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Comparative Efficacy of Initial Treatment Strategies in Patients with Transarterial Chemoembolisation-Unsuitable Hepatocellular Carcinoma

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Keywords
Tyrosine kinase inhibitors · Atezolizumab/bevacizumab · Locoregional treatment · Systemic therapy · Outcome

Abstract
Introduction: Transarterial chemoembolisation (TACE) is considered the standard-of-care for patients with intermediate-stage hepatocellular carcinoma (HCC), despite several patients exhibit features that may be associated with suboptimal outcome of treatment – also referred to as TACE-unsuitable. In this study, our aim was to provide real-world evidence that patients who are considered TACE-unsuitable may receive greater benefit by systemic therapy than by TACE. ***Methods:*** This study analysed 1,150 patients with TACE-unsuitable HCC, defined according to Asia-Pacific Primary Liver Cancer Expert criteria. Patients were initially treated with TACE (n = 842), sorafenib (n = 96), lenvatinib (n = 62), or atezolizumab/bevacizumab (n = 47). Overall survival (OS) was the primary endpoint. Inverse probability of treatment weighting was applied to adjust for baseline differences. ***Results:*** Compared to TACE, atezolizumab/bevacizumab reduced mortality risk (hazard ratio [HR]: 0.47, 95% confidence interval [95% CI]: 0.27–0.80; p = 0.008), lenvatinib was neutral (HR: 0.62, 95% CI: 0.35–1.08; p = 0.091), and sorafenib was associated with increased mortality (HR: 1.85, 95% CI: 1.28–2.65; p = 0.001). OS at 24 months was 60.2% for TACE, 31.9% for sorafenib, 68.3% for lenvatinib, and 70.5% for atezolizumab/bevacizumab (p < 0.0001). The disease control rate was 53.2% with TACE, 47.9% with sorafenib, 67.8% with lenvatinib (p = 0.030 versus TACE; p = 0.025 versus sorafenib), and 75.6% with atezolizumab/bevacizumab (p < 0.001 versus TACE; p < 0.001 versus sorafenib). ***Conclusions:*** In TACE-unsuitable patients, systemic treatment with atezolizumab/bevacizumab and, to a lesser extent, lenvatinib is associated with improved outcome compared to TACE. These findings support a paradigm shift in the initial management of intermediate-stage HCC, favouring the early use of systemic therapy in appropriately selected patients.

Plain Language Summary
Hepatocellular carcinoma (HCC) is a type of liver cancer and patients with intermediate-stage HCC have tumours that are unlikely to respond well to a common local treatment called transarterial chemoembolisation (TACE), which delivers chemotherapy directly into the liver. Researchers wanted to find out whether those patients might live longer if they received newer drugs instead of TACE. This study looked at 1,150 patients in Italy who were considered "TACE-unsuitable" because of tumour size, liver function, or other characteristics. At the time of their first treatment, they received either TACE, the oral drugs sorafenib or

lenvatinib, or an immunotherapy combination of atezolizumab and bevacizumab. The researchers adjusted the analysis to make sure the groups were comparable. The results showed that the immunotherapy combination reduced the risk of death by about half compared with TACE. Lenvatinib gave similar survival to TACE, while sorafenib did worse. After 2 years, about 70% of patients treated with immunotherapy were alive, compared with 68% of those taking lenvatinib, 60% of those receiving TACE, and 32% of those on sorafenib. The immunotherapy and lenvatinib groups also had better disease control, meaning their tumours stopped growing or shrank more often. These findings suggest that patients with intermediate-stage liver cancer who are unlikely to benefit from TACE might do better if they start with a systemic therapy, particularly the atezolizumab and bevacizumab combination or lenvatinib. Early use of these drugs could improve survival and control of the disease for this group of patients.

Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related deaths worldwide, accounting for approximately 800,000 deaths/year globally [1]. Epidemiological trends in HCC are rapidly changing, especially in Western countries, because of a progressive decline in cases associated infection with hepatitis virus and a relative increase in those associated with other aetiologies, particularly with metabolic dysfunction-associated steatotic liver disease [2–4]. Moreover, the clinical stage of patients with HCC at diagnosis is progressively shifting toward less advanced oncological stages, mainly due to the increased application of surveillance programmes [5, 6]. Lastly, the range of treatment strategies for HCC dramatically improved with the advent of more effective systemic therapies and with a progressive uptake of these treatments at earlier oncological stages thanks to their improved efficacy and enhanced tolerability, compared to sorafenib [7–10].

In this evolving scenario, the Asia-Pacific Primary Liver Cancer Expert (APPLE) Consensus suggested that, for some patients otherwise considered standard candidates to transarterial chemoembolisation (TACE) like those in the Barcelona Clinic Liver Cancer (BCLC) intermediate stage who show features potentially associated to early refractoriness, or response, or a higher risk of deterioration of liver function, systemic treatment might provide similar, if not better, oncological response and preserve liver function [11]. In this regard, the APPLE Consensus defined as TACE-unsuitable those patients with either tumours beyond the up-to-7 criteria, or with a modified albumin-bilirubin (mALBI) grade 2b or 3, or with some HCC characteristics, such as extranodular growth pattern, confluent multi-nodular or massive type, or poor histological differentiation [11]. The concept of TACE-unsuitable HCC was further elaborated postulating that, in these patients, the positive results obtained by systemic therapy might avoid repeated courses of (likely unsuccessful) TACE, which may eventually lead to deterioration in liver function with a detrimental effect on overall survival (OS) [12]. Preliminary proof-of-concept studies carried out in Japan, which included a limited number of patients treated with either lenvatinib or atezolizumab/bevacizumab, supported this assumption [13, 14]. However, this approach has never been tested in large, real-world studies comparing the outcome of similar cohorts of TACE-unsuitable patients treated with either TACE or various systemic therapies.

This study aimed to confirm, or confute, the hypothesis that patients who have predictors for suboptimal outcomes after TACE (TACE-unsuitable in the APPLE consensus) may receive greater benefit by systemic therapy rather than by TACE. To test this hypothesis, we assessed the therapeutic outcome of first-line TACE or systemic therapy with tyrosine kinase inhibitors (sorafenib, lenvatinib) or with atezolizumab/bevacizumab in a large, multicentre series of HCC patients considered TACE-unsuitable according to the APPLE Consensus definition [11]. The results of this real-world validation pave the road for the adoption of this conceptual framework in clinical practice.

Patients and Methods

Study Design

In this retrospective, multicentre, international study, we analysed data from 4,300 patients diagnosed with HCC between 2014 and 2022 included in the ITA.LI.CA, CLEO-AIGO, and Beaujon Hospital databases, selecting those classified as TACE-unsuitable according to the APPLE Consensus definition who underwent either first-line TACE or systemic therapy with sorafenib, lenvatinib, or atezolizumab/bevacizumab or who received best supportive care (BSC) alone [11]. According to these criteria, we included in this study patients with unresectable HCCs exceeding the up-to-7 criteria (i.e., up-to-7 out), those with a mALBI grade 2b and 3,

and those with non-simple nodular HCC types (e.g., confluent multi-nodular, massive/infiltrative). Exclusion criteria were the presence of a Child-Pugh score >7, the presence of tumoural macrovascular invasion and/or extrahepatic spread, and treatment others than TACE or systemic therapy. TACE-unsuitable patients who received BSC alone were included in the study to obtain survival figures also in untreated patients. According to these criteria, from the initial cohort of 4,300 patients, a total of 1,422 patients (20.9%) met the inclusion criteria, and after exclusion of 272 patients (17.8% of TACE-unsuitable patients) who received a first-line treatment other than those under investigation, 1,150 patients were finally included in the study. The flow of patients is shown in online supplementary Figure 1 (for all online suppl. material, see https://doi.org/10.1159/000551050).

