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Original Research

Determinants of long-term survival from atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma

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ABSTRACT

Background: Despite the proven superiority against sorafenib, atezolizumab plus bevacizumab (A+B) lacks long-term efficacy data in unresectable hepatocellular carcinoma (uHCC). This study assessed clinicopathologic factors associated with long-term survival with A+B.

Methods: We analyzed patients receiving first-line A+B within AB-Real, a large multicenter registry across Europe, Asia, and the USA. Long-term survivors (LTS) were defined as patients surviving at 24 months. Landmark survival outcomes and associations between baseline clinicopathologic factors and overall survival (OS) were evaluated.

Results: Of 1346 patients enrolled, 1085 with Child-Pugh A and ECOG 0–1 received first-line A+B. The median OS was 19.2 months (95% CI: 17.6–20.9), and 2- and 3-year survival rates were 41.4% and 29.3%. Among 695 patients with adequate follow-up, 190 were classified as LTS. The overall response rate was 24.7%, and long-term survivorship was significantly enhanced in radiologic responders (52.2% vs 8.8%, $p < 0.001$). Compared to non-LTS, LTS more frequently had ALBI grade 1 liver reserve (64.6% vs 38.5%), less PVI (17.9% vs 36.4%), smaller maximum tumor size (3.8 vs 7.0 cm), and lower AFP (median 23.0 vs 240.8 ng/mL) (all $p < 0.001$). Notably, nearly half (48.8%) of radiologic responders who did not achieve long-term survival had ≥ 2 adverse baseline features, underscoring that tumor burden and liver reserve remain prognostically relevant even among responders.

Conclusions: AB-Real provides the first global real-world evidence of long-term efficacy of A+B in uHCC. Long-term survivorship is enhanced in radiological responders and strongly associated with pre-treatment tumor factors and liver function.

1. Introduction

Hepatocellular carcinoma (HCC) is a major global health burden and remains one of the leading causes of cancer-related mortality worldwide due to its high incidence and poor prognosis, particularly in advanced stages [1]. Recent advances in immunotherapy have reshaped the therapeutic landscape of unresectable HCC (uHCC), most notably through immune checkpoint inhibitor (ICI)-based combination regimens [2]. The combination of atezolizumab, a programmed death-ligand 1 (PD-L1) inhibitor, and bevacizumab, a monoclonal antibody against vascular endothelial growth factor, has emerged as a standard first-line therapy following the pivotal phase III IMbrave150 trial [3,4]. This regimen harnesses synergistic immune activation and angiogenesis inhibition and demonstrated superior survival outcomes compared to sorafenib, the former standard of care.

Despite these advances, many patients treated with atezolizumab plus bevacizumab (A+B) ultimately experience disease progression due to primary or acquired resistance, limiting long-term benefit [5]. Notably, the superiority of A+B over sorafenib in IMbrave 150 was demonstrated early, in the context of a median follow-up of just 8.6 months: a finding that was sufficient to establish A+B as a new standard of care [3]. A subsequent update reported a median overall survival (OS) of 19.2 months for A+B [4], but the definitive analysis had a median follow-up of only 15.6 months, restricting the ability to draw conclusions about long-term survival. Long-term survival benefit from ICI-based immunotherapy has been documented across several solid tumors in both clinical trials and real-world settings [6–9]. In advanced HCC, recent dual-ICI trials have similarly shown durable survival, particularly in patients achieving tumour control [10–14]. As no further updates from IMbrave150 are anticipated, real-world evidence is essential for understanding long-term outcomes in patients treated with A+B. Robust observational real-world studies can complement trial data by capturing outcomes in routine practice, including populations consistent with current treatment recommendations [15,16].

AB-Real was the first observational study to demonstrate the reproducible efficacy and tolerability of A+B in real-world patients with uHCC outside clinical trials [17]. In this extended analysis of the AB-Real cohort, we aimed to characterize long-term survival—focusing on patients who survived beyond 24 months after treatment initiation—and to identify clinicopathologic factors associated with long-term benefit from first-line A+B therapy in uHCC.

2. Materials and methods

2.1. Study population

AB-Real is a prospectively maintained registry designed to evaluate the long-term outcomes of first-line A+B therapy in patients with uHCC [17,18]. Patients were treated consecutively outside clinical trials at 24 tertiary referral centers across Europe, Asia, and the United States between January 2019 and June 2024, including the United States (n = 110), Italy (n = 165), Germany (n = 93), Austria (n = 57), United Kingdom (n = 24), South Korea (n = 590), Taiwan (n = 224), and Japan (n = 83).

To minimize bias from including patients unsuitable for systemic therapy, we applied pre-specified selection criteria to define a clinically eligible real-world population. Eligible patients were $\geq$ 18 years old with HCC diagnosed according to AASLD guidelines [19], had unresectable disease (BCLC stage C or B not amenable to locoregional therapy), Child-Pugh class A liver function, and ECOG performance status 0–1.

For the assessment of long-term outcomes, the primary endpoint was the 2-year survival rate, defined as the proportion of patients alive at 24 months following treatment initiation. Patients who were alive but had $<$ 24 months of follow-up without documented conditions were excluded, as their long-term outcome status could not be reliably assessed. This ensured a mature study cohort for robust estimation of long-term survival. The patient selection algorithm is summarized in 4.

Secondary objectives included overall survival (OS), defined as the time from treatment initiation to death or loss to follow-up; progression-

free survival (PFS), defined as the time from treatment initiation to disease progression or death; objective response rate (ORR), defined as the proportion achieving complete or partial response; and disease control rate (DCR), defined as objective response or stable disease as the best radiologic response. We also described long-term safety by reporting treatment-related adverse events (AEs). The study was conducted in accordance with the Declaration of Helsinki and approved by the Imperial College Tissue Bank (R16008) and institutional review boards at each participating site. Given the retrospective nature of the analysis, informed consent was waived.

2.2. Treatment and outcome assessment

Atezolizumab (1200 mg) and bevacizumab (15mg/kg) were administered intravenously every three weeks according to the IMbrave150 protocol. [3,4] Treatment was initiated following multidisciplinary assessment as part of routine practice and continued until disease progression, death, unacceptable toxicity, or other clinically determined reasons. Demographic and clinical data were collected retrospectively and prospectively maintained at each site.

Radiological response was assessed every 9–12 weeks using CT or MRI per RECIST v1.1. Primary resistance, defined as time to progression $<$ 6 months [20], classified patients as non-responders. Responders were defined according to Society for Immunotherapy of Cancer (SITC) consensus as those without disease progression during follow-up, or those who progressed only after achieving an objective response or maintaining stable disease for $\geq$ 6 months [20]. AEs were evaluated at each visit and graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Only treatment-related AEs (TRAEs) were recorded, with causality determined by known toxicity profiles of atezolizumab and bevacizumab, and by clinical judgment at each center.

