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Efficacy of atezolizumab–bevacizumab combination therapy early after recurrence of hepatocellular carcinoma following resection or ablation with a curative intent

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Abstract

Background The pattern of hepatocellular carcinoma (HCC) recurrence after resection/ablation is intrahepatic and/or systemic. The efficacy of atezolizumab–bevacizumab treatment as early therapy after recurrence has not been extensively evaluated.

Methods We evaluated 32 patients (group A) with early HCC recurrence after resection/ablation and 24 patients (group B) initially diagnosed as Barcelona Clinic Liver Cancer (BCLC)-C, all treated with atezolizumab–bevacizumab. Group A was subdivided in group A1 (progression to BCLC-C, n=14) and group A2 (progression to BCLC-B, n=18).

Results Groups A1/A2 were comparable for all baseline parameters. Objective response was observed in 14.3% and 33.3% of patients in groups A1 and A2, respectively. Median overall survival (OS) was impressive and comparable between the 2 groups (22 and 26 months, respectively, P=0.71), as was median progression-free survival (PFS) (15 and 6 months, respectively, P=0.126). Patients categorized in the advanced stage (groups A1/B) were comparable for all baseline characteristics. Median OS was significantly higher in group A1 compared to B (26 vs. 6 months, P<0.001), as was median PFS (6 vs. 3 months, P=0.086).

Conclusions Early initiation of atezolizumab–bevacizumab after recurrence following curative therapy results in impressive survival rates, irrespective of recurrence pattern. Survival of atezolizumab–bevacizumab treated patients who were initially diagnosed in the BCLC-C stage is significantly different from those who recurred to BCLC-C following potentially curative therapies.

Keywords Hepatocellular carcinoma, recurrence, resection, ablation, atezolizumab–bevacizumab

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Conflict of Interest: None

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Introduction

Liver cancer is the sixth most common cancer worldwide and the fourth leading cause of cancer-related mortality [1]. Hepatocellular carcinoma (HCC) accounts for most liver cancer cases and frequently has a dismal prognosis [2,3]. Most cases of HCC are diagnosed in the intermediate and advanced stages, where curative interventions are not feasible [3]. Therefore, early diagnosis is crucial, as it guarantees the applicability of potentially curative procedures. Nevertheless, even in patients with early HCC treated with a curative intent, recurrence rates after liver resection (LR) or radiofrequency ablation (RFA) range from 50-70% within the first 5 years [4,5].

The pattern of HCC recurrence after curative procedures has been associated with survival outcomes [6,7]. Following

LR, 2 distinct recurrence patterns have been recognized: extrahepatic recurrence (ER) and intrahepatic recurrence (IR) [8]. ER frequently presents with pulmonary nodules and is typically associated with worse survival, whereas IR can be subdivided into intrahepatic metastasis (IM), which typically presents within the first 2 years, and multicentric occurrence (MO), which is typically driven by *de novo* carcinogenesis (with new lesions having different clonality) and commonly results in higher survival rates [8,9]. Early HCC recurrence post-LR/RFA is defined in the current literature as the appearance of recurrent disease within 2 years after LR/RFA [7,8,10,11].

The Barcelona Clinic Liver Cancer (BCLC) HCC staging system is currently the most accepted classification system, and links tumor stage with prognosis and the ideal first-line therapeutic strategy [12]. According to the currently revised BCLC algorithm, systemic treatment is proposed for BCLC-C patients with either extrahepatic disease (EHD) or macrovascular invasion (MVI), as well as in patients with diffuse, massive or infiltrative intrahepatic spread not amenable to locoregional treatment [13]. The proposed first-line systemic treatment is either atezolizumab–bevacizumab or tremelimumab–durvalumab, based mainly on results from the registrational IMBRAVE150 and HIMALAYA trials, respectively [14,15]. These trials recruited a significant proportion of patients who had been previously treated with LR or RFA and had obviously progressed subsequently to a more advanced stage. Whether the general prognosis and the efficacy of immunotherapy in these patients are similar to those in patients initially diagnosed and treated in the advanced HCC stage, is still debated in the current literature.

