Liver Cancer

Research Article

Liver Cancer
DOI: 10.1159/000547669

Received: January 24, 2025
Accepted: July 18, 2025
Published online: September 19, 2025

Vessels That Encapsulate Tumor Cluster+ Unresectable Hepatocellular Carcinomas Benefit of Antiangiogenic Therapy

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Keywords
Hepatocellular carcinoma · Vessels that encapsulate tumor clusters · Biomarker · Antiangiogenic treatment

Abstract
Introduction: Two distinct molecular groups of HCC have been recently associated with a better response to atezolizumab-bevacizumab. One of these, "angiogenesis-driven," is related to HCC vascularization. Vessels that encapsulate tumor clusters (VETCs) is a morphological form of angiogenesis associated with worse prognosis in resected and transplanted HCC. The aim of this study was to explore if VETC can be used, at morphological level, to potentially surrogate the angiogenesis-driven molecular subgroup to identify HCC patients who might benefit of antiangiogenic treatments. ***Methods:*** The significance of VETC was first explored in a retrospective, single institution series of 75 patients with unresectable HCC (study cohort) and later validated in an external, retrospective series of 82 patients (validation cohort). The VETC phenotype was identified in the liver biopsy obtained just before the onset of systemic treatment. ***Results:*** Patients with VETC+ HCC experienced a significant survival benefit from antiangiogenic drugs, as tyrosine kinase inhibitors and/or bevacizumab (TKI/BEVA), across the study, validation, and overall cohorts. In the whole series of 157 patients, those with VETC+ HCC (n = 70, 45%) treated with TKI/BEVA had a significantly longer overall survival (OS) as compared to those receiving immune checkpoint inhibitors (19.8 months vs. 8.8 months; HR: 0.34; 95% CI: 0.20–0.59; p = 0.0001). The significant treatment-by-biomarker interaction test (p = 0.002) demonstrated that treatment effect varies by VETC status. Case with higher extent of VETC+ or with VETC+ detected before the onset of 1st-line treatment showed even longer survival. ***Conclusion:*** VETC+ predicts a significantly longer OS in patients with unresectable HCC treated with TKI/BEVA and can be used as surrogate marker on liver biopsy of angiogenesis-driven molecular class.

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Introduction

Hepatocellular carcinoma (HCC) has been rising in the past 3 decades and similar trends are expected through 2030 [1]. HCC is diagnosed at advanced stage in more than 70% of the cases [2] and has a 5-year survival rate of about 20% [3]. In this grave context, the first-line systemic therapies, namely, atezolizumab-bevacizumab (A/B), durvalumab-tremelimumab, and more recently, nivolumab/ipilimumab significantly improved the overall survival (OS) achieved with tyrosine kinase inhibitors (TKIs) [4–9]. However, there is a critical need for predictive biomarkers to tailor these regimens.

A recent study unveils two distinct group of HCC associated with a better response to A/B [10]. The first is characterized by the presence of CD8 effector cells and pro-inflammatory macrophages. This "immune-competent" subset [10] overlaps the previously reported A/B response signature [11] and is characterized by an inflamed tumor microenvironment and molecular features suggestive of an increased vulnerability to atezolizumab, in particular, and more broadly to immune checkpoint inhibitors (ICIs). The second group of responders lack anti-tumoral immune component, rather they are characterized by a modulation of the VEGF/VEGFr axis, in particular a downregulation of NRP1. This latter favors vascular remodeling upon anti-VEGF therapy (bevacizumab) [12] and has been already reported as a predictive biomarker of response to bevacizumab [13]. Accordingly, the "angiogenesis-driven" HCC benefits of the antiangiogenic effect of bevacizumab [10].

Hepatocarcinogenesis is characterized by a progressive vascular enrichment and advanced HCCs are typically hypervascular [14]. Vessels that encapsulate tumor clusters (VETCs) are a peculiar subtype of this vascular enrichment characterized by the presence of HCC cell nests surrounded by endothelial cells [15, 16]. HCCs presenting this peculiar aspect, highlighted by staining for the endothelial marker CD34, are characterized by increased vascular invasion and distant metastases [17]. In keeping with these features, VETC+ HCC has a worse prognosis after hepatectomy [17–21] and liver transplantation [22, 23]. In addition to this well-established prognostic role, VETC has been associated with a predictive role on transarterial chemoembolization [24, 25] and on sorafenib [26]. Interestingly enough, VETC has been linked to overexpression of angiopoietin-2 (Ang2) [16], VEGF, and FGF2 [27, 28]. In the present study, we show that VETC overlaps with the "angiogenesis-driven" class [10] in predicting a better outcome upon treatment with drugs targeting angiogenesis and thus might be helpful, at clinical level on HCC biopsy, to select patients eligible for these treatments.

Methods

Study Cohort

Seventy-five consecutive patients with unresectable HCC were treated at IRCCS Humanitas Research Hospital (Milan, Italy) from August 2016 to September 2021.

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Validation Cohort

Eighty-two patients with unresectable HCC were treated, during the same period of the study cohort, at the University Hospitals of Hong Kong Special Administrative Region of China, National Taiwan University Hospital (Taiwan), University Hospital of Modena (Italy), Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan (Italy), Veneto Institute of Oncology IOV – IRCCS of Padua (Italy), and IRCCS San Raffaele Scientific Institute Hospital of Milan (Italy).

Inclusion Criteria

Ultrasound-guided liver biopsy performed using 18–20-G needles before receiving the latest systemic treatment, with at least 2 mm of HCC tissue available. In accordance with what is done in other tumors, this biopsy, the latest before treatment, was considered as representative of tumor features. Morphological and immunohistochemical evaluation was centralized in a single Institution (Humanitas) and performed by three expert liver pathologists (M.R., L.T., and L.D.T.). Complete medical data including clinical presentation at baseline (gender, age, ECOG performance status, etiology, Child-Pugh class, BCLC stage, prior locoregional treatments, previous systemic treatments), outcome (progression-free survival [PFS]; OS), and radiological response (according to mRECIST) were collected at each center. The study does not include a control group without pharmacological treatment; this should have included patients treated before the approval of sorafenib and would have had different clinical characteristics from the patients considered in this study. The study was approved by the Ethics Committee of each hospital. Informed consent was waived due to the retrospective nature of the study.