2.3. Analysis workflow

We first reported the distribution of clinicopathologic characteristics and survival outcomes in all Child-Pugh A, ECOG 0–1 patients. We then compared long-term survivors (LTS) and non-LTS, with baseline characteristics stratified by long-term survival status; detailed variables are provided in the 4. Efficacy outcomes, including OS and PFS, were initially assessed using univariable analyses. To evaluate the prognostic role of radiologic response, OS and PFS were further analyzed according to best tumour response. A 3-month landmark analysis was performed to mitigate immortal time bias by excluding patients who progressed or died before this time point.

Multivariable associations between baseline characteristics and OS/PFS were assessed using Cox regression models after variable selection with elastic net regularization [21]. Seventeen clinical variables were selected *a priori* based on clinical relevance and availability. Missing data were addressed using multiple imputation by chained equations (MICE) with predictive mean matching across five imputed datasets [22]. To mitigate site-level heterogeneity arising from variable censoring before 24 months, we adopted a conditional interpretation using a shared frailty term for enrolling center to account for clustering effects. To enhance clinical interpretability and support bedside risk stratification, significant mortality predictors were descriptively combined to summarize patient risk profiles associated with long-term outcomes. We also reported the cumulative incidence of TRAEs and treatment discontinuation rates due to toxicity. For patients with available data, discontinuation reasons were categorized to identify patterns associated with survival.

Finally, to explore hierarchical and potentially non-linear associations between baseline characteristics and long-term survival, we performed a descriptive classification tree analysis using the CART (Classification and Regression Tree) algorithm based on the same 17 baseline variables. This method was selected for its capacity to uncover complex interactions without assumptions regarding linearity, additivity, or specific variable distribution, making it well-suitable for real-world datasets with potential multicollinearity and sparsity. Additional statistical details are provided in the 4.

3. Results

3.1. Baseline demographic characteristics of patients

At the data cut-off, the registry included 1346 consecutive patients treated with first-line A+B therapy across all participating centers. After excluding patients with baseline Child-Pugh class B or C (n = 211) and those with ECOG-PS $>$ 1 (n = 50), 1085 patients with preserved liver function and performance status were included to describe the primary survival outcomes. For subsequent investigations focused on long-term survival benefit, we further excluded patients who were censored before reaching 24 months of follow-up (n = 390); resulting in a final analytic cohort of 695 patients (4). At a median follow-up of 34.2 months (95% confidence interval [CI]: 31.7 – 36.6), 190 out of 695 patients were alive at the 24-month landmark and were classified as LTS.

Baseline clinicopathologic characteristics of patients with Child-Pugh A and ECOG 0–1, as well as those in the final study cohort are summarized in the 4 and Table 1, respectively**.** Among patients classified as LTS or non-LTS (Table 1), patients were predominantly male (79.1%) with a median age of 62.8 years. The most common etiology of underlying liver disease was chronic hepatitis B virus infection (51.4%), followed by hepatitis C virus infection (19.4%) and alcohol-related liver disease (19.1%). Approximately half of the patients had cirrhosis at baseline (48.8%). While all individuals had preserved liver function (Child-Pugh class A), more than half (54.1%) were classified as ALBI grade $>$ 1. Most patients had advanced-stage disease, with 78.1% classified as BCLC stage C, and a substantial proportion presenting with portal vein invasion (PVI, 31.4%), extrahepatic metastases (50.6%), and elevated alpha-fetoprotein (AFP $>$400 ng/mL, 42.2%).

Compared to non-LTS, LTS were significantly more likely to have ALBI grade 1 liver function (64.6% vs 38.5%, $p < 0.001$). They also exhibited a lower prevalence of PVI of any degree (17.9% vs 36.4%, $p < 0.001$) and reduced involvement of the main portal vein trunk (Vp4: 13.2% vs 24.6%, $p = 0.001$). Tumor burden was generally lower among LTS, as reflected by smaller maximum tumor size (median: 3.8 cm vs 7.0 cm, $p < 0.001$), fewer tumor nodules ($\geq$3 nodules: 47.0% vs 60.8%, $p = 0.072$), and lower AFP levels (median: 23.0 ng/mL vs. 240.8 ng/mL, $p < 0.001$). Additionally, a greater proportion of LTS had received prior loco-regional treatment before initiating systemic therapy (47.9% vs 36.0%, $p = 0.004$).

3.2. Efficacy outcomes

In patients with Child-Pugh A and ECOG-PS 0–1, the median OS was 19.2 months (95% confidence interval [CI]: 17.6 – 20.9) with 2-year and 3-year survival rates of 41.4% and 29.3%, respectively (4). In the 3-month landmark analysis, the median OS was 20.4 months, with a 2-year survival rate of 43.6% (4). However, only 190 patients could be confirmed by documentation to be alive at 24 months after treatment initiation. In terms of PFS, the median was 6.9 months (95% CI: 6.2 – 7.7) in 1025 assessable patients, and 7.6 months by 3-month landmark analysis (4**-D**).

Among LTS and non-LTS, 651 out of 695 were evaluable for radiologic response. 24.7% of them achieved an objective response, including 27 patients (4.1%) with a complete response (CR) and 134 (20.6%) with a partial response (PR). Additionally, 291 patients (44.7%) experienced stable disease (SD), resulting in a DCR of 69.4%. In contrast, 340 patients (53.4%) showed progressive disease (PD) within the first 6 months and were classified as having primary resistance to A+B therapy (non-responders). Long-term survival status was significantly associated with higher ORR (52.2% vs 13.8%, $p < 0.001$) and DCR (91.4% vs 60.6%,

Table 1
Baseline characteristics according to the long-term survival status at 24 months of follow-up.