All patients provided written informed consent to undergo each diagnostic and therapeutic procedure and to have their clinical data recorded anonymously in the databases, whose use for scientific research was approved by the Institutional Review Boards of the participating centres. The study was conducted in accordance with both the Declaration of Helsinki and the Declaration of Istanbul.

Data Collection and Outcome Analysis

For each patient, we recorded demographic data (age, gender, body mass index), biochemical variables, stage of liver disease evaluated using the Child-Pugh classification, the Model for End-Stage Liver Disease (MELD) score, and the mALBI grade, functional status assessed by the Eastern Cooperative Oncology Group Performance Status (ECOG-PS), and tumour characteristics (size of larger nodule, number of lesions, and histology when available) as well as the type of oncological treatment [15–17].

The primary endpoint of the study was OS, defined as the time elapsed from the start of treatment to death from any cause or to the last available follow-up visit. Due to intrinsic differences in follow-up among treatment groups because of different calendar time of the availability of the various systemic treatments in clinical practice, OS was also assessed using landmark analyses at 6, 12, and 24 months to avoid bias related to different duration of follow-up. Moreover, we performed a sensitivity sub-analysis including only patients treated in the period in which all the systemic treatments were available (2018–2022). Best oncological response to treatment was subdivided into complete response (CR), partial response (PR), stable disease (SD), and progressive disease, using modified the Response Evaluation Criteria in Solid Tumors criteria [18, 19]. Objective response (OR) was considered as the sum of CR and PR, while disease control was defined as the sum of OR and SD. In addition, we recorded data on downstream therapies used after HCC progression.

Therapeutic Strategies and Group Balancing

Patients were subdivided according to the first-line treatment received (TACE, sorafenib, lenvatinib, atezolizumab/bevacizumab) or BSC. Patients were treated in clinical practice, and treatment decisions were mainly based on the indications provided by the local guidelines valid at the time of diagnosis, in particular those set forth by the Italian Association for the Study of the Liver, that included a multidisciplinary approach to the management of patients with HCC [20, 21]. Considering the intrinsic differences in the baseline characteristics among groups, we applied the inverse probability of treatment weighting (IPTW) adjustment to balance the characteristics of the groups. A multinomial logistic regression model was used to estimate the probability of receiving each treatment. Covariates with an absolute standardised mean difference ≥0.1 between the treatment groups were included in the multivariate analysis. The predicted probability corresponding to the treatment received was extracted and used to compute the IPTW as the reciprocal of that probability. To limit the influence of extreme weights and improve estimator precision, we calculated stabilised weights by multiplying each raw IPTW by the marginal (overall) probability of receiving the corresponding treatment. This procedure allowed for balancing the baseline characteristics between the treatment groups, reducing selection bias, and facilitating direct comparisons of the efficacy of the different therapeutic approaches.

A secondary analysis was conducted after adjustment of baseline differences using propensity score matching (PSM) between patients treated with TACE and those who received either sorafenib, lenvatinib, or atezolizumab/bevacizumab. Initially, covariates or factors to be included in the PSM model were identified through univariate analysis, with a significant difference threshold $p \leq 0.05$ for inclusion. The PSM estimation utilised a logistic regression model, with a calliper width of 0.2 deemed appropriate.

Statistical Analysis

Main analyses were conducted in the IPTW-derived pseudo-populations, ensuring that the estimates were adjusted for potential confounders. Continuous data are expressed as mean ± standard deviation or median and

interquartile range and discrete variables as absolute and relative frequencies. The normal distribution of the variables was tested using standard procedures such as Levene's test and the Kolmogorov-Smirnov test. Comparisons of continuous variables were made with the Student's *t* test, and changes over time were assessed using analysis of the variance. Discrete variables were compared with the χ^2 test. Differences between groups were evaluated using unpaired *t* tests, Wilcoxon, Mann-Whitney U (for variables not normally distributed), and Fisher's exact tests (when comparing proportions), as appropriate. OS was estimated using the IPTW-weighted Kaplan-Meier survival analysis, and differences between survival curves were assessed with the log-rank test. We performed landmark analyses at 6, 12, and 24 months, redefining time zero at each landmark and including patients alive and event-free at that time, with follow-up from the landmark to outcome or censoring. To assess the robustness of the estimated treatment effects to potential unmeasured confounding, we additionally computed E-values for the main hazard ratios, defined as the minimum strength of association that an unmeasured confounder would need to have with both treatment allocation and the outcome, conditional on the measured covariates, to fully explain away the observed association. A two-tailed p value <0.05 was considered statistically significant. All statistical analyses were performed with SPSS v27.0 (Apache Software Foundation, Chicago, IL, USA), R (the R Project, R version 3.4.3; R Foundation for Statistical Computing, Vienna, Austria and EZR: https://github.com/jinkim3/ezr), and STATA 18.0 (StataCorp, 4905 Lakeway Drive, College Station, TX, USA).

Results

Baseline Characteristics of the Study Population

Table 1 shows the baseline demographic and clinical characteristics of the study population subdivided into the four treatment groups and BSC. Overall, 842 patients (73.2%) were initially treated with TACE, 96 (8.3%) with sorafenib, 62 (5.4%) with lenvatinib, and 47 (4.1%) with atezolizumab/bevacizumab, while 103 patients (9.0%) received BSC alone. The median age of the study population was 69.2 years (interquartile range 62.0–75.6), with a prevalence of male patients (874, 76.0%). The baseline characteristics of patients differed across treatments, and in particular, significant differences were observed in terms of median age ($p = 0.007$), prevalence of male sex ($p = 0.008$), presence of cirrhosis ($p < 0.001$), median ECOG-PS ($p < 0.001$), mALBI grade distribution ($p < 0.001$), Child-Pugh class (class A vs. B7: $p = 0.003$), MELD score ($p < 0.001$), number of HCC nodules ($p < 0.001$), and median of the maximum HCC diameter ($p < 0.001$). Following IPTW adjustment, the demographic and clinical characteristics of patients were well balanced with no significant differences across treatment groups for any of the variables considered (online suppl. Table 1).

Survival Analysis

Using TACE as reference treatment, the Cox regression analysis showed that, before IPTW adjustment, BSC (hazard ratio [HR]: 3.29, 95% confidence interval [95% CI]: 2.63–4.12; $p < 0.001$; E-value 6.03, 95% CI: 4.70–7.71) and treatment with sorafenib (HR: 2.06, 95% CI: 1.62–2.61; $p < 0.001$; E-value 3.54, 95% CI: 2.62–4.66) were associated with a higher risk of death, while treatment with lenvatinib showed no significant difference (HR: 0.80, 95% CI: 0.49–1.30; $p = 0.363$) and treatment with atezolizumab/bevacizumab was associated with a significantly lower risk of death (HR: 0.57, 95% CI: 0.36–0.91; $p = 0.019$; E-value 2.90, 95% CI: 1.43–5.00; Fig. 1a). The landmark analyses before IPTW adjustment at 6, 12, and 24 months are shown in online suppl. Fig. 2).

After IPTW adjustment and considering treatment with TACE as reference, treatment with sorafenib (HR: 1.85, 95% CI: 1.28–2.65; $p = 0.001$; E-value 3.10, 95% CI: 1.88–4.74) was associated with a higher mortality risk, while treatment with lenvatinib was associated with a similar mortality risk (HR: 0.62, 95% CI: 0.35–1.08; $p = 0.091$), and treatment with atezolizumab/bevacizumab was associated with a significantly lower risk of death (HR: 0.47, 95% CI: 0.27–0.80; $p = 0.008$; E-value 3.68, 95% CI: 1.81–6.87; Fig. 1b).