Morphological and Immunohistochemical Evaluation

Formalin fixed, paraffin-embedded HCC tissue sections were routinely stained with hematoxylin/eosin and with CD34 according to manufacturer's instructions using a fully automatic stainer (Benchmark Ultra, Ventana, Tucson, AZ, USA). Hematoxylin/eosin was used to determine HCC grade and histotype according to WHO [29] and to determine the presence of intratumoral vague, ill-defined clusters of lymphocytes (from now on referred to as intratumoral immune infiltrate) according to Calderaro et al. [30]; CD34 was used to identify VETC [17]. We previously showed (see online supplementary material of reference [10]) that VETC+ has a significant impact also if detected in small percentage of tumor (5%), and with increasing values, it retains this impact, behaving as a continuous parameter. We thus considered as VETC+ cases showing this vascular phenotype in ≥5% HCC area (Fig. 1). In addition, to explore the effect of a different threshold on the predictive effect, we also used the cutoff (≥55%) of the original study [17]. A detailed description of criteria to asses VETC on liver biopsy is discussed and illustrated in the online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000547669). Intratumoral immune infiltrate and VETC were then evaluated as potential tissue biomarkers to be used, at clinical level on HCC biopsy, to select patients eligible for any specific treatment.

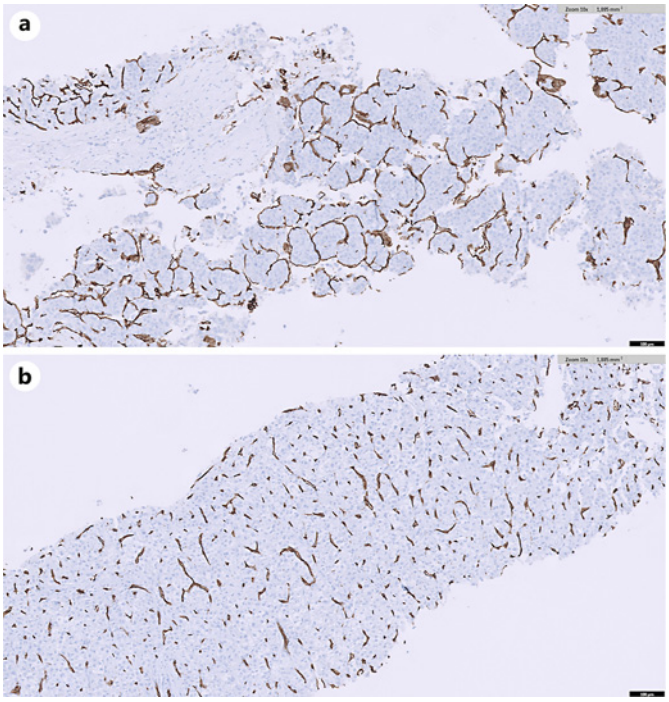

Fig. 1. Morphological aspect of VETC+ and VETC– HCC. **a** In this HCC, a complete wrapping of CD34+ endothelial cells surrounding tumoral cells, namely, VETC+, characterizes about 70% of the tumor area (CD34 immunostaining. ×10). **b** In this HCC, endothelial cells expressing CD34 show a regular, linear distribution along pre-existing sinusoids, the so called capillary pattern (CD34 immunostaining. ×10).

Statistical Analysis

The differences in patient survival were assessed using the Kaplan-Meier method and analyzed using the log-rank test in univariable analysis. Significant variables identified in the univariable analysis with p values lower than 0.05 were subsequently included in the multivariable

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analysis. To investigate the interaction between morphological biomarkers (VETC; intratumoral immune infiltrate) and treatment benefit (p of interaction), we used a Cox proportional hazard regression model containing treatment group, the biomarkers status and the treatment-by-biomarker interaction, as suggested by a seminal paper on the predictive versus prognostic nature of biomarkers [31]. Statistical analyses were performed using RStudio 2022.07.1 Build 554.