Recently, the IMBRAVE050 study showed positive preliminary results in the adjuvant setting with the use of atezolizumab–bevacizumab post-LR/RFA [16]. However, data on overall survival (OS) are still premature, and more results from this study are eagerly awaited in the future. Moreover, the efficacy of atezolizumab–bevacizumab treatment after the diagnosis of early HCC recurrence in resected or ablated patients has not been yet evaluated. The aim of this study was to evaluate the efficacy of atezolizumab–bevacizumab treatment in patients with early diffuse multinodular intrahepatic or extrahepatic HCC recurrence following LR or RFA with a curative intent, compared to those initially diagnosed and treated in the advanced stage.

Patients and methods

We conducted a retrospective study of patients from a single HCC referral center in Greece. The study included 56 patients with intermediate or advanced stage HCC who received first-line systemic treatment with the atezolizumab–bevacizumab combination between January 2021 and April 2024.

For all patients, demographic data were collected on the first day of immunotherapy infusion, together with clinical, laboratory and imaging data. More specifically, we collected data on sex, age, body mass index (BMI), diabetes, albumin–bilirubin (ALBI) grade [17], MVI, EHD, α-fetoprotein (aFP) values, morphomolecular characteristics according to HCC histology, as well as presence of cirrhosis or varices. BCLC stage was assessed at the time of immunotherapy initiation, using the most recent 2022 classification, according to tumor burden, liver function and performance status (PS), assessed using the Eastern Cooperative Oncology Group (ECOG) scale [18]. Patients with MVI and/or EHD were stratified as BCLC-C. HCC etiology was categorized as viral or non-viral, according to the presence or absence of chronic viral hepatitis (HBV or HCV). All patients with active HCV and HBV infection had to have received prior treatment and achieved non-detectable HCV-RNA and HBV-DNA, respectively, before treatment initiation.

Liver histology was assessed for all patients to study tumor characteristics, as well as the presence or absence of concomitant cirrhosis. Liver biopsy was performed in all patients who underwent RFA at the same time as the procedure, while the histology of all patients who underwent LR was studied on the surgical specimen. All patients who were initially diagnosed in the advanced stage and received immunotherapy without prior LR/RFA had a histological diagnosis using imaging guided biopsy before the initiation of immunotherapy. All HCCs were further categorized according to the morphomolecular classification, as proliferative or non-proliferative [19]. Proliferative subgroup HCCs frequently expressed TP53 mutations, were aFP-high, and mostly HBV-related, while non-proliferative subgroup HCCs were characterized by β-catenin mutations, mostly appeared with a steatohepatic or HCV background, and rarely expressed high aFP values. In addition, the presence of cirrhosis was assessed histologically at the same time in all patients. Upper gastrointestinal endoscopy assessed the presence or absence of clinically significant portal hypertension and the presence of varices during the last 6 months before the start of immunotherapy.

A total of 56 patients with locally advanced and/or metastatic HCC who received first-line systemic treatment with atezolizumab–bevacizumab were initially separated into 2 groups. Group A included 32 patients who had previously undergone LR or RFA and experienced early HCC recurrence in advanced BCLC-B or BCLC-C stage (within 2 years from the procedure), while group B patients were initially diagnosed in the BCLC-C stage and received immunotherapy without receiving prior non-systemic therapy or any other kind of therapy. Early HCC recurrence was defined, according to the existing literature, as the appearance of recurrent disease within 2 years after LR/RFA. Group A patients were further subdivided in 2 groups: A1 and A2. Group A1 included 14 patients with early recurrence in the advanced stage (BCLC-C), mainly histologically documented extrahepatic pulmonary or bone disease, and/or MVI, while group A2 included 18 patients who

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had early HCC recurrence with diffuse multifocal disease not amenable to locoregional therapies or resection. In the first part of the study, groups A1 and A2 (patients with different HCC recurrence patterns) were compared according to their baseline characteristics, treatment response and survival rates, and in the second part, groups A1 and B (patients with established advanced HCC according to BCLC system) were compared with regard to the same parameters.