In a landmark analysis after IPTW adjustment (Fig. 2), the 6-month OS was 97.4% (95% CI: 95.6–99.4) for TACE, 81.9% (95% CI: 74.1–83.1) for sorafenib, 95.5% (95% CI: 93.2–98.0) for lenvatinib, and 98.6% (95% CI: 95.8–99.6) for atezolizumab/bevacizumab ($p < 0.001$). At 12 months, OS was 85.9% (95% CI: 81.7–89.1) for TACE, 60.9% (95% CI: 60.2–65.2) for sorafenib, 88.0% (95% CI: 84.1–91.1) for lenvatinib, and 88.2% (95% CI: 82.9–91.0) for atezolizumab/bevacizumab ($p < 0.001$). Lastly, at 24 months, OS was 60.2% (95% CI: 54.3–64.9) with TACE, 31.9% (95% CI: 25.9–37.9) with sorafenib, 68.3% (95% CI: 57.3–78.5) with lenvatinib, and 70.5% (95% CI: 62.8–76.1) with atezolizumab/bevacizumab ($p < 0.001$). In the IPTW-adjusted population, the median OS was 28.4 months (95% CI:

Table 1. Baseline demographic and clinical characteristics of patients subdivided by treatment and BSC

	TACE, *n* = 842 (73.2%)	Sorafenib, *n* = 96 (8.3%)	Lenvatinib, *n* = 62 (5.4%)	Atezolizumab/ bevacizumab, *n* = 47 (4.1%)	BSC, *n* = 103 (9.0%)	SMD[a]	*p* value[a]
Age, years	68.7 (62.0–74.8)	67.4 (59.7–73.6)	72.1 (64.0–77.6)	68.0 (58.0–78.0)	75.1 (68.0–81.1)	0.011	0.007
Sex (male)	631 (74.9)	85 (88.5)	53 (85.5)	37 (78.7)	68 (66.0)	0.106	0.008
Body mass index, kg/m^2	25.4 (23.4–28.3)	26.5 (22.6–28.7)	25.3 (23.2–28.4)	26.1 (21.6–29.7)	24.2 (22.5–27.4)	0.019	0.102
Cirrhosis presence	800 (95.0)	79 (82.3)	53 (85.5)	36 (76.6)	94 (91.3)	0.204	<0.001
Aetiology, *n* (%)							
Viral	614 (72.9)	64 (66.7)	44 (71.0)	34 (72.3)	68 (66.0)	0.041	0.630
Non-viral	228 (27.1)	32 (33.3)	18 (29.0)	13 (27.7)	35 (34.0)		
ECOG-PS points	0 (0–0)	0 (0–1)	0 (0–1)	0 (0–1)	1 (0–2)	0.033	<0.001
MELD score	10 (8–12)	9 (8–12)	9 (8–10)	7 (6–9)	11 (9–14)	0.053	<0.001
mALBI grade							
1–2a	141 (16.8)	34 (35.4)	31 (50.0)	25 (53.2)	18 (17.5)	0.274	<0.001
2b–3	701 (83.2)	62 (64.6)	31 (50.0)	22 (46.8)	85 (82.5)		
Child-Pugh class							
A	511 (60.7)	61 (63.6)	49 (79.0)	37 (78.7)	45 (43.7)	0.115	0.003
B7	331 (39.3)	35 (36.5)	13 (21.0)	10 (21.3)	58 (56.3)		
Nodules, *n*							
One	454 (54.3)	33 (40.2)	9 (14.7)	3 (7.0)	38 (40.8)	0.239	<0.001
2–3	179 (21.4)	12 (14.6)	5 (8.2)	16 (37.3)	22 (23.7)		
>3	203 (24.3)	37 (45.1)	47 (77.1)	24 (55.9)	33 (35.6)		
Maximum diameter, cm	3.4 (2.4–5)	6.5 (3.9–9.6)	4.6 (3–7)	5.5 (2.5–8.3)	4.1 (2.7–7)	0.135	<0.001
Alpha-fetoprotein, ng/mL	170 (80–320)	215 (111–865)	220 (120–753)	225 (130–410)	210 (115–1,210)	0.005	0.153

Data are shown as absolute value and percentage or median and interquartile range. BSC, best supportive care; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; SMD, standardised mean difference; mALBI, modified albumin-bilirubin; MELD, Model for End-Stage Liver Disease; TACE, transarterial chemoembolisation. [a]Statistical significance and standardised mean difference were calculated excluding patients who were managed with best supportive care alone.

17.2–44.2) after TACE, 14.2 months (95% CI: 7.1–14.2) with sorafenib, 35.8 months (95% CI: 15.1–45.1) with lenvatinib, and 46.2 months (95% CI: 38.2–57.4) with atezolizumab/bevacizumab (Fig. 1b).

Oncological Response

Before IPTW adjustment, the distribution of oncological response varied across treatments (online suppl. Fig. 3). The distribution of oncological response across treatments after IPTW adjustment is reported in Figure 3. CR was observed in 35 patients treated with TACE (4.2%), none with sorafenib ($p = 0.030$ compared to TACE), 3 with lenvatinib (5.1%), and 2 with atezolizumab/bevacizumab (4.4%). PR was recorded in 128 patients treated with TACE (15.2.%), 4 with sorafenib (4.3%; $p < 0.001$ compared to TACE), 14 with lenvatinib (23.7%; $p = 0.002$ compared to sorafenib), and 9 with atezolizumab/bevacizumab (20.0%; $p = 0.002$ compared to sorafenib); SD was reported in 284 patients treated with TACE (33.8%), 41 treated with sorafenib (43.6%; $p = 0.044$ compared to TACE), 23 with lenvatinib (39.0%), and 23 with atezolizumab/bevacizumab (51.1%; $p = 0.040$ compared to TACE). Lastly, progressive disease was documented in 393 patients who received TACE