Results

The study and validation series showed homogeneous and consistent results (online suppl. material and online suppl. Tables 1, 2), suggesting presenting the whole data together. Clinical and pathological features of the whole series are shown in Table 1, and their impact on survival is shown in Table 2. Briefly, the series included 157 patients, mostly presenting with BCLC stage C (73%), extrahepatic involvement (54%), vascular invasion (24%), a history of prior locoregional therapy (66%), and at least one previous systemic treatment (51%). VETC+ phenotype was observed in 45% and intratumoral immune infiltrate in 27%. Several parameters were associated with outcome. Tumor grade had a significant impact on PFS, both at univariable and multivariable analysis. Portal vein thrombosis, Child-Pugh score, and tumor grade had a significant impact on OS at univariable analysis; for portal vein thrombosis, this was retained also at multivariable analysis. Other features, including VETC status and intratumoral immune infiltrate, did not affect PFS or OS (online suppl. Fig. 1). VETC+ is associated with a better survival upon treatment with A/B and TKI. The absence of a prognostic impact associated with VETC contrasts with several studies that have consistently demonstrated the ominous prognosis for patients with VETC+ HCC [17–25] but was not unexpected. Indeed, an inversion of the survival trend for patients with VETC+ HCC has been reported upon treatment with sorafenib [26]. Accordingly, VETC+ was considered a predictor of sorafenib benefit [26]. Building on the insights of this latter study [26] and on the suggestions of a seminal work on biomarkers [31], we thus stratified patients according to VETC status (VETC+ n = 70; VETC– n = 87; see online suppl. Table 3) and explored the effect of different treatments (at least one TKI n = 74; A/B n = 17; pure ICI, alone or in combination n = 66) on survival. Interestingly, while no differences were observed for PFS, patients with VETC+ HCC showed a significantly longer OS upon treatment with TKI as compared to pure ICI (median OS: 19.2 vs. 8.8 months; HR: 0.36; 95% CI: 0.21–0.64; p = 0.0004; see online suppl. Table 4 for details regarding specific TKI). The significant interaction test (p = 0.004; HR: 0.31; 95% CI: 0.14–0.70) supported the role of VETC+ as predictive biomarker of benefit to TKI. Similar results were observed upon treatment with A/B versus pure ICI alone or in combination (median OS: 21.7 vs. 8.8 months; HR: 0.49; 95% CI: 0.22–1.08; p = 0.08); the significant interaction test (p = 0.02; HR: 0.22; 95% CI: 0.06–0.83) supported the role of VETC+ as predictive biomarker also for A/B. By contrast, VETC+ HCC upon treatment with A/B compared to TKI did not show significant survival benefit. No survival benefit was observed in patients with VETC– HCC. We next explored the effect of different treatments on radiological response. Briefly, in the whole series, we observed complete response, partial response, stable disease, and disease control rate in 3%, 19%, 41%, 60%, respectively. ORR was observed in 22% of cases. No significant differences were observed between different treatments or to VETC status (online suppl. Table 5). Taking into consideration that both TKI and A/B interact significantly with VETC+ warranting a survival benefit, we then clustered patients receiving these treatments (from now on referred as TKI/BEVA). Patients with VETC+ HCC upon treatment with TKI/BEVA showed a significant longer OS compared to ICI (median OS: 19.8 months versus median OS: 8.8 months, HR: 0.34; 95% CI: 0.20–0.59; p = 0.0001; Fig. 2a), supporting the role of VETC+ as a predictive biomarker to TKI/BEVA (p of interaction = 0.002; HR: 0.30; 95% CI: 0.14–0.65). The same benefit was not observed in patients with VETC– HCC (Fig. 2b). A multivariable analysis showed that in patients receiving ICIs the expected negative effect of VETC was totally retained (8.7 months for VETC+ versus 15.8 for VETC–; HR: 2.40; 95% CI: 1.40–4.10; p = 0.001), suggesting that TKI/BEVA but not ICI exert their survival benefit by mitigating the pro-metastatic attitude of VETC+ (online suppl. material and online suppl. Table 6). To further explore this hypothesis, we evaluated in a subgroup of patients (n = 11) receiving a 2nd biopsy after the end of 1st line treatment the effect of therapy (TKI/BEVA vs. ICI). Interestingly, VETC disappeared only in patients receiving TKI/BEVA (p = 0.04). In keeping with the method followed for VETC, we thus stratified patients according to the presence of

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Table 1. Baseline patients' characteristics (whole cohort number 157 patients)

Characteristics	
Age, median (range), years	66 (33–90)
Gender	
Male	121 (77%)
Female	36 (23%)
ECOG PS	
0	103 (65%)
1	53 (34%)
2	1 (1%)
Liver cirrhosis	
Yes	103 (65%)
No	54 (35%)
Disease etiology[1]	
HBV	37 (24%)
HCV	53 (34%)
Alcohol	32 (20%)
NAFLD	15 (10%)
Other/unknown	23 (15%)
Child-Pugh class	
A5	109 (70%)
A6	43 (27%)
B	5 (3%)
BCLC stage	
B	42 (27%)
C	115 (73%)
Disease extent	
Liver only	71 (45%)
MVI	38 (24%)
EHS	84 (54%)
MVI and EHS	18 (11%)
AFP levels ≥400 ng/mL	53 (34%)
Prior locoregional treatments[2]	
None	53 (34%)
Surgery	60 (38%)
RFA/MWA	35 (22%)
TACE/TARE/EBRT	68 (43%)
Prior lines of systemic treatments	
0	76 (48%)
1	71 (45%)
2 or more	10 (6%)
Antiangiogenic treatment	
TKI single agent	52 (33%)
TKI plus ICI anti-VEGF plus ICI	22 (14%)
ICI (alone; combination) treatment	17 (11%)
ICI single agent	38 (24%)
ICI plus ICI	17 (11%)
ICI plus other (not antiangiogenic)	11 (7%)
Grade	
1–2	74 (47%)
3–4	83 (53%)

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Table 1 (continued)

Characteristics	
MTM	18
Intratumoral immune infiltrate	40 (27%; data available for 148 patients)
VETC+	70 (45%)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; RFA, radiofrequency ablation; MWA, microwave ablation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; EBRT, external beam radiotherapy; TKI, tyrosine kinase inhibitors; ICI, immune checkpoint inhibitor; VEGF, vascular endothelial growth factor; MVI, macrovascular invasion; EHS, extrahepatic spread. [1]Presence of co-occurring etiologies. [2]Patients might have received more than one prior locoregional treatment.

Table 2. Impact of clinical and pathological features on PFS and OS in the whole cohort