Baseline characteristics	All N = 695	LTS ≥ 24 m n = 190	Non-LTS n = 505	p value
Age, y	62.8 (55.2 – 70.5)	61.0 (54.0 – 69.9)	63.1 (56.3 – 71.0)	0.103
missing	32	5	27	
Sex (male), n (%)	550 (79.1)	157 (82.6)	393 (77.8)	0.164
missing	–	–	–	
BMI, kg/m^2	24.2 (21.7 – 27.3)	25.0 (22.2 – 27.4)	24.0 (21.4 – 27.2)	0.142
missing	239	64	175	
HBsAg-positive, n (%)	357 (51.4)	97 (51.1)	260 (51.5)	0.919
missing	–	–	–	
Anti-HCV-positive, n (%)	135 (19.4)	42 (22.1)	93 (18.4)	0.273
missing	–	–	–	
Alcohol-related liver disease, n (%)	133 (19.1)	31 (16.3)	102 (20.2)	0.246
missing	–	–	–	
MASLD, n (%)	69 (9.9)	15 (7.9)	54 (10.7)	0.272
missing	–	–	–	
Cirrhosis, n (%)	339 (48.8)	101 (53.2)	238 (47.1)	0.156
missing	–	–	–	
Ascites, n (%)	74 (10.6)	14 (7.4)	60 (11.9)	0.086
missing	–	–	–	
Gastroesophageal varices, n (%)	175 (25.2)	51 (26.8)	124 (24.6)	0.536
missing	–	–	–	
ECOG PS 0/1, n (%)	262/433 (37.7/62.3)	82/108 (43.2/56.8)	180/325 (35.6/64.4)	0.068
missing	–	–	–	
Child-Pugh score 5/6, n (%)	450/245 (64.7/35.3)	158/32 (83.2/16.8)	292/213 (57.8/42.2)	< 0.001
missing	–	–	–	
ALBI grade 1/2/3, n (%)	283/329/4 (45.9/53.4/0.6)	113/62/0 (64.6/35.4/0)	170/267/4 (38.5/60.5/0.9)	< 0.001
missing	79	15	64	
Total bilirubin, mg/dL	0.71 (0.50 – 1.01)	0.60 (0.42 – 0.88)	0.76 (0.53 – 1.11)	< 0.001
missing	–	–	–	
Albumin, g/dL	3.8 (3.5 – 4.1)	4.0 (3.7 – 4.2)	3.7 (3.4 – 4.0)	< 0.001
missing	79	15	64	
White blood cell, /mm^3	5450 (4195 – 7000)	5270 (4025 – 6853)	5600 (4200 – 7120)	0.080
missing	18	2	16	
Platelet count, K/mm^3	160 (114 – 223)	157 (113 – 208)	163 (115 – 233)	0.183
missing	1	0	1	
AFP, ng/mL	124.0 (8.0 – 2914.0)	23.0 (4.0 – 507.5)	240.8 (17.0 – 5311.8)	< 0.001
AFP > 400 ng/mL, n (%)	187 (42.2)	32 (26.9)	155 (47.8)	< 0.001
missing	253	71	182	
Max. tumor size, cm	5.5 (3.0 – 10.0)	3.8 (2.2 – 6.9)	7.0 (3.5 – 10.5)	< 0.001
missing	250	73	177	
Tumor number 1/ 2/ ≥ 3, n (%)	85/95/269 (18.9/21.2/59.9)	29/33/55 (24.8/28.2/47.0)	56/62/214 (16.9/18.7/60.8)	0.072
missing	246	73	173	
Portal vein invasion, n (%)	218 (31.4)	34 (17.9)	184 (36.4)	< 0.001
Main portal trunk invasion (Vp4), n (%)	149 (21.4)	25 (13.2)	124 (24.6)	0.001
missing	–	–	–	
Extrahepatic metastasis, n (%)	351 (50.6)	92 (48.4)	259 (51.5)	0.471
missing	2	0	2	
BCLC stage B/C, n (%)	152/543 (21.9/78.1)	44/146 (23.2/76.8)	108/397 (21.4/78.6)	0.591
missing	–	–	–	
Prior loco-regional treatment (LRT) for HCC	273 (39.3)	91 (47.9)	182 (36.0)	0.004
missing	–	–	–	

Abbreviations: AFP, alpha-fetoprotein; ALBI grade, albumin-bilirubin grade; BCLC stage, Barcelona Clinic Liver Cancer stage; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; LTS, long-term survivor; MASLD, metabolic dysfunction associated steatotic liver disease.
Missing values were excluded for the calculation of denominators and the computation of p-values.

p < 0.001). Similarly, patients exhibiting primary resistance were less likely to cluster within the LTS group (4).

Consistent with these findings, treatment exposure differed significantly between groups. The median duration of treatment was significantly longer in the LTS group compared with the non-LTS group (9.5 months [interquartile ration (IQR) 3.5–19.6] vs 3.1 months [IQR 1.4–6.1], p < 0.001). The median time-to-response was 2.7 months (IQR 1.4–6.8) in LTS and 1.9 months (IQR 1.4–2.7) in non-LTS patients (p < 0.001).

As shown in Fig. 1A, patients who achieved an objective tumour response had a significantly longer median OS of 36.3 months, compared with 14.4 months in those with SD and 6.8 months in those with PD (p < 0.001). This association remained consistent in the 3-month landmark analysis (Fig. 1B). Moreover, patients who initially responded and subsequently progressed to A+B (responders) had significantly longer OS compared to those who exhibited primary progression (non-responders) (Fig. 1C–D). Subgroup analyses stratified by age (<50, 50–70, and >70 years) did not demonstrate significant differences in overall survival or the proportion of LTS (4).

Consistently, median PFS was longest among patients achieving an objective response by RECIST v.1.1 criteria (16.6 months), compared with those with SD (5.8 months) and those with PD (1.9 months, p < 0.001; 4). The 3-month landmark analysis confirmed a significant stratification of PFS based on best radiologic response (4). Finally, LTS had significantly longer median PFS than non-LTS patients (20.3 vs 3.4 months, p < 0.001), with a significantly higher 12-month PFS rate (65.7% vs 7.2%). These differences remained consistent in the 3-month landmark analysis (4-**D**).

3.3. *Multivariable risk modeling and clinical interpretability*

The Elastic Net regression analysis for the risk of death and disease progression/death was conducted using optimal penalty parameters (λ) of 0.107 and 0.230, respectively. From the baseline panel of 17 variables, only a few key predictors had non-zero coefficients. Tumor size > 5 cm (HR: 1.57, 95% CI: 1.28–1.92), presence of PVI (HR: 1.41, 95% CI: 1.17–1.71), AFP > 400 ng/mL (HR: 1.29, 95% CI: 1.06–1.56) and ALBI grade 2–3 (HR: 1.81, 95% CI: 1.49–2.18) were retained as significant predictors of increased risk of death (Table 2), while only the presence of PVI (HR: 1.33, 95% CI: 1.11–1.63) and ECOG-PS 1 (HR: 1.35, 95% CI: 1.12–1.63) as predictors of worse PFS (4).

We then combined the independent predictors of survival to improve clinical interpretability. As illustrated in Fig. 2A, patients presenting with one or more adverse baseline features — namely tumor size > 5 cm, PVI, AFP > 400 ng/mL, or ALBI grade 2–3 — had significantly shorter OS compared to those without these features. The worst survival outcomes were observed in patients with all four adverse features, with a median OS of 4.7 months (95% CI: 0.9–8.5). In contrast, patients without any of these features achieved the most favorable outcomes, with a median OS of 25.5 months (95% CI: 20.1–31.0).