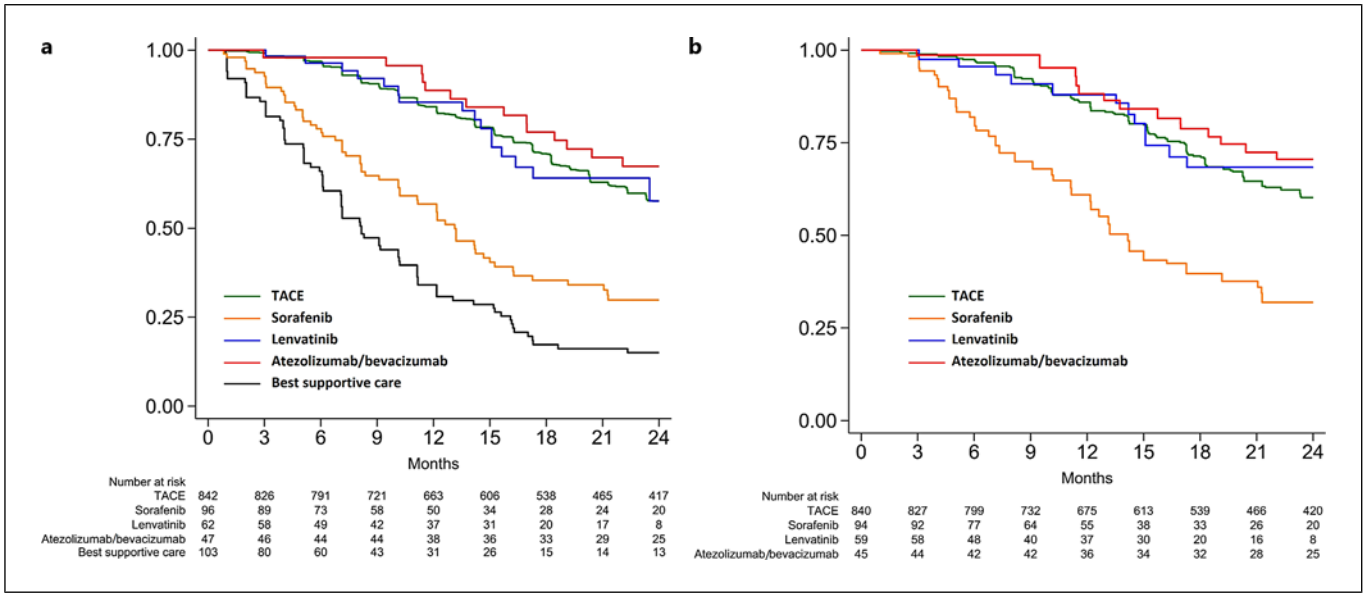


Fig. 1. Kaplan-Meier survival curves stratified by treatment groups before (**a**) and after (**b**) inverse probability of treatment weighting (IPTW) adjustment. The numbers at risk at different time points (months) are presented below each panel. Survival probabilities were assessed up to 24 months of follow-up.

(46.8%), 49 treated with sorafenib (52.1%), 19 with lenvatinib (32.2%; $p = 0.035$ compared to sorafenib), and 11 with atezolizumab/bevacizumab (24.4%; $p = 0.015$ compared to TACE, $p = 0.010$ compared to sorafenib).

Overall, an OR was observed in 19.4% of patients treated with TACE, 4.3% with sorafenib ($p < 0.001$ compared to TACE), 28.8% with lenvatinib ($p < 0.001$ compared to sorafenib), and 24.4% with atezolizumab/bevacizumab ($p < 0.001$ compared to sorafenib), while DC was observed in 53.2% of patients treated with TACE, 47.9% with sorafenib, 67.8% with lenvatinib ($p = 0.030$ compared to TACE, $p = 0.025$ compared to sorafenib), and 75.6% with atezolizumab/bevacizumab ($p < 0.001$ compared to TACE, $p < 0.001$ compared to sorafenib).

Sensitivity Sub-Analyses of Patients Treated in the Period 2018–2022

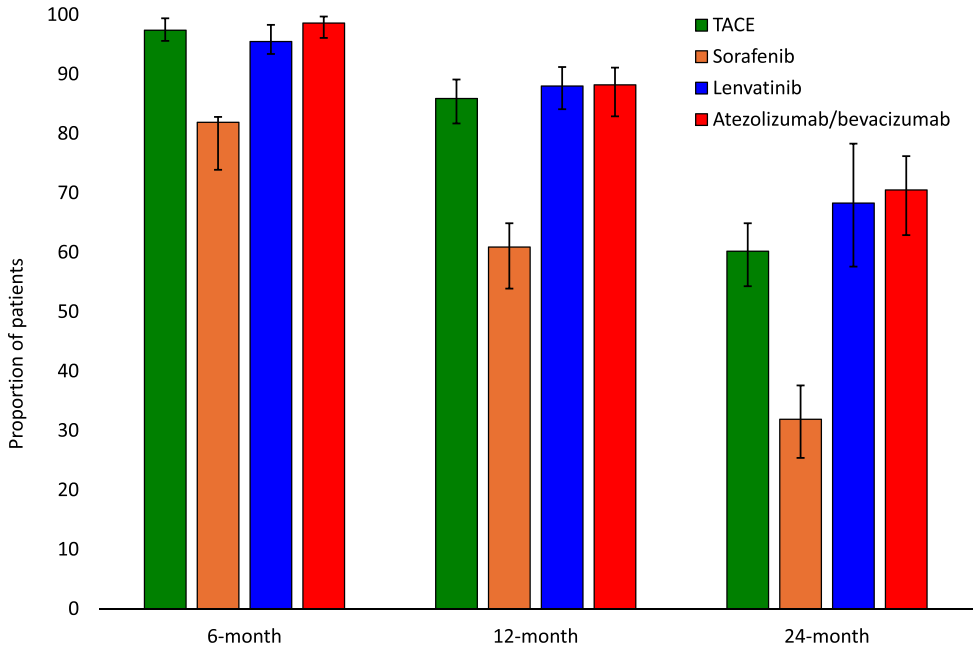
In a sensitivity sub-analysis carried out restricting the period of enrolment to the era of availability of all the systemic drugs evaluated in the study (2018–2022), we included a total of 642 IPTW-weighted patients: 483 received TACE, 54 received sorafenib, 59 received lenvatinib, and 46 received atezolizumab/bevacizumab. Considering TACE as the reference (Table 2), the HRs for overall mortality were 2.06 (95% CI: 1.36–3.12; $p = 0.001$) for treatment with sorafenib, 0.71 (95% CI: 0.39–1.27; $p = 0.245$) with lenvatinib, and 0.47 (95% CI: 0.26–0.84; $p = 0.010$) with atezolizumab/bevacizumab. A landmark analysis after IPTW adjustment at 6, 12, and 24 months is reported in Table 2.

Overall oncological response was consistent with the one observed in the whole cohort, with an OR observed in 21.8% of patients treated with TACE, 7.4% with sorafenib, 33.9% with lenvatinib, and 28.2% with atezolizumab/bevacizumab, while DC was observed in 58.2% of patients treated with TACE, 51.8% with sorafenib, 69.5% with lenvatinib, and 76.1% with atezolizumab/bevacizumab (Table 2).

Sensitivity Sub-Analyses Using PSM

We performed additional complementary sensitivity sub-analyses using PSM between patients treated with TACE and those who received sorafenib, lenvatinib, and atezolizumab/bevacizumab. Baseline characteristics before and after PSM are reported in online supplementary Table 2–4, respectively.

After PSM adjustment and considering treatment with TACE as the reference, treatment with sorafenib (HR: 1.41, 95% CI: 1.11–2.02; $p = 0.032$; E-value 2.20, 95% CI: 1.37–3.03; Fig. 4a) was associated with a higher mortality risk, treatment with lenvatinib was associated with a similar mortality risk (HR: 0.91, 95% CI: 0.49–1.67; $p = 0.754$; Fig. 4b), and treatment with



	TACE	Sorafenib	Lenvatinib	Atezolizumab/bevacizumab	p
6-month	97.4 (95% CI: 95.6–99.4)	81.9 (95% CI: 74.1–83.1)	95.5 (95% CI: 93.2–98)	98.6 (95% CI: 95.8–99.6)	0.001
12-month	85.9 (95% CI: 81.7–89.1)	60.9 (95% CI: 60.2–65.2)	88 (95% CI: 84.1–91.1)	88.2 (95% CI: 82.9–91)	0.001
24-month	60.2 (95% CI: 54.3–64.9)	31.9 (95% CI: 25.9–37.9)	68.3 (95% CI: 57.3–78.5)	70.5 (95% CI: 62.8–76.1)	0.001

Fig. 2. Landmark analyses of survival rates (with 95% confidence interval) at 6, 12, and 24 months in inverse probability of treatment weighting-adjusted populations treated with transarterial chemoembolisation (TACE), sorafenib, lenvatinib, and atezolizumab/bevacizumab.

atezolizumab/bevacizumab was associated with a significantly lower risk of death (HR: 0.55, 95% CI: 0.28–0.98; p = 0.045; E-value 2.55, 95% CI: 1.12–5.93; Fig. 4c).

