-FAtE score in the present analysis, while also its on-treatment dynamic changes may bear further prognostic and predictive information on response but possibly also on toxicities. Another important missing point concerns treatment interruptions and their putative impact on disease outcome of patients treated with either lenvatinib or AB. Furthermore, the variability of second-line treatments and beyond received by patients from different centers may have biased OS comparison analyses.

In conclusion, the α-FAtE is an easy-to-use tool because it is made up of factors widely used in clinical practice for HCC patients. It

is also instrumental to stratification of HCC patients who are candidates for atezolizumab plus bevacizumab or lenvatinib from a prognostic point of view. Despite the consistent number of patients included in our analysis, these data need to be confirmed and validated in prospective studies to eventually provide clinicians with a novel and easily accessible tool to select the best treatment option for different patients.

AUTHOR CONTRIBUTIONS

The work reported in the paper has been performed by the authors, unless clearly specified in the text. *Conception and design*: Federico Rossari, Andrea Casadei-Gardini, and Margherita Rimini. *Acquisition of data (acquired and managed patients)*: All authors. *Analysis and interpretation of data*: Federico Rossari, Andrea Casadei-Gardini, and Margherita Rimini. *Writing, review, and/or revision of the manuscript*: Federico Rossari, Andrea Casadei-Gardini, and Margherita Rimini. *Final approval of manuscript*: All authors.

AFFILIATIONS

[1]Department of Oncology, Vita-Salute San Raffaele University, IRCCS San Raffaele Scientific Institute Hospital, Milan, Italy
[2]San Raffaele Telethon Institute for Gene Therapy (SR-Tiget), IRCCS San Raffaele Scientific Institute Hospital, Milan, Italy
[3]Department of Internal Medicine, Japanese Red Cross Himeji Hospital, Himeji, Japan
[4]Department of Gastroenterology and Hepatology, Graduate School of Medicine, Hokkaido University, Sapporo, Hokkaido, Japan
[5]Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Kurume, Fukuoka, Japan
[6]Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka, Japan
[7]Department of Oncology, ASAN Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[8]Department of Medical Oncology, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Korea
[9]Department of Internal Medicine 1, University Hospital Frankfurt, Goethe University, Frankfurt am Main, Germany
[10]Department of Medicine, Samsung Medical Center, School of Medicine, Sungkyunkwan University, Seoul, Korea
[11]Liver Unit-CHTMAD, Vila Real, Portugal
[12]Unit of Medical Oncology 2, University Hospital of Pisa, Pisa, Italy
[13]Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy
[14]Oncology Unit 1, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy
[15]Department of Nursing, Gifu Kyoritsu University, Japan
[16]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico di Milano, Division of Gastroenterology and Hepatology, Milan, Italy
[17]Section of Gastroenterology and Hepatology, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties PROMISE, University of Palermo, Palermo, Italy
[18]Department of Internal Medicine, Ospedale di Faenza, Faenza, Italy
[19]Department of Gastroenterology and Metabology, Ehime University Graduate School of Medicine, Ehime, Japan
[20]Department of Gastroenterology, Okayama City Hospital, Okayama, Japan
[21]Department of Gastroenterology and Hepatology, Kagawa University, Kagawa, Japan
[22]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Nippon Medical School, Tokyo, Japan
[23]Department of Hepatology, Kagawa Prefectural Central Hospital, Takamatsu, Japan
[24]Department of Gastroenterology, Asahi General Hospital, Asahi, Japan
[25]Department of Gastroenterology, Osaka Medical and Pharmaceutical University, Osaka, Japan
[26]Center of Gastroenterology, Teine Keijinkai Hospital, Sapporo, Japan
[27]Department of Gastroenterology, Saiseikai Niigata Hospital, Niigata, Japan
[28]Department of Gastroenterology, Toyama University Hospital, Toyama, Japan
[29]Hepato-biliary Center, Japanese Red Cross Matsuyama Hospital, Matsuyama, Japan
[30]Department of Gastroenterology and Hepatology, Ogaki Municipal Hospital, Ogaki, Japan
[31]Department of Gastroenterology, Japanese Red Cross Takamatsu Hospital, Takamatsu, Japan
[32]Department of Internal medicine, Division of Gastroenterology and Hepatology, Hyogo Medical University, Nishinomiya, Japan
[33]Department of Gastroenterology, Gunma Saiseikai Maebashi Hospital, Maebashi, Japan
[34]Department of Clinical Research, National Hospital Organization Takasaki General Medical Center, Takasaki, Japan
[35]Division of Gastroenterology and Hepatology, Otakanomori Hospital, Kashiwa, Japan
[36]Department of Hepatology, Hamamatsu University School of Medicine, Hamamatsu, Japan
[37]Gastroenterology Center, Ehime Prefectural Central Hospital, Matsuyama, Japan
[38]Department of Surgery, Kansai Medical University, Osaka, Japan
[39]Department of Gastroenterology, National Hospital Organization Takasaki General Medical Center, Takasaki, Japan
[40]Medical Oncology, University and University Hospital of Cagliari, Cagliari, Italy
[41]Division of Internal Medicine, Hepatobiliary and Immunoallergic Diseases, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

CONFLICT OF INTEREST STATEMENT

Andrea Casadei-Gardini has received grants and personal fees from MSD, Eisai, Bayer, Bristol-Myers Squibb, AstraZeneca and GSK. Atsushi Hiraoka received lecture's fees from Chugai, Lilly, AstraZeneca. Fabian Finkelmeier has received speaker fees from AbbVie, MSD, Ipsen, Eisai and Fresenius. Fabio Piscaglia has received fees from

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The current study was approved by the ethics committees at each center, and it followed the Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws, as well as the European Parliament and Council Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data, which was enacted on April 27, 2016. Written informed consent was obtained from all patients.

ORCID

Federico Rossari https://orcid.org/0000-0003-4493-6380
Caterina Vivaldi https://orcid.org/0000-0001-9307-2326
Naoshi Nishida https://orcid.org/0000-0002-9111-5668
Asahiro Morishita https://orcid.org/0000-0002-0760-3045
Andrea Casadei-Gardini https://orcid.org/0000-0001-6289-7202
Margherita Rimini https://orcid.org/0000-0002-4047-2585

TWITTER

Andrea Casadei-Gardini *casadei_gardini*

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

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