When stratified into three subgroups based on the number of adverse features (Fig. 2B), survival decreased progressively: patients with two or more features had a median OS of 8.1 months (95% CI: 6.9–9.4), those with one feature had a median OS of 16.0 months (95% CI: 12.4–19.6), and those with none had the longest survival (25.5 months; p < 0.001). This pattern was further reflected in the 24-month survival probability (Fig. 2C–D), which was inversely proportional to the number of adverse features: over 50% of patients without any of the four features survived

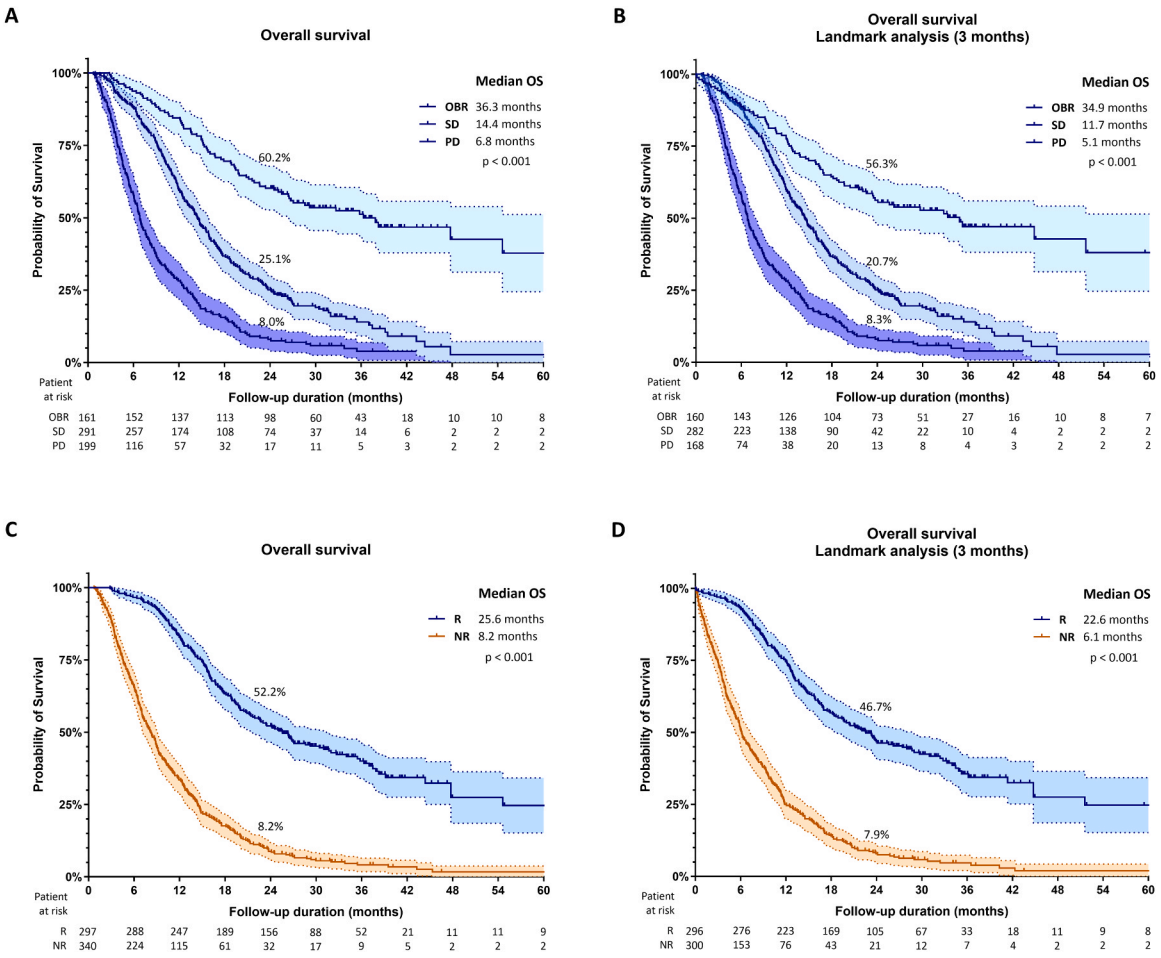

Fig. 1. Overall survival of patients. Overall survival (OS) of patients stratified by (A) best radiologic response of the tumor, and (B) landmark analysis at 3 months. (C) OS comparison between responders (R) and non-responders (NR), and (D) landmark analysis at 3 months.

Table 2
Factors associated with overall survival benefit.

		Univariate analysis			Multivariate analysis		
Factors	Comparisons	HR	95% (CI)	p value	HR	95% (CI)	p value
Age, y	> 65 vs ≤ 65	1.082	0.911 – 1.285	0.370			
Sex	Male vs Female	0.849	0.694 – 1.037	0.109			
Etiology of liver disease	Viral vs Non-viral	0.922	0.770 – 1.104	0.376			
Cirrhosis	Yes vs No	0.932	0.789 – 1.101	0.411			
Tumor size, cm	> 5 vs ≤ 5	1.629	13.71 – 1.934	< 0.001	1.57	1.28 – 1.92	< 0.001
Tumor number	multiple vs single	1.186	0.905 – 1.554	0.216			
Portal vein invasion	Yes vs No	1.681	1.411 – 2.003	< 0.001	1.41	1.17 – 1.71	< 0.001
Main portal trunk invasion (Vp4)	Yes vs No	1.602	1.316 – 1.950	< 0.001			
Extrahepatic metastasis	Yes vs No	1.020	0.863 – 1.204	0.820			
BCLC stage	Stage C vs B	1.137	0.927 – 1.393	0.217			
AFP, ng/mL	> 400 vs ≤ 400	1.547	1.256 – 1.907	< 0.001	1.29	1.06 – 1.56	0.011
Platelet count, K/mm^3	> 100 K vs ≤ 100 K	0.830	0.661 – 1.043	0.109			
Ascites	Yes vs No	1.547	1.192 – 2.008	0.001			
Gastroesophageal varices	Yes vs No	0.988	0.814 – 1.200	0.906			
ECOG PS	≥ 1 vs 0	1.211	0.821 – 1.437	0.208			
ALBI grade	Grade 2,3 vs 1	1.941	1.618 – 2.327	< 0.001	1.81	1.49 – 2.18	< 0.001
Prior LRT for HCC	Yes vs No	0.770	0.648 – 0.915	0.003			

[#]Elastic Net fitted cox regression model was used for multivariable analysis.
Abbreviations: AFP, alpha–fetoprotein; ALBI grade, albumin–bilirubin grade; BCLC stage, Barcelona Clinic Liver Cancer stage; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; HR, hazard ratio; iRAE, immunotherapy related adverse events; LRT, loco–regional treatment; n.a., not adopted; n.s., not significant; Vp4, main portal trunk.

beyond 24 months, while only 13.9% of those with two or more features reached that landmark. Notably, none of the patients with all four adverse features survived beyond 24 months.