Therapies Administered after First-Line Treatment

Figure 5 shows the treatment trajectories and patient outcomes based on first- and second-line therapies and management during follow-up. Overall, 871 patients (75.8%) died during the observation period, while 279 (24.3%) were still in follow-up after a median of 20.3 (95% CI: 10.2–35.5) months.

Among the 842 patients initially treated with TACE, 35 patients were still alive with no further line of treatment (4.1%), while in the 807 patients who progressed after TACE, the second-line treatment was represented by sorafenib in 118 patients (14.6%) and lenvatinib in 24 patients (3.0%), while 109 patients (13.5%) transitioned to BSC alone, and 547 patients (67.8%) received a second TACE at first progression. In this last group, 261 patients (47.7%) died and 24 (4.4%) were still alive at follow-up, while 262 (52.1%) received an additional (third) TACE. Among these 262 patients, 152 (58.0%) died and 38 (14.5%) were alive at follow-up, and 72 (27.5%) underwent a further (fourth) TACE. Lastly, among these, 43 (59.7%) died and 29 (40.3%) were still alive at follow-up. Among patients initially treated with sorafenib (n = 96), most continued with the same treatment or died, with 9 patients (9.4%) were treated with lenvatinib and 8 patients with metronomic capecitabine (8.3%) as second-line treatment. Lastly, all patients who received first-line lenvatinib (n = 62) or atezolizumab/bevacizumab (n = 47) continued with the same treatment or died during follow-up.

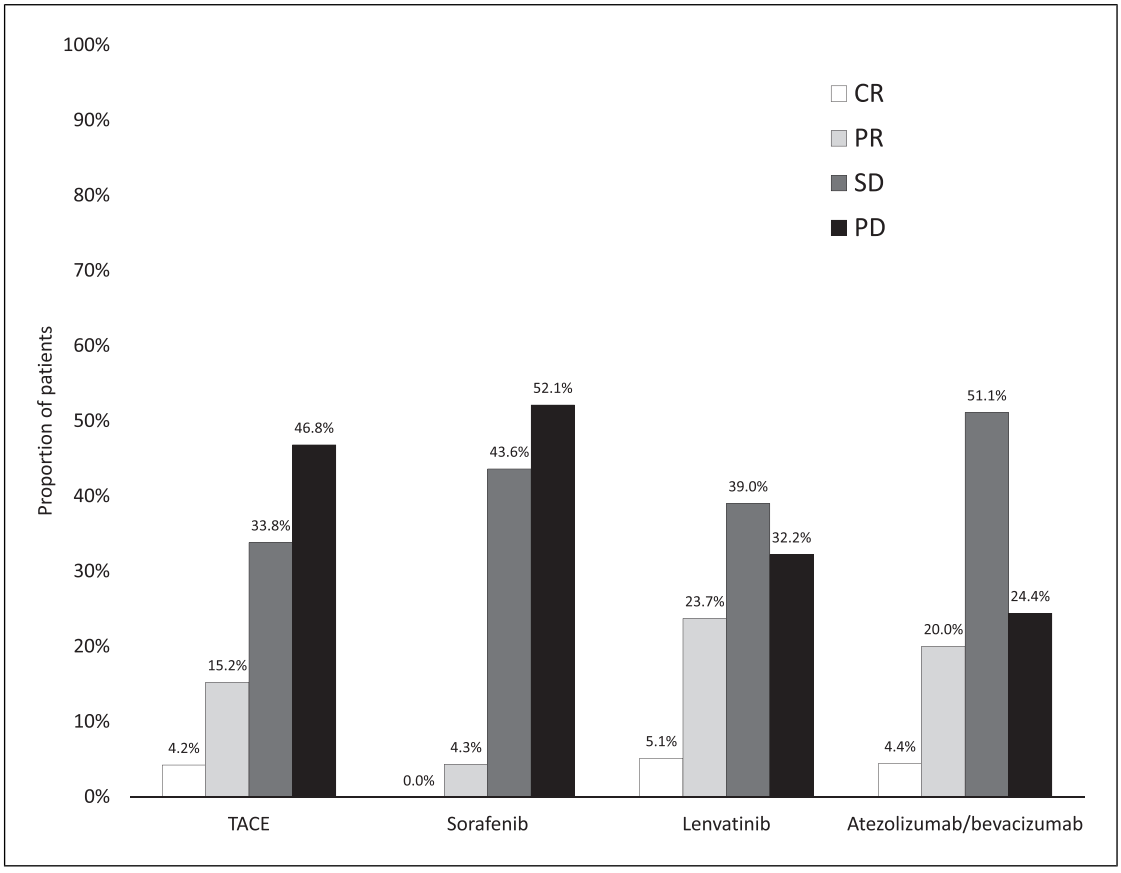


Fig. 3. Tumour response distribution across treatment groups after inverse probability of treatment weighting (IPTW) adjustment. Tumour response categories: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD). Percentages represent the proportion of patients achieving each response category within each treatment group.

Discussion

This study aimed to test the hypothesis that patients who are considered TACE-unsuitable according to the definition proposed by the APPLE Consensus may achieve a better outcome if treated with systemic therapy rather than with TACE [11]. Although this concept has previously been explored in other series, these studies did not include a control group treated with TACE and a comparison with all the systemic treatments was not available [13, 22–25]. Therefore, to provide a solid, real-world basis to test the study hypothesis, we evaluated a large, multicentre population of TACE-unsuitable patients with HCC treated with either TACE, sorafenib, lenvatinib, or atezolizumab/bevacizumab and assessed their outcomes in terms of survival and response to treatment. The various subpopulations varied in terms of baseline characteristics such as severity of liver disease, ECOG-PS, and some tumour characteristics, but use of the IPTW adjustment allowed us to equalise the subpopulations and to create comparable groups adequately matched for the principal confounding factors, thus providing unbiased results. Lastly, the oncological outcomes obtained with TACE in the studied population are consistent with previous results obtained in patients with similar characteristics, thus supporting the validity of the comparison group [26].

Overall, our study clearly provides real-life evidence supporting the APPLE Consensus, as it shows that patients classified as TACE-unsuitable obtained a survival benefit if treated with atezolizumab/bevacizumab as compared to TACE [11]. Results from earlier, smaller, proof-of-concept studies provided results that well align with ours, although these studies assessed a smaller series of patients, mainly included in registration trials, were focussed on patients beyond the up-to-7 criteria alone,

Table 2. Inverse probability of treatment weight-adjusted hazard ratios for overall mortality subdivided by treatment received in the period 2018–2022

Treatment	Overall mortality	Landmark analysis			Oncological response			
	hazard ratio (95% CI)	6 months, median (95% CI)	12 months, median (95% CI)	24 months, median (95% CI)	CR, *n* (%)	PR, *n* (%)	SD, *n* (%)	PD, *n* (%)
TACE (*n* = 483)	1.00 (reference)	97.5 (94.4–99.8	85.5 (80.4–90.2)	59.7 (52.5–66.4)	25 (5.2)	80 (16.6)	176 (36.4)	230 (47.6)
Sorafenib (*n* = 54)	2.06 (1.36–3.12)	79.6 (71.3–84.5)	59.2 (58.2–67.7)	30.8 (24.1–39.6)	0 (0)	4 (7.4)	24 (44.4)	26 (48.1)
Lenvatinib (*n* = 59)	0.71 (0.39–1.27)	95.8 (91.6–99.4)	88.1 (82.6–94.1)	68.7 (55.1–81.0)	4 (6.8)	16 (27.1)	21 (35.6)	18 (30.5)
Atezolizumab/ bevacizumab (*n* = 46)	0.47 (0.26–0.84)	98.7 (93.4–99.8)	88.3 (80.5–94.3)	70.8 (59.9–78.3)	3 (6.5)	10 (21.7)	22 (47.8)	11 (23.9)

Percentages are calculated within each inverse probability of treatment weight-adjusted group. 95% CI, 95% confidence interval; BSC, best supportive care; CR, complete response; HR, hazard ratio; PD, progressive disease; PR, partial response; SD, stable disease; TACE, transarterial chemoembolisation.