Patients who had received prior non-systemic treatment had to have undergone LR or RFA and subsequently been on a stable 3-month surveillance program. Once recurrence was diagnosed, it had to be in the advanced stage (BCLC-C) or in the progressed intermediate stage (BCLC-B), where the HCC burden would not permit further locoregional treatment or redo hepatectomy. Immunotherapy with atezolizumab–bevacizumab was initiated as soon as HCC recurrence was observed, in the form of a stable regimen of 1200 mg intravenous atezolizumab combined with 15 mg per kilogram of intravenous bevacizumab every 21 days. All patients had to have received at least 3 consecutive treatment cycles and had a follow up of at least 2 months, including at least 1 radiological tumor assessment. The latter was performed in all patients, using computed tomography or magnetic resonance imaging every 3 treatment cycles, and the response was assessed using the mRECIST criteria for HCC [20].

An informed consent form was collected from all living patients who participated in this retrospective study at the time of treatment initiation and study recruitment period. The study protocol was based on the Declaration of Helsinki for human trials and received approval from the Ethics Committee and the Scientific Board of the "Agioi Anargyroi" General Oncology Hospital of Kifisia, Athens, Greece.

Statistical analysis

Analysis was conducted using the IBM SPSS Statistics software (IBM SPSS statistics for Windows, Version 29.0.2.0, Armonk, NY: IBM Corp.). We present numerical values using mean ± standard deviation and categorical values using numbers and percentages. Comparison between different groups was done using the independent samples *t*-test for numerical values, while the chi-square test was used for categorical values. Survival analysis was done using the Kaplan-Meier curves for OS and progression-free survival (PFS) and the log-rank test was used for comparisons. P-values lower than 0.05 were considered statistically significant.

Results

Of the 56 patients, 45 were males (78.9%), 19 had diabetes (33.9%), 24 had viral (42.8%), and 32 had non-viral HCCs (57.2%), 29 were ALBI-I (51.8%), 27 were ALBI-II (48.2%), 22 had aFP ≥400 ng/mL (39.3%), 26 were categorized as proliferative (46.4%), and the remaining 30 as non-proliferative (53.6%) histological disease. Cirrhosis presented histologically in 29 patients (51.8%), while varices were observed in 15 patients (26.8%). From patients categorized as BCLC-C (groups A1 and B, n=38 patients) at immunotherapy initiation, 20 presented with MVI (52.6%) and 21 patients (55.3%) were diagnosed with EHD. The median time of observation was 11 months, and the median number of treatment cycles received was 8. The mean age of the whole study population was 66.1±11.18 years and the mean BMI was 27.3±4.9 kg/m^2. Group A1 and A2 patients, who had undergone prior LR/RFA, included a total of 32 patients (14 in group A1 and 18 in group A2), of whom 14 (43.8%) had undergone prior LR (6/14 [42.9%] in group A1 and 8/18 [44.4%] in group A2), and the remaining 18 participants (56.2%) had undergone prior RFA (8/14 [57.1%] in group A1 and 10/18 [55.6%] in group A2).

The median OS of the total population was 11 months and the median PFS was 6 months, while an objective response was observed in only 8 of the 56 patients (14.3%). One-, 2- and 3-year survival was observed in 44.6%, 17.9% and 7.1% of patients, respectively. Concerning safety, the most common side-effects were hypothyroidism (18/56, 32.1%) and hypertension (17/56, 30.4%), while other side-effects included non-gastrointestinal bleeding (11/56, 19.6%), proteinuria (10/56, 17.9%), acute kidney injury (9/56, 16.1%), gastrointestinal bleeding (7/56, 12.5%), diarrhea (6/56, 10.7%), and others (11/56, 19.6%). Liver decompensation was observed in 8 treated patients (14.3%) during the observational period. Grade 3 or 4 side-effects, which eventually led to discontinuation of immunotherapy, were reported in 11/56 patients (19.6%).

Patients with early recurrence post-LR/RFA according to recurrence pattern

We initially compared all patients who underwent prior LR/RFA (group A) according to the pattern of progression after early HCC recurrence. These patients (n=32) were further subdivided into 2 groups. Group A1 included patients with progression to the advanced HCC stage following recurrence, according to the updated BCLC staging system (BCLC-C, n=14). Of these 14 patients, 7 presented with MVI and 8 had histological confirmed EHD (3 with bone, 3 with lung, 1 with adrenal, and 1 with lymph node metastasis). Group A2 included early recurred patients who progressed to the intermediate stage with diffuse multinodular intrahepatic spread not amenable to further locoregional or surgical therapies (n=18). All patients were treated with atezolizumab–bevacizumab therapy and the 2 groups were compared for their baseline characteristics, response to treatment and survival. The median number of atezolizumab–bevacizumab cycles was 11 for group A1 and 13.5 for group A2 patients (P=0.749). Baseline characteristics of the 2 groups are presented in Table 1. As we can see, the 2 groups were completely comparable for all baseline parameters evaluated. Regarding treatment response, objective responses were more frequently observed in patients who were categorized as progressed BCLC-B stage (6/18, 33.3%) compared to BCLC-C staged patients (2/14, 14.3%), but these results did