While achieving a radiologically measurable response to A+B was associated with improved survival, the presence of any of the four adverse baseline features remained prognostically relevant, even among

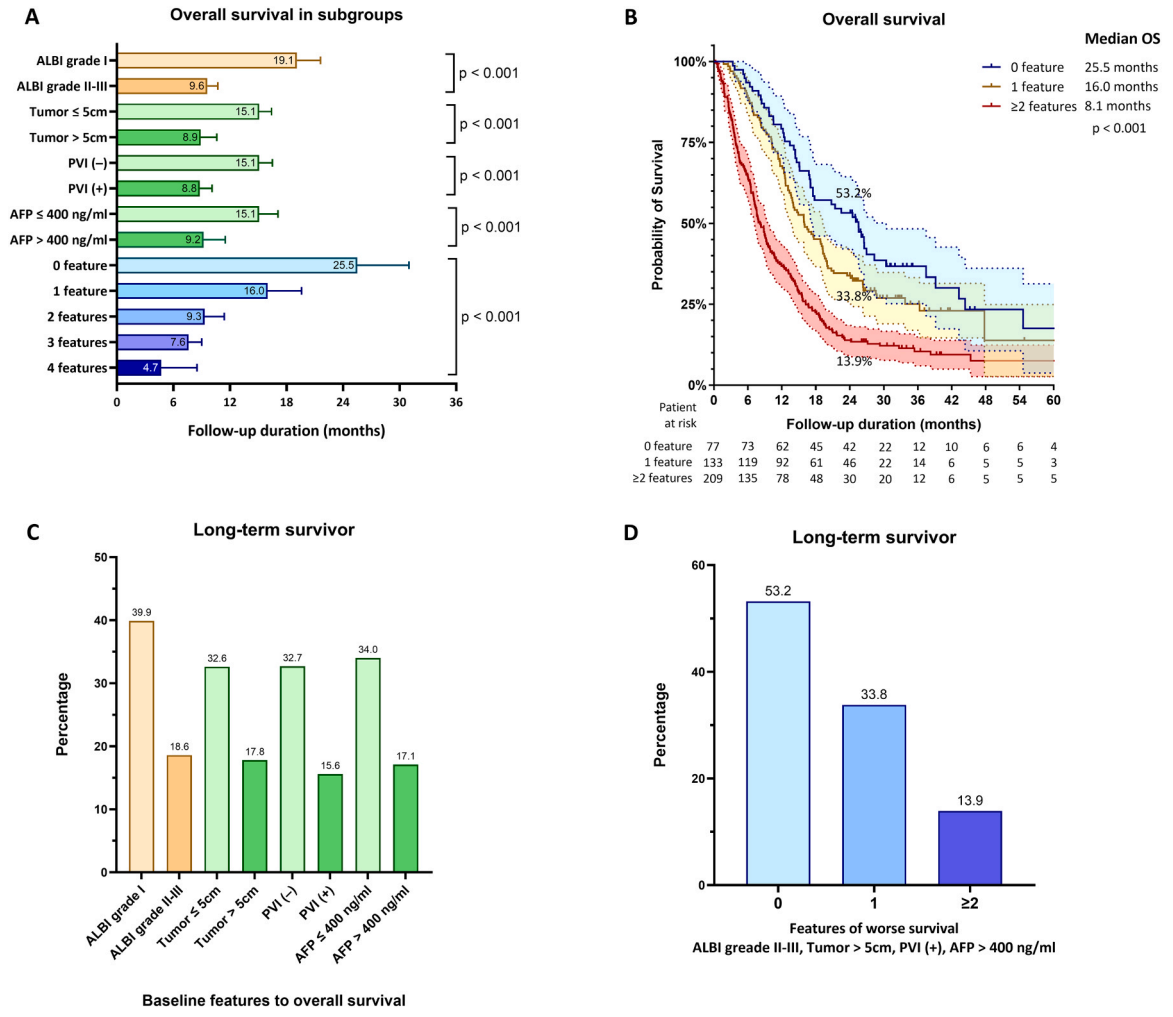

Fig. 2. Overall Survival and proportion of long-term survivors stratified by adverse baseline features Overall survival (OS) stratified by (A) individual adverse features at baseline, including albumin-bilirubin (ALBI) grade, tumor size, portal vein invasion (PVI), and serum alpha-fetoprotein (AFP) level; as well as (B) an integrated grouping of these features. Proportion of long-term survivors stratified by (C) each adverse feature and (D) the integrated three-group classification.

responders (Fig. 3A). Responders without any of these features had a median OS of 37.5 months (95% CI: 22.3–52.6), with 72.7% alive beyond 24 months (Fig. 3A–B). Among primary non-responders, those without adverse features still achieved a median OS of 12.5 months (95% CI: 9.8–15.2), with 22.6% surviving beyond 24 months. Importantly, only 52.2% of all responders were alive beyond 24 months, most of whom had one or no adverse features. In contrast, 48.8% of responders who did not achieve long-term survival had two or more of the identified adverse features (Fig. 3C). To address potential immortal time and temporality bias, we performed a 3-month landmark analysis, which yielded consistent findings (4-C).

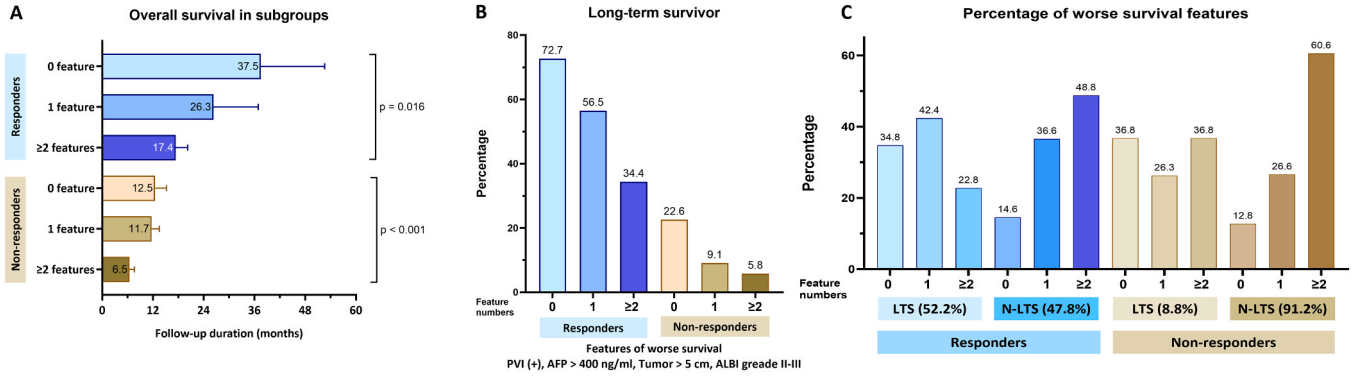

Fig. 3. Adverse feature-determined overall survival and proportion of long-term survivors in responders and non-responders (A) Overall survival (OS) and (B) proportion of long-term survivors stratified by the integrated grouping of adverse baseline features in responders and non-responders. (C) The rate of adverse features presented according to long-term survivorship and tumor response status.

3.4. Hierarchical stratification of 2-year survival

The CART analysis provided a hierarchical stratification of 2-year survival based on 17 candidate clinicopathologic variables. As illustrated in Fig. 4, nine variables were retained in the final model. The root node (N = 695) was first split by ALBI grade, identifying a large subgroup of 412 patients with ALBI grade 2–3 or missing, who exhibited poor 2-year survival (18.7%, 95% CI: 14.9–22.5%). The remaining 283 patients with ALBI grade 1 were further stratified based on tumor size: 87 patients with tumors > 5 cm had a 2-year survival rate of 25.3% (95% CI: 16.2–34.4%). The other 196 patients (tumor size ≤ 5 cm) underwent additional splits based on AFP, number of tumour nodules, presence of GEV, etiology of chronic liver disease, BCLC stage and presence of extra-hepatic spreads as illustrated in the Sankey diagram.