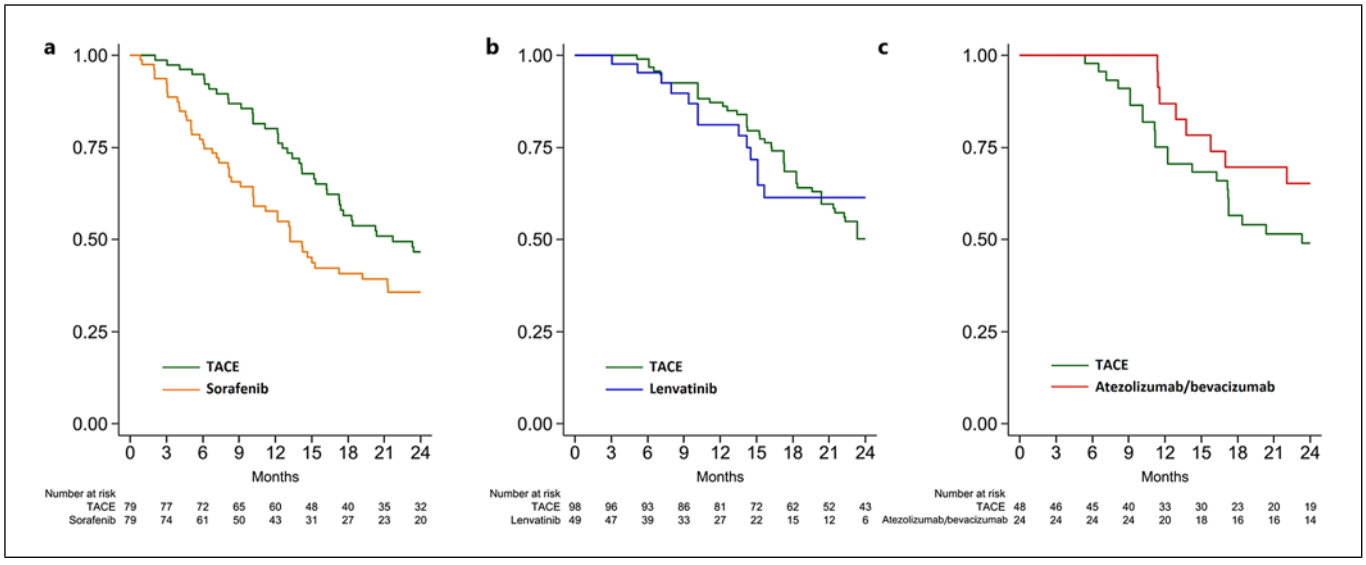


Fig. 4. Kaplan-Meier survival curves in propensity score-matched cohorts comparing transarterial chemoembolisation (TACE) with sorafenib (**a**), lenvatinib (**b**), and atezolizumab/bevacizumab (**c**). The numbers at risk at different time points (months) are presented below each panel.

and mostly evaluated the outcome of just one systemic treatment [13, 22–25]. Despite these differences, the median OS that we observed in the IPTW-adjusted populations of patients treated with lenvatinib (35.8 months) and atezolizumab/bevacizumab (46.2 months) is in keeping with the results previously obtained in a proof-of-concept study carried out in 30 up-to-7 out patients treated with lenvatinib (37.9 months) [13]. Moreover, our results closely align with those obtained in the phase II REPLACEMENT study, which enrolled 74 TACE-naïve, Child-Pugh class A, BCLC intermediate-stage patients, of whom roughly one-third were up-to-7 out, who had never received any prior systemic therapy, and who were treated with atezolizumab/bevacizumab [22, 23]. The final analysis of this landmark study recently reported a median OS of

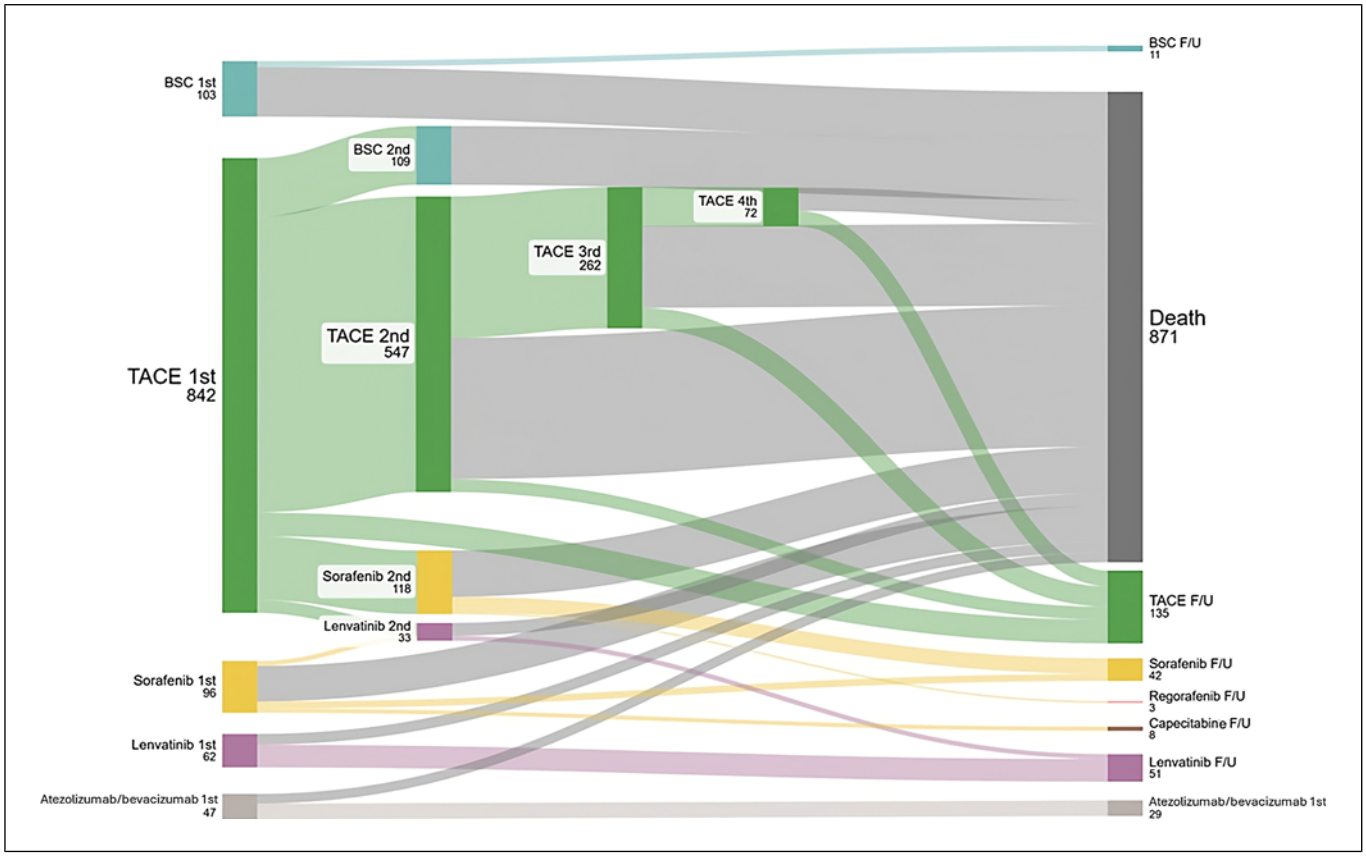


Fig. 5. Sankey diagram illustrating patient treatment sequences and outcomes. The diagram depicts the transitions between various lines of treatment and follow-up (F/U) treatments among patients. The widths of the flows represent the number of patients transitioning between treatments or progressing toward death. The total number of patients at each treatment stage or outcome (death) is indicated numerically.