	PFS				OS			
	univariable analysis		multivariable analysis		univariable analysis		multivariable analysis	
	HR (CI 95%)	*p* value	HR (CI 95%)	*p* value	HR (CI 95%)	*p* value	HR (CI 95%)	*p* value
Clinical features								
Sex	1.31 (0.86–2.08)	0.24			1.02 (0.67–1.55)	0.91		
Cirrhosis	1.05 (0.72–1.52)	0.78			1.19 (0.81–1.75)	0.35		
HCV infection	0.93 (0.63–1.37)	0.72			1.04 (0.71–1.53)	0.80		
HBV infection	1.22 (0.78–1.92)	0.36			1.04 (0.67–1.60)	0.85		
NAFLD	0.85 (0.46–1.58)	0.62			0.61 (0.35–1.08)	0.35		
PVT	1.45 (0.94–2.24)	0.08			3.09 (1.85–5.15)	<**0.0001**	2.21 (1.45–3.35)	**0.0002**
Extrahepatic metastases	1.05 (0.72–1.53)	0.76			1.20 (0.82–1.75)	0.33		
Child-Pugh score	1.13 (0.74–1.72)	0.07			1.80 (1.15–2.81)	**0.01**	1.27 (0.97–1.68)	0.08
AFP >400 ng/mL	1.24 (0.84–1.84)	0.26			1.40 (0.93–2.12)	0.10		
Pathological features								
Edmondson grade (G3–4 vs. G1–G2)	1.54 (1.05–2.25)	**0.02**	1.56 (1.05–2.32)	**0.02**	1.50 (1.03–2.19)	**0.03**	1.39 (0.95–2.04)	0.08
MTM vs. other histotypes	1.09 (0.65–1.84)	0.72			1.55 (0.84–2.87)	0.15		
Intratumoral immune infiltrate (present)	1.27 (0.85–1.89	0.22			1.10 (0.72–1.67)	0.63		
VETC+	1.07 (0.75–1.54)	0.67			1.26 (0.88–1.82)	0.20		

HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; PVT, portal vein thrombosis; AFP, alpha-fetoprotein; MTM, macro-trabecular massive HCC.

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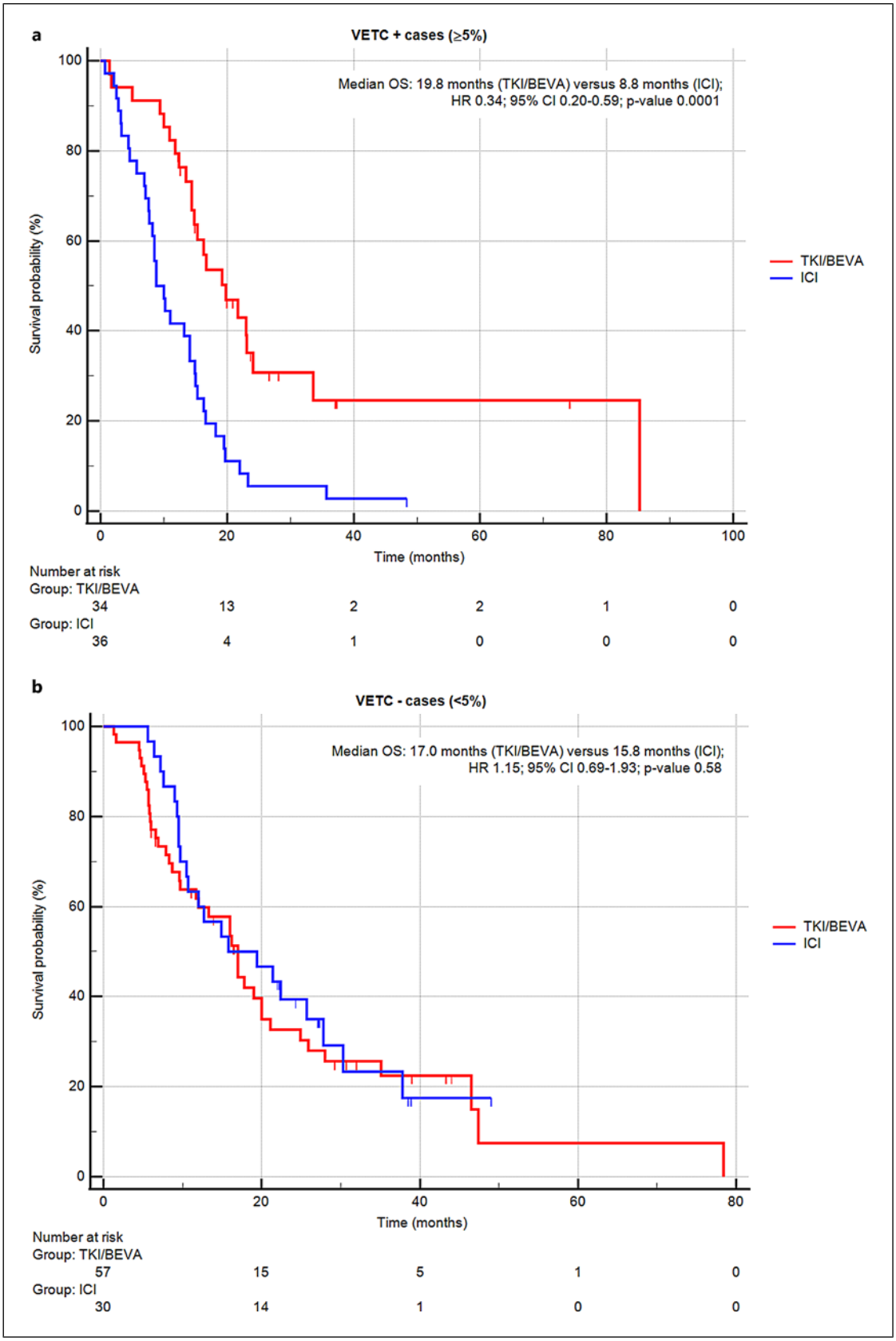