Each internal node in the tree was supported by a statistically significant reduction in deviance, with corresponding p-values derived from chi-squared tests with 1 ° of freedom (4). These p-values were provided for descriptive purposes only; no correction for multiple testing was applied, and the analysis was not intended to be inferential. Deviance values at each split quantify the reduction in impurity and aid in interpreting the relative importance of each variable in the model.

3.5. Safety profile and treatment discontinuation analysis

Among all patients with Child-Pugh A and ECOG-PS 0–1, 45.1% experienced TRAE, with 129 patients developing grade 3 or 4 TRAEs, as assessed by investigators. In addition, 55 patients discontinued treatment due to intolerable toxicity.

Among patients classified as LTS and non-LTS, 318 patients (48.2%) experienced at least one TRAE during the study follow-up. Grade 3 or 4 TRAEs were reported in 86 patients (12.4%) (Table 3). AEs attributed specifically to atezolizumab and bevacizumab occurred in 35.0% and 35.6% of patients, respectively, with grade 3–4 events reported in 5.0% and 8.8% of cases. There were no significant differences in the incidence of TRAEs, either any grade or grade ≥ 3, between LTS and non-LTS. Variceal bleeding occurred in 8 patients (1.2%) overall, including 1 (0.5%) in the LTS group and 7 (1.4%) in the non-LTS group, without a

Table 3
Treatment-related adverse events and discontinuation rates.

Adverse events, n (%)	All cohort N = 695	LTS n = 190	Non–LTS n = 505	p value
Any TRAE	318 (48.2)	85 (47.0)	233 (48.6)	0.700
Any iRAE	243 (35.0)	65 (34.2)	178 (35.2)	0.798
Any Bevacizumab-related AE	235 (35.6)	68 (37.6)	167 (34.9)	0.517
Any TRAE ≥ G3	86 (12.4)	25 (13.2)	61 (12.1)	0.697
Any iRAE ≥ G3	35 (5.0)	10 (5.3)	25 (5.0)	0.876
Any Bevacizumab-related AE ≥ G3	61 (8.8)	19 (10.0)	42 (8.4)	0.494
Variceal bleeding	8 (1.2)	1 (0.5)	7 (1.4)	0.690
Reasons of discontinuation, n (%)	All cohort N = 448[a]	LTS n = 110[a]	Non–LTS n = 338[a]	p value
Progressive disease	272 (60.7)	67 (60.9)	207 (60.7)	< 0.001
Toxicity of treatment	41 (9.2)	9 (8.2)	32 (9.5)	
Complete remission	27 (6.0)	22 (20.0)	5 (1.5)	
Clinical deterioration/death	86 (19.2)	2 (1.8)	84 (24.8)	
Others reasons	21 (4.7)	10 (9.1)	11 (3.3)	

Abbreviations: LTS, long-term survivor (alive more than 24 months); iRAE, immunotherapy-related adverse event; TRAE, treatment-related adverse event.
[a] Patients recorded with reasons of immunotherapy discontinuation.

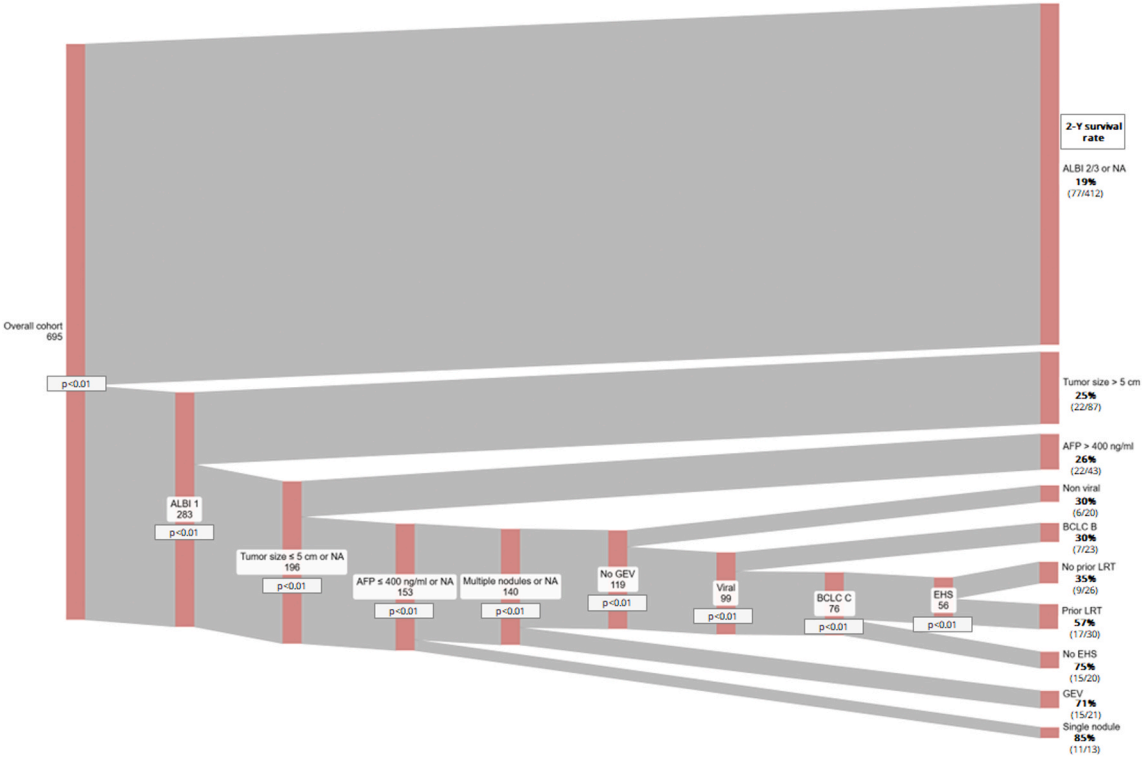

Fig. 4. Classification and regression tree (CART) analysis of determinants of the 2-year survival. Sankey diagram reporting the descriptive CART analysis performed using an alpha level of 0.1. Included factors were: age (>65 vs ≤65 years), sex (male vs female), ECOG-PS (0 vs 1), liver cirrhosis (yes vs no), ascites (yes vs no), gastroesophageal varices (GEV, yes vs no), portal vein invasion (PVI, yes vs no), main portal trunk involvement (yes vs no), extrahepatic spread (EHS, yes vs no), BCLC stage (B vs C), prior locoregional therapy (Prior-LRT, yes vs no), viral etiology (yes vs no), tumor size (>5 vs ≤5 cm), platelet count (>100 K vs ≤ 100K/mm^3), alpha-fetoprotein (AFP >400 vs ≤400ng/mL), number of tumor nodules (multiple vs single), and ALBI grade (2–3 vs 1). Variables not included in the final model were those that did not produce significant splits in 2-year survival within the population.

significant difference between groups.