33.8 months, a 12-month OS of 84.7%, and an OR rate of 24.3% by RECIST 1.1 criteria, all data that compare quite favourably with those observed in our study for patients treated with atezolizumab/bevacizumab: an OS of 46.2 months, a 12-month OS of 88.0%, and an OR rate of 24.4% [25]. Noteworthy, our study supports the results obtained in the REPLACEMENT study and further expands their reach by providing an independent validation in a larger, Western population with different ethnic and aetiological background, as patients with viral hepatitis represented 72.3% of patients treated with atezolizumab/bevacizumab in our study and 41.9% of the REPLACEMENT cohort [25].

As far as efficacy of the various treatments is concerned, following IPTW adjustment we observed a significantly higher rate of DC among patients treated with either lenvatinib (67.8%) or atezolizumab/bevacizumab (75.6%) as compared to patients treated with TACE (53.2%). This finding was mainly driven by the significantly higher rate of SD observed in patients treated with atezolizumab/bevacizumab as compared to those undergoing TACE (51.1% vs. 33.8%), and, to a lesser extent, in patients treated with lenvatinib (39.0%). Likely, as a reflection of these oncological results and of the liver function-sparing effect of these systemic therapies, the risk of mortality of patients treated with atezolizumab/bevacizumab was halved as compared to TACE and was decreased, though not significantly, in patients treated with lenvatinib. Overall, these findings resulted in an extended long-term OS in patients treated with atezolizumab/bevacizumab and lenvatinib, with a 24-month survival rate of 70.5% and 68.3%, and a median OS 46.2 and 35.8 months, respectively. Lastly, we observed that – among systemic therapies – sorafenib was not associated with improved outcomes as compared to TACE, with a median OS of 14.2 months, a finding that is in keeping with the results obtained in registration trial of this drug in intermediate-stage

patients (i.e., 14.5 months) [27]. As far as this finding is concerned, in our study, patients treated with TACE had slightly worse liver function (presence of cirrhosis: 95.0% vs. 82.3%; MELD score: 10 vs. 9; mALBI grade 2b–3: 83.2% vs. 64.6%) and slightly more favourable tumoural burden (>3 nodules: 24.3% vs. 45.1%; maximum HCC diameter: 3.4 vs. 6.5 cm) as compared to patients treated with sorafenib, although these differences were equalised in the final analysis by IPTW adjustment. Unfortunately, in our study, the lack of more detailed data regarding dose intensity, treatment duration, and adverse events in patients treated with systemic therapies makes it difficult to determine whether the observed survival differences might have reflected true drug efficacy or differences in tolerability and treatment delivery. Lastly, the absence of detailed data regarding progression-free survival and time-to-tumour progression did not allow us to perform additional efficacy analyses, thus limiting the potential to mitigate OS confounding from post-progression treatments.

We feel that the results provided by our study support, in a treatment hierarchy-based algorithm, the indication to systemic therapy in TACE-unsuitable patients, considering that treatment with atezolizumab/bevacizumab was superior to TACE, and the outcome with lenvatinib can be considered similar – if not slightly better – to the one provided by TACE [28–30]. Moreover, the rates of CR or PR achieved with systemic therapy in this study highlight a potential role for conversion therapy in TACE-unsuitable patients, although actually none of the patients in this cohort underwent curative conversion treatment, as this approach is relatively novel and likely was not considered as a potential option at the time of initial treatment for the patients included in this study [12, 14, 31]. To support this finding, the results of a recent international study that assessed the potential for conversion in 2,379 patients treated with either with lenvatinib or atezolizumab/bevacizumab in the period 2019–2023 showed that despite an OR rate of 24–29%, the overall proportion of patients who might have benefit from conversion to potentially curative treatments was 13–16%, and only 3% of patients actually underwent curative conversion treatment [32]. We feel that these findings, collectively considered, should serve to emphasise the fact that OR does not necessarily translate into conversion curative treatment, but that efforts should be made to raise awareness of considering this potential approach in patients who display an OR to systemic treatment [31].

Although a potential drawback of this study might have been inherent to the inclusion of patients treated in periods where not all the various treatments assessed in the study were contemporaneously available, we carried out a sensitivity sub-analysis in the subpopulation of patients treated in the period 2018–2022, replicating the main analyses performed in the whole cohort. These sub-analyses confirmed the results obtained in the main cohort, with a risk of death significantly halved by treatment with atezolizumab/bevacizumab as compared to TACE, and rates of oncological response that were in keeping with those observed in the whole study population.

Our study did not include patients treated with both TACE and systemic therapy, either lenvatinib or atezolizumab/bevacizumab; therefore, we were not able to assess whether the combination of locoregional and systemic therapy might have provided a further improvement in patients outcome as compared to TACE or systemic therapy alone or a higher rate of potential conversion [14]. Recent studies carried out in patients with similar oncological burden of disease (i.e., up-to-7 out) but less advanced liver disease (e.g., mainly Child-Pugh A5, up to ALBI grade 2b) have shown promising results with the association of TACE plus lenvatinib, although it has to be emphasised that the inclusion in our study of patients with more advanced liver disease makes the comparison of outcomes unpractical [33, 34].

The results of our study further support not only the notion that intermediate-stage HCCs cannot be considered a single entity but also generate evidence-based data in support of the proposed paradigm shift in clinical guidelines treatment indications [35–38]. Indeed, even the most recent iteration of the BCLC classification considers the possibility to treat intermediate-stage patients with systemic therapy rather than with TACE, although it does not report any clinical practice result to support this indication [39]. Our results may add this piece of evidence delineating the patients suitable for this treatment shift and the systemic therapies that might provide the best outcome.

The decision to include in our study a group of TACE-unsuitable patients managed with BSC alone was motivated by the need to assess their outcome so as to provide potential benchmark figures for the present and future studies in this population, as the survival rates generated by real-life analysis serve to assess the therapeutic gain of other treatments, should they become available, in patients with well-defined characteristics, as previously demonstrated [40].

The tenet that TACE has long been considered the treatment of choice in patients with the characteristics of this study population is testified by the finding that most

TACE-treated patients continued with the same treatment modality upon both first and further progression, with only approximately 20% of patients treated with systemic therapy upon first progression [41]. This may also be related to the suggestions provided by the results of registration trials with tyrosine kinase inhibitors, which mainly included patients with macrovascular invasion and/or extrahepatic spread, which translated – in clinical practice – into their main use in patients with these characteristics rather than in intermediate-stage patients [42, 43]. In this regard, our findings also suggest that continuing with TACE upon progression may be further detrimental, as roughly half of these patients died after the second TACE, with just a minority showing long-term benefit. This indication is supported by the landmark analyses of survival at 24 months showing that treatment with TACE was clearly outperformed by treatment with lenvatinib and, even more, with atezolizumab/bevacizumab, which presented the peculiar long-term response of immunotherapy [44]. Moreover, the finding that patients on systemic therapy mostly continued with the same drug rather than being switched to a different agent was likely due to several factors such as the restricted use of second-line treatments in certain jurisdictions and by the real-life evidence that minority of patients progressing under atezolizumab/bevacizumab are shifted to a tyrosine kinase inhibitors, with rather dismal results [45–47].