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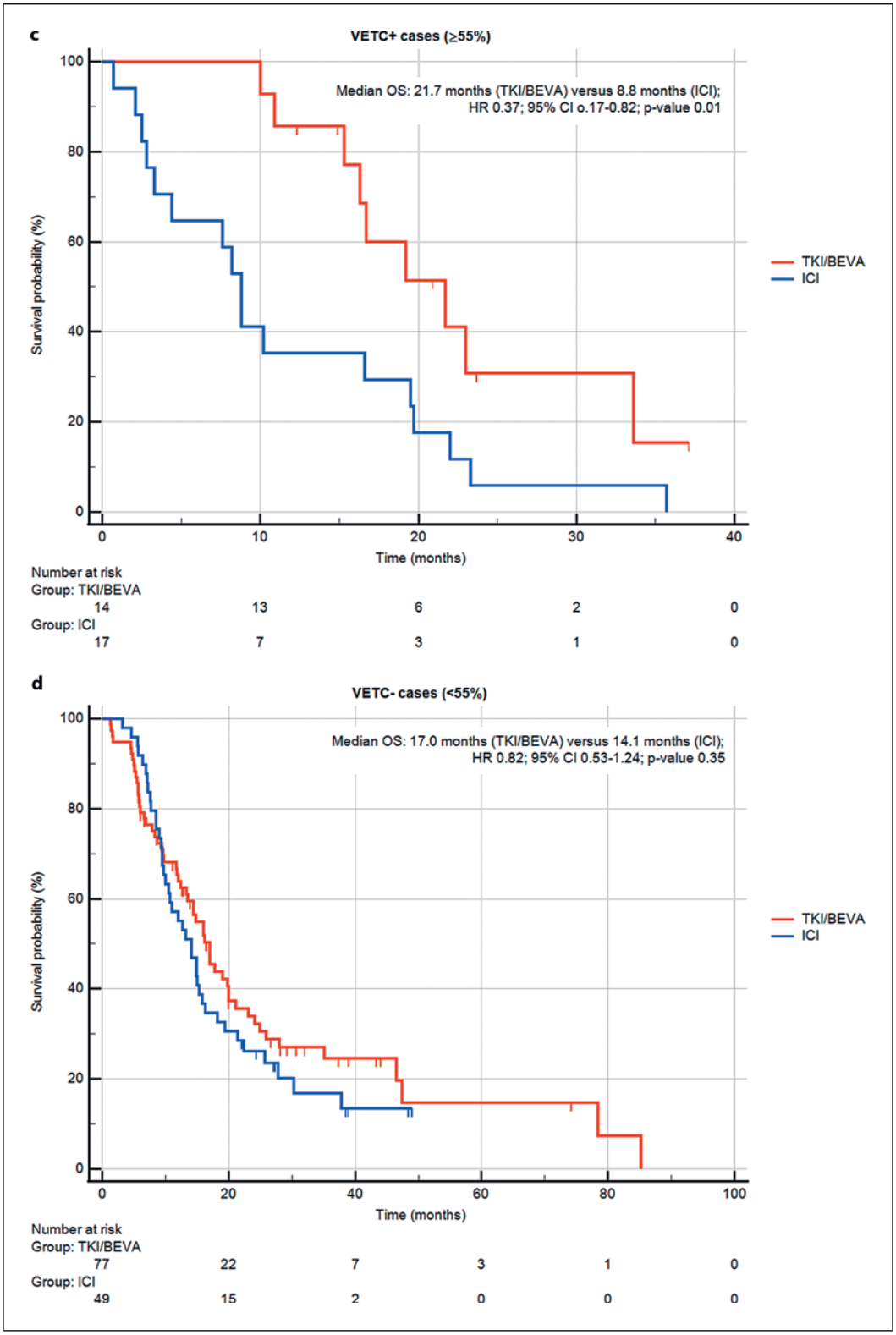

Fig. 2. Impact of VETC on treatment's benefit. **a**, **b** Patients showing VETC in ≥5% HCC area, but not those with VETC–, had a significant survival benefit upon treatment with TKI/BEVA as compared to those receiving ICI. **c**, **d** By adopting a more stringent cutoff (VETC observed in ≥55% of tumor area), the survival benefit upon treatment with TKI/BEVA was even higher.

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intratumoral immune infiltrate (present $n = 40$; absent $n = 108$) and explored in these subgroups the effect of at least one ICI (including A/B) compared to pure TKI on survival. However, none of these treatments had any significant benefit on PFS or OS. A further analysis, restricted to HCC with intratumoral immune infiltrate and VETC– ($n = 24$), showed no significant differences (online suppl. Table 7). Intratumoral inflammatory infiltrate did not show any changes when comparing pre- and post-treatment biopsies ($n = 11$) regardless of VETC status and treatment. Taken as a whole, these data suggested that VETC, but not intratumoral immune infiltrate, could be used, at morphological level, to surrogate the molecular categories of HCC responding to A/B described recently [10]. In particular, our data suggest that VETC, a specific type of HCC angiogenesis associated to Ang2, VEGF, and FGF2 [27, 28, 32], is a predictive biomarker for A/B and TKI. Survival benefit upon treatment with TKI/BEVA is higher in patients with larger extent of VETC+ and in first line. Taking into consideration the nature of biopsy sampling, ranging from tiny to abundant material, we next explored if the extent of VETC can impact on its predictive role. The results reported in the previous section considered as VETC+ cases showing this vascular phenotype in ≥5% HCC area. By adopting a more stringent cutoff (≥55%), patients with VETC+ HCC upon treatment with TKI/BEVA ($n = 31$) had an even longer OS (21.7 months versus 8.8 months, HR: 0.37; 95% CI: 0.17–0.82; $p = 0.01$; Fig. 2c). This was not detected in patients with VETC– HCC (Fig. 2d). In keeping with these data, we noticed that in the study series, showing a higher extent of VETC as compared to the validation series (mean area = 30.5%, range 5–100% versus mean area = 14.1%, range 5–100%; $p = 0.001$), the survival benefit upon treatment with TKI/BEVA was more pronounced (online suppl. Fig. 2).