Treatment discontinuation due to intolerable toxicity occurred in 9.2% of patients, with similar rates observed in the LTS and non-LTS groups (8.2% vs 9.5%, respectively). Among the 448 patients with a documented reason for A+B discontinuation (Table 3), the most common cause was disease progression (60.7%), followed by clinical deterioration or death (19.2%), and treatment-related toxicity. Notably, 20% of LTS discontinued therapy due to sustained complete tumor remission. Overall, this subgroup achieved a favorable outcome, with a median OS of 54.5 months (95% CI: 46.0–62.9) after a median treatment duration of 8.4 months (IQR: 2.8–24.2). Among these patients, 6 subsequently underwent curative-intent interventions (3 surgical resections, 2 radiofrequency ablations, and 1 liver transplantation), all of whom remained disease-free. Tumor recurrence after discontinuation was documented in 13 patients at a median interval of 5.7 months (IQR 2.7–14.9). Subsequent therapies included lenvatinib plus TACE (n = 5), TACE alone (n = 1), SBRT (n = 2), lenvatinib monotherapy (n = 2), and clinical trial regimens (n = 3). Five patients achieved complete response and two achieved partial response, while the remaining patients maintained stable disease with subsequent treatment.

In contrast, treatment discontinuation due to clinical deterioration or death was significantly more frequent among non-LTS (24.8% vs 1.8%). Patients who discontinued A+B therapy following complete tumor remission had the most favorable prognosis, whereas those who discontinued due to death or clinical deterioration experienced the poorest outcomes (4).

4. Discussion

Unlike chemotherapy or molecularly targeted therapy, ICIs may lead to long-term survivorship in a small but significant proportion of patients with cancer. Melanoma survivors develop long-lasting of T-cell effector and resident memory subsets [23], which demonstrates the immunologic underpinnings of durable responses to ICI. In uHCC, recognition of long-term survivors remains elusive and characteristics of this population are poorly described.

Drawing on a large international, multi-center cohort, our study is the first to report on the long-term efficacy of A+B in patients with uHCC. Over a prolonged median follow-up period of over 34 months, up to 27.3% of patients survived beyond 24 months, with a favorable median OS of up to 47.8 months. Long-term survival was more common in patients achieving radiological response to treatment and was predicated upon by pre-treatment tumour characteristics (PVI, tumor size $>$ 5 cm, and AFP $>$400 ng/mL) as well as indicators of hepatic dysfunction (ALBI grade), validating previous observations in large case series [24,25].

Long-term survival benefits associated with immunotherapy have been demonstrated across various cancer types, particularly in melanoma and non-small cell lung cancer [6,7,9]. Indeed, landmark long-term outcomes in patients with uHCC remain underreported. Recently, extended follow-up data from two pivotal clinical trials have shown promising results. In the phase III HIMALAYA study, the STRIDE regimen achieved a 60-month OS rate of 19.6% [12], while the phase I/II CheckMate-040 study reported a 60-month OS rate of 29.0% with nivolumab (1 mg/kg) plus ipilimumab (3mg/kg) administered every 3 weeks [11]. Despite these encouraging findings, both trials were conducted in eligible populations under rigorously protocol-mandated clinical management that is often different from routine clinical practice. Furthermore, it remains unclear whether the observed long-term benefit on OS exclusively applies to CTLA-4 blockade or whether it extends to other ICI combinations including A+B.

A+B is the first, globally approved ICI-combination treatment becoming available for unresectable/advanced-stage HCC. Our long-term AB-Real study helps to address the knowledge gap around long-term survivorship in patients receiving A+B. In our large, cross-continental, real-world cohort, more than one-quarter of patients survived beyond 24 months; the median OS for this subgroup of LTS approached four years. Although responders exhibited far better survival outcomes than non-responders, it is important to note that only 52.2% of responders were classified as long-term survivors, suggesting that other factors beyond tumor response alone may play a critical role in determining long-term benefit to A+B. Given that radiological response is a post-treatment, time-dependent variable, we performed a 3-month landmark analysis to mitigate potential immortal time and temporality bias; importantly, this approach yielded consistent survival patterns across subgroups, supporting the robustness of our findings.

Impaired liver function is a key barrier in the delivery of systemic therapy. Even within Child-Pugh A criteria, the ALBI grade offers an objective and accurate evaluation of hepatic dysfunction [26]. ALBI is a validated predictor of patients' OS across BCLC stages of HCC [27], including immunotherapy recipients [28,29], and shapes the risk of subsequent hepatic decompensation [30,31]. Our study demonstrates that the ALBI grade significantly influences long-term OS in patients treated with A+B, irrespective of pre-treatment tumour characteristics and response to treatment. Alongside its emergence as an independent predictor of OS in multivariable models, hierarchical clustering of pre-treatment variables by CART analysis provides a strong indication for enrichment of ALBI 1 in LTS, suggesting that preserved liver function is essential to fully realize the therapeutic benefits of A+B therapy.

A key concern in the delivery of A+B is represented by the risk of bleeding, an event of clinical interest in a patient population where portal hypertension is highly prevalent. Our CART analysis showed that the presence of gastroesophageal varices of any grade, a marker of clinically significant portal hypertension and advanced liver cirrhosis [28], does not preclude the achievement of long-term survivorship, given their association with a 71% two-year survival rate in one of the terminal nodes of our model. These findings are reassuring in a population where routine endoscopic screening for gastroesophageal varices and appropriate prophylactic treatment for gastroesophageal bleeding is consolidated practice [29]. Consistently, the incidence of variceal bleeding in our cohort was low and did not differ according to long-term survivorship status.

Another novel finding from our study comes from the assessment of treatment-related toxicity over an extended follow-up period, a point of greater consequence in the safe and effective delivery of systemic therapy in HCC. Despite the notable increase in follow-up time compared to IMbrave150, the reported incidence rate of any TRAE in our cohort was 48.2%, inclusive of 12.4% events graded as $\geq$ 3. Importantly, our study found no significant difference in the incidence of any-grade or grade $\geq$ 3 TRAEs according to long-term survivorship, uncoupling toxicity from survival outcomes in our population. Discontinuation of treatment due to TRAEs remained low with extended follow-up amounting to 9.2% of the cohort, a finding that supports the long-term safety of A+B.