From a methodological standpoint, we sought to further mitigate confounding bias and to assess the robustness of our findings using complementary approaches. In addition to the IPTW-based analyses, we performed a PSM and the direction and magnitude of the treatment effects in the PSM cohorts were broadly consistent with those observed in the IPTW pseudo-populations, reinforcing the robustness of our conclusions, although the matching procedure inevitably reduced the effective sample size – particularly for patients treated with atezolizumab/bevacizumab – and thus warrants cautious interpretation of these estimates. Furthermore, we calculated E-values for the main treatment contrasts to quantify the potential impact of unmeasured confounding. While residual confounding cannot be entirely excluded, the relatively large E-values for the comparison between atezolizumab/bevacizumab and TACE, and for the excess risk observed with sorafenib, suggest that only unmeasured factors with strong associations with both treatment choice and prognosis could overturn our main findings.

All in all, these findings precluded potential speculations regarding the influence of post-progression treatment on OS, as the vast majority of patients initially treated with TACE continued to be treated with the same modality, and just a minority was switched to an obligated choice of sorafenib as until 2018 this was the only drug available, and after this date the number of patients become small to allow us drawing meaningful conclusions on this issue.

This study has some limitations, beginning with its retrospective, non-randomised nature, and by the fact that the various systemic therapies were not contemporaneously available in clinical practice, thus introducing a potential selection bias. However, we considered this confounding factor in our analyses, matching patients' characteristics using IPTW adjustment, and although this cannot avoid an era-related bias, it can provide results in cohorts with comparable clinical and oncological profiles. Moreover, the sensitivity subanalysis in patients treated in the period of availability of all the systemic therapies (2018–2022) showed complete consistency of the main results, thus supporting the robustness of our findings in the whole cohort. Lastly, we used landmark analyses to assess OS at predefined time points, thus obviating the bias inherent to different follow-up durations of the various treatments. In addition, our analyses focused on OS, while data on progression-free survival, time-to-tumour-progression, and dates of radiologic progression were not systematically collected, which precluded additional efficacy analyses and limits our ability to mitigate OS confounding from post-progression treatments (including atezolizumab/bevacizumab). This may be considered a relevant limitation, and calls for further, prospective studies that necessarily need to take into account progression-free survival and time-to-tumour-progression data, and also the potential impact of post-progression therapies on OS. Moreover, it would also be informative to present longitudinal trajectories of liver function (ALBI grade, Child-Pugh score) to evaluate whether deterioration differs between groups, but serial measurements were not consistently available, thus preventing such analyses in this study. Another limitation of the study derives from the fact that none of our patients received a conversion to curative treatment: in fact, while missed conversion to surgical resection may seem understandable given the initial severe oncological and liver-related characteristics of the population, it does not allow us to explore whether the oncological response figures obtained with systemic therapy can be exploited to further improve patients' prognosis with liver transplantation. Lastly, we have no data on the duration of systemic therapies, dose intensity, dose modifications, treatment discontinuations – including withdrawal of bevacizumab in patients on immunotherapy – or

occurrence and nature of adverse events; therefore, we cannot provide a clear analysis of the impact of these issues on patients' outcome. This, too, represents a relevant limitation of the current study, and calls for caution in interpretation of the results.

In conclusion, the results of this international, multicentre, real-life study carried out in patients with TACE-unsuitable HCC showed that treatment with systemic therapy, and in particular with atezolizumab/bevacizumab, increases the oncological response and improves patients' prognosis as compared to TACE. These results, that need to be confirmed in other patient series, can nevertheless serve to support treatment decisions and further inform HCC treatment algorithms based on therapeutic hierarchy.

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Statement of Ethics

The use of the ITA.LI.CA database for scientific research was approved by the Institutional Review Board of the ITA.LI.CA Coordinating Centre (Approval No. 99/2012/O/Oss), and the study was conducted following the ethical guidelines of the 1975 Declaration of Helsinki. The management of the ITA.LI.CA database conforms to the current Italian legislation on privacy. According to Italian law, patient consent is not required for retrospective data analysis. Nonetheless, all patients provided written informed consent to undergo each diagnostic and therapeutic procedure and to have their clinical data recorded anonymously in the ITA.LI.CA database.

Conflict of Interest Statement

Edoardo G. Giannini acted as a speaker for AbbVie, AstraZeneca, EISAI, Gilead, Roche, and Ipsen; served as an advisor for Ipsen and Gilead; and was a member of the journal's Editorial Board at the time of submission. Mohamed Bouattour received consulting fees from Bayer, MSD, Sirtex Medical, and Roche; served as an advisor for Bayer, MSD, Sirtex Medical, Eisai, AstraZeneca, Ipsen, Servier, Taiho, BMS, and Terumo; and received honoraria for lectures, presentations, and speakers' bureaus from Bayer, Roche, MSD, Sirtex Medical, and AstraZeneca. Clémence Hollande consulted for AbbVie, AstraZeneca, and Roche. Ciro Celsa acted as a speaker for AstraZeneca, Ipsen, Eisai, and MSD; served as an advisor for Eisai and MSD; and received travel support from Roche. Franco Trevisani received research grants from AbbVie, AstraZeneca, Gilead, MSD, and Roche and served as an advisor for EISAI and Roche. Alessandro Vitale was a member of the journal's Editorial Board at the time of submission. Andrea Pasta, Giulia Pieri, Sara Labanca, Simona Marenco, Mario Strazzabosco, Clemence Hollande, Antonio Facciorusso, Paolo Gallo, Angelo Sangiovanni, Fabio Piscaglia, Claudia Campani, Gabriele Missale, Gianpaolo Vidili, Giorgia Ghittoni, Elisa Pinto, Francesco Giuseppe Foschi, Filomena Morisco, Paolo Caraceni, Gianluca Svegliati-Baroni, Francesco Azzaroli, Carlo Saitta, Maurizia Rossana Brunetto, Rodolfo Sacco, Francesca Romana Ponziani, Sara Boninsegna, Gerardo Nardone, Andrea Martini, Andrea Mega, David Sacerdoti, Daniela Magalotti, Maria Di Marco, and Laura Bucci declare no competing interests.

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Author Contributions

Edoardo G. Giannini, Andrea Pasta. Laura Bucci, and Franco Trevisani: contributed to conceptualisation, literature search, figures, study design, data collection, data analysis, and writing the first draft and had access to and verified the data. Giulia Pieri, Sara Labanca, Simona Marenco, Mario Strazzabosco, Mohamed Bouattour, Clémence Hollande, Antonio Facciorusso, Paolo Gallo, Ciro Celsa, Angelo Sangiovanni, Bernardo Stefanini, Claudia Campani, Gabriele Missale, Gianpaolo Vidili, Giorgia Ghittoni, Elisa Pinto, Francesco Giuseppe Foschi, Filomena Morisco, Giacomo Zaccherini, Gianluca Svegliati-Baroni, Francesco Azzaroli, Carlo Saitta, Maurizia Rossana Brunetto, Rodolfo Sacco, Francesca Romana Ponziani, Sara Boninsegna, Gerardo Nardone, Andrea Martini, Andrea Mega, David Sacerdoti, Daniela Magalotti, Mariella Di Marco, and Alessandro Vitale: contributed for resources, investigation, data collection, data analyses, writing – review and editing. All authors approved the final draft submitted.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants. Access to anonymised patient-level data is restricted to participating site staff who are registered and approved by the Institutional Review Boards. Aggregated data outputs, however, are available from Edoardo G. Giannini and Andrea Pasta upon reasonable request and with permission from the Data Review Boards of the ITA.LI.CA consortium (egiannini@unige.it; laura.bucci2@unibo.it).

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