Next, we explored if different timing of liver biopsy influenced the predictive role of VETC. We thus subdivided patients into those undergoing HCC biopsy before the onset of the 1st-line treatment and those receiving biopsy before the beginning of a 2nd or even 3rd line of treatment. The prevalence of VETC+ was almost identical in the two groups (45% vs. 42%). In patients undergoing first-line treatment, those with VETC+ HCC (cutoff 5%) upon treatment with TKI/BEVA, compared to ICI, obtained a higher survival benefit (median OS: 23.2 months versus 14.1 months; HR: 0.36; 95% CI: 0.15–0.82; $p = 0.01$; Fig. 3a, b). A significant benefit, despite lower than in 1st line, was observed also in VETC+ HCC receiving biopsy just before the onset of 2nd or 3rd line of treatment (median OS: 15.3 months versus 7.7 months; HR: 0.37; 95% CI: 0.18–0.77; $p = 0.008$; Fig. 3c, d).

Discussion

In the present study, we showed that patients with unresectable HCC presenting a peculiar morphological form of angiogenesis known as VETC had a significant survival benefit upon treatment with antiangiogenic drugs, including A/B and TKI. Our results replicate those of a previous study, published before the advent of A/B, showing that VETC is a predictive biomarker upon treatment with sorafenib [26]. Furthermore, our findings closely align with those of a recent study, which demonstrated that a subset of HCC patients characterized by an "angiogenesis-driven" pattern respond to A/B [10]. On the other hand, we observed that patients with VETC+ HCC upon treatment with ICI had significantly worse prognosis. A significant interaction test highlighted the predictive significance of VETC+ on TKI/BEVA and ruled out a detrimental effect of ICI, suggesting that TKI/BEVA, but not ICI, exert their survival benefit by mitigating the pro-metastatic attitude of VETC+. This is also supported by the morphological analysis of post-treatment tissue showing VETC disappearance only in patients upon TKI/BEVA.

The survival benefit observed in patients with VETC+ HCC upon antiangiogenic drugs is in keeping with the biology of VETC. This is a peculiar form of HCC angiogenesis characterized by the presence of endothelial cells wrapping HCC clusters and thus facilitating metastases. VETC onset has been related to an overexpression of Ang2 by HCC cells [16]. This is well in line with a previous research showing that *ANGPT2* gene is part of a signature distinguishing HCC with a worse outcome [32], as well as with the SHARP trial showing that Ang2 was an independent predictor of worse survival [33]. In addition to the role of Ang2, it has been reported that VETC+ HCCs overexpress VEGF and FGF2 [27, 28] and are characterized by a reduced immune infiltrate [17, 28, 34], lower immune activation [35], and higher number of M2 macrophages [36]. This interplay between "corrupted," prone-to-metastases, endothelial cells and the immune-suppressed tumor microenvironment that characterizes VETC+ reverberates the clinical findings of our study. Indeed, VETC+

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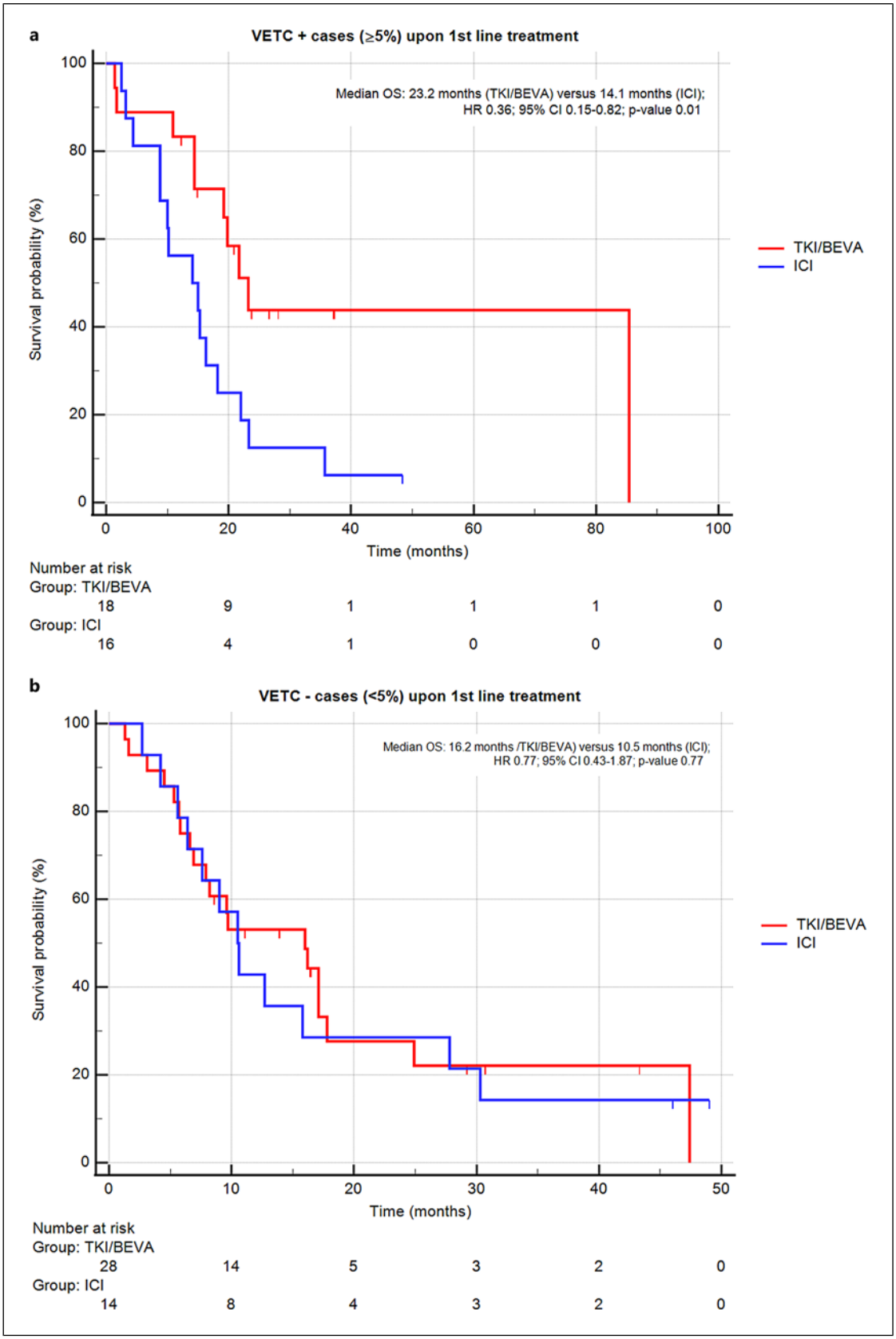