Amongst the major limitations to our study, its retrospective design comes with the risk of incomplete data collection. In this study, we attempted to overcome this issue using MICE with 5 imputed datasets to mitigate selection bias, parameter estimate bias and underestimation of variance [22]. Besides, the elastic net fitted regression model was used for multivariable analysis that helps dealing with multi-collinearity and selecting variables [32]. Second, because patients censored prior to the 2-year landmark were unevenly distributed across participating sites, potentially introducing center-specific heterogeneity in baseline risk and bias, we accounted for site-level clustering to reduce potential heterogeneity in baseline risk. Although exclusion of patients censored before the 2-year landmark was methodologically required, a potential risk of informative censoring, such as differential loss to follow-up or undocumented subsequent treatments, cannot be entirely excluded and may have influenced the estimated proportion of long-term survivors and survival outcomes. Third, the absence of independent radiological reviews warrants cautious evaluation of response outcomes. Moreover, while prior locoregional therapies and the presence of gastroesophageal varices were recorded and incorporated into our analyses, the potential

influence of concurrent treatment heterogeneity during A+B therapy and post-progression treatments was not systematically captured across centers. Despite the application of multivariable modeling and penalized regression techniques, residual confounding inherent to observational studies cannot be fully excluded. These limitations leave room for bias from unmeasured confounders and unaccounted treatment effects. Approximately 70% of patients had chronic viral hepatitis, including about 50% with hepatitis B virus infection. This distribution is however comparable to that observed in the IMbrave150 trial, the study which led to the global approval of atezolizumab plus bevacizumab in unresectable HCC. Despite these limitations, which apply to all registry studies of this kind, our study features the broadest geographic representation of patient origin, and the longest follow-up period reported to date for outcomes associated with atezolizumab and bevacizumab treatment.

In conclusion, long-term survivorship is an achievable goal in patients treated with A+B initiation, with up to 27.3% of subjects remaining alive at 24 months after treatment initiation. LTS is more likely in patients ALBI grade 1 and favourable pre-treatment tumour characteristics, including lack of portal vein invasion, dominant tumor size < 5 cm, and AFP < 400 ng/mL—factors that are readily applicable in clinical practice. Although patients achieving a radiologic response appear more likely to achieve long-term survival, only 52% did so, indicating that radiologic response alone is not the exclusive determinant of long-term survivorship. Ongoing translational efforts should be concentrated to the discovery of predictive biomarkers of long-term survivorship in patients with uHCC.

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Giulia Francesca Manfredi: Data curation. **Andrea Dondo:** Data curation. **Lorenza Rimassa:** Visualization, Supervision. **Mario Pirisi:** Supervision. **Alessandra Auriemma:** Data curation. **Pei-Chang Lee:** Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **David Sacerdoti:** Data curation. **Alessio Cortellini:** Software, Methodology, Formal analysis. **Alessandro Parisi:** Data curation. **Bernardo Stefanini:** Investigation, Data curation. **Martin Schönlein:** Data curation. **Johann von Felden:** Visualization, Supervision. **Amit G Singal:** Visualization, Supervision. **Masatoshi Kudo:** Data curation. **Naoshi Nishida:** Data curation. **Bernhard Scheiner:** Data curation. **Matthias Pinter:** Data curation. **Changhoon Yoo:** Data curation. **Hong Jae Chon:** Data curation. **Jaekyung Cheon:** Data curation. **Robert Thimme:** Visualization, Supervision. **Yi-Hsiang Huang:** Writing – review & editing, Visualization, Supervision. **David James Pinato:** Writing – review & editing, Visualization, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Neehar Dilip Parkih:** Supervision, Data curation. **Pasquale Lombardi:** Data curation. **Haripriya Andanamala:** Supervision, Data curation. **Claudia Angela Maria Fulgenzi:** Data curation. **Susanna Ulahannan:** Visualization, Supervision. **Antonio D′Alessio:** Data curation. **Natascha Roehlen:** Supervision, Data curation. **Aria Torkpour:** Methodology, Data curation. **Elena Valenzi:** Data curation. **Fionnuala Crowley:** Data curation. **Thomas U Marron:** Supervision, Data curation. **Leonardo Brunetti:** Data curation. **Peter Robert Galle:** Supervision, Data curation. **Wei-Fan Hsu:** Data curation. **Ciro Celsa:** Data curation. **Giuseppe Cabibbo:** Data curation. **Calogero Cammà:** Data curation. **Rohini Sharma:** Data curation. **Ryan Po-Ting Lin:** Data curation. **Chun-Yen Lin:** Data curation. **Brooke Wietharn:** Data curation. **Caterina Vivaldi:** Data curation. **Gianluca Masi:** Data curation. **Anwaar Saeed:** Supervision, Data curation. **Francesco Tovoli:** Supervision. **Fabio Piscaglia:** Visualization, Supervision. **Andrea Dalbeni:** Data curation.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests

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Lorenza Rimassa reports a relationship with AbbVie that includes: consulting or advisory and funding grants. Lorenza Rimassa reports a relationship with AstraZeneca that includes: consulting or advisory, funding grants, speaking and lecture fees, and travel reimbursement. Lorenza Rimassa reports a relationship with Basilea that includes: consulting or advisory. Lorenza Rimassa reports a relationship with Bayer that includes: consulting or advisory and speaking and lecture fees. Lorenza Rimassa reports a relationship with Bristol Myers Squibb that includes: consulting or advisory and speaking and lecture fees. Lorenza Rimassa reports a relationship with Eisai that includes: consulting or advisory and speaking and lecture fees. Lorenza Rimassa reports a relationship with Elevar Therapeutics that includes: consulting or advisory. Lorenza Rimassa reports a relationship with Exelixis that includes: consulting or advisory and funding grants. Lorenza Rimassa reports a relationship with Genenta that includes: consulting or advisory. Lorenza Rimassa reports a relationship with Hengrui that includes: consulting or advisory. Lorenza Rimassa reports a relationship with Incyte that includes: consulting or advisory, funding grants, and speaking and lecture fees. Lorenza Rimassa reports a relationship with Ipsen that includes: consulting or advisory, funding grants, and speaking and lecture fees. Lorenza Rimassa reports a relationship with Jazz Pharmaceuticals Inc that includes: consulting or advisory and funding grants. Lorenza Rimassa reports a relationship with MSD that includes: consulting or advisory and funding grants. Lorenza Rimassa reports a relationship with Nerviano Medical Sciences Srl that includes: consulting or advisory and funding grants. Lorenza Rimassa reports a relationship with Roche that includes: consulting or advisory, funding grants, and speaking and lecture fees. Lorenza Rimassa reports a relationship with Servier that includes: consulting or advisory, funding grants, speaking and lecture fees, and travel reimbursement. Lorenza Rimassa reports a relationship with Taiho Oncology Inc that includes: consulting or advisory and funding grants. Lorenza Rimassa reports a relationship with Zymeworks that includes: consulting or advisory and funding grants. Lorenza Rimassa reports a relationship with Guerbet that includes: speaking and lecture fees. Lorenza Rimassa reports a relationship with BeiGene that includes: funding grants. Lorenza Rimassa reports a relationship with Fibrogen that includes: funding grants. Lorenza Rimassa reports a relationship with ThansThera Sciences that includes: funding grants.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2026.116749.

Data availability

The data that support the findings of this study are not publicly available due to privacy and ethical restrictions but are available from the corresponding author upon reasonable request.

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