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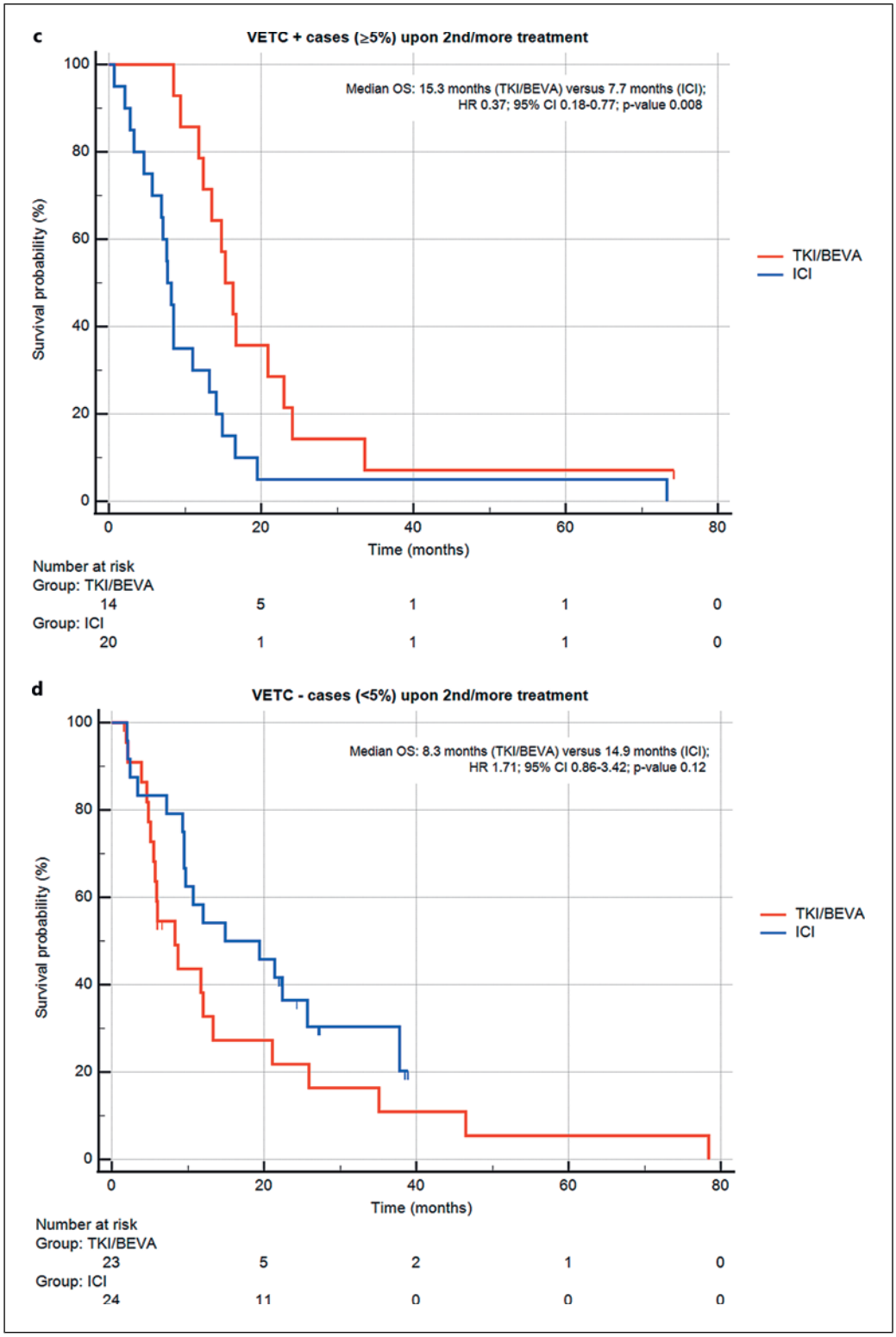

Fig. 3. Impact of VETC in different lines of treatment. **a**, **b** Patients showing VETC (cutoff ≥5%) in biopsy performed before the onset of 1st-line treatment showed the greatest survival benefit upon treatment with TKI/BEVA. **c**, **d** Also in patients undergoing HCC biopsy before the onset of 2nd or 3rd line of treatment, VETC+ predicts a significant, despite shorter, survival benefit upon treatment with TKI/BEVA.

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HCC are characterized by an angiogenic milieu, including VEGFa and FGF2, which blocks immune infiltration within the tumor, in particular that of lymphocytes, and this matches with the lack of benefit observed with ICI-based treatments. By contrast, the same angiogenic factors can be target by TKI and bevacizumab, thus explaining their efficacy. In keeping with this, it has been suggested that the combination A/B, and in particular bevacizumab, targeting the VEGF/VEGFR axis, "normalize" HCC vascularization, thus facilitating repopulation with a more favorable immune component [10]. This hypothesis is sustained by the experimental data reported in HCC mouse model using anti-PD-1 and anti-VEGFR-2 [37]. Our morphological findings further strengthen it by proving VETC disappearance after TKI/BEVA.

The present study has admittedly the restraint of the retrospective nature and limited number of patients. However, it is interesting to observe that three predictive biomarkers commonly used in the clinical practice for other solid tumors, hormone receptors, FGFR, KRAS were retrospectively identified in small series of patients [38]. We thus think that the results presented herein are robust enough to prompt prospective studies and, if confirmed and validated, suggest new potentially therapeutic strategies. Moreover, we think that the results of our study support the renewed interest for liver biopsy in HCC. Indeed, we showed that even a small percentage of VETC (>5%, corresponding to 4–5 clusters of HCC cells for 2-mm sample) is adequate and sufficient to recognize patients who might benefit of TKI/BEVA. Moreover, we proved that VETC is informative regardless of the treatment line in the history of patients. An alternative to the evaluation of VETC on HCC biopsy can be represented by imaging [39–41]. In particular, MRI studies based on the hepatobiliary-specific contrast Gd-EOB-DTPA proved to be useful in predicting VETC and patient prognosis preoperatively [41–43].

In conclusion, we showed that the VETC, a distinct feature of the HCC vascular TME, recognizes patients with unresectable HCC who benefit from antiangiogenic drugs. Our findings suggest that VETC overlaps with the recently reported "angiogenesis-driven" HCC [10] and thus might be used, at clinical level on HCC biopsy, to select patients eligible to antiangiogenic treatments.

Statement of Ethics

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by Comitato Etico Territoriale Lombardia 5 – approval: 52/24. Informed consent was waived due to the retrospective nature of the study.

Conflict of Interest Statement

Lorenza Rimassa has received consulting fees from AbbVie, AstraZeneca, Basilea, Bayer, BMS, Eisai, Elevar Therapeutics, Exelixis, Genenta, Hengrui, Incyte, Ipsen, IQVIA, Jazz Pharmaceuticals, MSD, Nerviano Medical Sciences, Roche, Servier, Taiho Oncology, and Zymeworks; received lecture fees from AstraZeneca, Bayer, BMS, Guerbet, Incyte, Ipsen, Roche, and Servier; and received travel expenses from AstraZeneca; and institutional research funding from AbbVie, Agios, AstraZeneca, BeiGene, Eisai, Exelixis, Fibrogen, Incyte, Ipsen, Jazz Pharmaceuticals, Lilly, MSD, Nerviano Medical Sciences, Roche, Servier, Taiho Oncology, ThansThera Sciences, and Zymeworks. Armando Santoro is a member of Advisory board of Bristol Meyer Squibb, Servier, Gliead, Pfizer, Eisai, Bayer, and Merck Sharp & Dohme; he serves in the speaker's Bureau of Takeda, Bristol Meyer Squibb, Roche, AbbVie, Amgen, Celgene, Servier, Gliead, AstraZeneca, Pfizer, Lilly, Sandoz, Eisai, Novartis, and Merck Sharp & Dohme; he received consulting fees from Sanofi and Incyte. Massimo Iavarone has received consulting fees from AstraZeneca, Roche, Ipsen, Eisai, MSD, Roche Diagnostic, Gilead, and Bayer. Margherita Rimini has received lecture fees from Eisai. Andrea Casadei Gardini has received consulting fees from AstraZeneca, Bayer, BMS, Eisai, Incyte, Ipsen, IQVIA, MSD, Roche, Servier; received lecture fees from AstraZeneca, Bayer, BMS, Eisai, Incyte, Ipsen, Roche, and Servier; received travel expenses from AstraZeneca; and received research grants (to Institution) from AstraZeneca and Eisai. Sara Lonardi has research funding (to Institution) from Amgen, Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Daichii Sankyo, Hutchinson, Incyte, Merck Serono, Mirati, MSD, Pfizer, Roche, and Servier and received personal honoraria as invited speaker from Amgen, AstraZeneca, Bristol Myers Squibb, Incyte, GSK, Lilly, Merck Serono, MSD, Pierre-Fabre, Roche, Servier; she participated in advisory board for Amgen, Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Daiichi-Sankyo, GSK, Incyte, Lilly, Merck Serono, MSD, Servier, Takeda, and Rottapharm. Irene Oi-Lin Ng, Young Nyun Park, and Andrea Casadei Gardini were members of the journal's Editorial Board at the time of submission.

Funding Sources

The research leading to these results has received funding from AIRC under IG 2020-ID. 25087 (project – P.I. Di Tommaso Luca); "National Research Foundation of Korea (NRF) funded by the Korean Government, MSIT (NFR-2020R1A2B5B01001646, NFR-2016M3A9D5A01952416) to Young Nyun Park"; "Fondation ARC, Fondation de l'Avenir, Fondation Bristol Myers Squibb pour la Recherche Biomédicale, Ipsen, and Institut National contre le Cancer to Julien Calderarò"; "the Research Grants Council of Hong Kong – Theme-based Research Scheme (T12-716/22R)" and "Innovation and Technology Commission grant to State Key Laboratory of Liver Research (ITC PD/17-9)" to Irene Oi-Lin Ng and to Tan T Cheung; "Italian Ministry of Health ("Ricerca Corrente RC2022/105-1")" to Massimo Iavarone; "Ministry of Science and Technology, Taiwan (MOST-111-2314-B-002-120), and National Science and Technology Council, Taiwan (NSC-112-2314-B-002-267 and NSC-113-2923-B-002-001-MY3)"

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to Yu-Yun Shao; "Associazione Italiana sulla Ricerca sul Cancro ("AIRC; Grant No. IG 2020-ID. 24858 project – P.I. Erica Villa" and "AIFA Independent Research grant TRS-2018-00001238")" to Erica Villa.

Author Contributions

Concept and design: L.D.T., L.R., C.D.C., and R.A. Case selection and database management: B.D., J.C., L.R., T.P., E.Va., I.O.N., T.T.C., A.E., P.S., M.I., M.M., Y.Y.S., S.L., M.F., A.P., V.A., M.D.R., A.D.R., F.P., M.Ri., A.C.G., Y.N.P., and A.S. Experiments and procedures: C.D.C., R.A., B.D., L.D.T., S.L.R., and S.P. Writing of article: L.D.T., L.R., M.Ro., E.Vi., Y.Y.S., and L.T.

Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials. Further inquiries can be directed to the corresponding author.

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