Table 1 Baseline characteristics of patients treated with atezolizumab–bevacizumab who had early recurrence after prior LR/RFA according to the pattern of recurrence

Characteristics	Group A1 Early recurrence in BCLC-C stage after prior LR/RFA *(N=14)*		Group A2 Early recurrence in BCLC-B stage after prior LR/RFA *(N=18)*		*P*-value
	N	%	N	%	
Sex					0.244
Male	13	92.9	14	77.8	
Female	1	7.1	4	22.2	
Age (mean, SD)	69.7 (mean)	11.2 (SD)	65.8 (mean)	7.4 (SD)	0.267
BMI (kg/m^2) (mean, SD)	27.6 (mean)	4.4 (SD)	27.7 (mean)	5.2 (SD)	0.950
Diabetes					0.854
No	9	64.3	11	61.1	
Yes	5	35.7	7	38.9	
ALBI					0.821
Grade 1	8	57.1	11	61.1	
Grade 2	6	42.9	7	38.9	
aFP					0.888
<400	9	64.3	12	66.7	
≥400	5	35.7	6	33.3	
Proliferative					0.476
No	6	42.9	10	55.6	
Yes	8	57.1	8	44.4	
Cirrhosis					0.198
No	7	50	13	72.2	
Yes	7	50	5	27.8	
Varices					0.095
No	9	64.3	16	88.9	
Yes	5	35.7	2	11.1	
mRECIST	2				0.217
OR	12	14.3	6	33.3	
Non-OR		85.7	12	66.7	

BCLC, Barcelona Clinic Liver Cancer classification; LR, liver resection; RFA, radiofrequency ablation; SD, standard deviation; BMI, body mass index; OR, objective response

not reach statistical significance (P=0.217). Fig. 1, 2 present Kaplan-Meier curves for the OS and PFS of these 2 groups, respectively. Median OS for group A1 was 26 months, slightly better than that of group A2 patients (22 months), but there was no statistically significant difference between the survival of the 2 groups (P=0.710). Median PFS was numerically better in group A2 compared to group A1 (15 vs. 6 months), but the difference was not statistically significant (P=0.126). For group A1 patients the 1-year, 2-year and 3-year survival rates were 64.3%, 42.8% and 7.1%, respectively, while for group A2 the corresponding survival rates were 61.1%, 33.3% and 16.7%, respectively.

Early recurrence to BCLC-C after prior LR/RFA compared to BCLC-C without prior LR/RFA

We then studied 38 patients classified as BCLC-C at initiation of immunotherapy, including group A1 patients (n=14) who received prior surgical or locoregional therapy and rapidly recurred to BCLC-C, and group B patients (n=24) who were initially diagnosed and treated in the BCLC-C stage. Of the 24 group B patients, 11 (45.8%) had MVI and 12 presented with EHD (7 with lung and 5 with bone metastasis). Baseline characteristics of the 2 groups are shown in Table 2. Of a total of 20 patients with MVI, 18 (90%) presented with PVT and the remaining 2 (10%) with invasion of the inferior *vena cava*. Groups A1 and B were comparable regarding all baseline parameters. In these patients, objective responses were rarely reported in both groups: in only 2/14 patients of group A1 compared to none in group B (P=0.056). Survival curves are presented in Fig. 3, 4 for OS and PFS, respectively. As we can see in Fig. 3, patients who presented in BCLC-C early after prior LR/RFA had significantly better median OS than patients who presented in BCLC-C initially (26 vs. 6 months, respectively, P<0.001). We performed Cox regression analysis with all the baseline parameters for OS, and the multivariate analysis showed statistically significant values for male sex

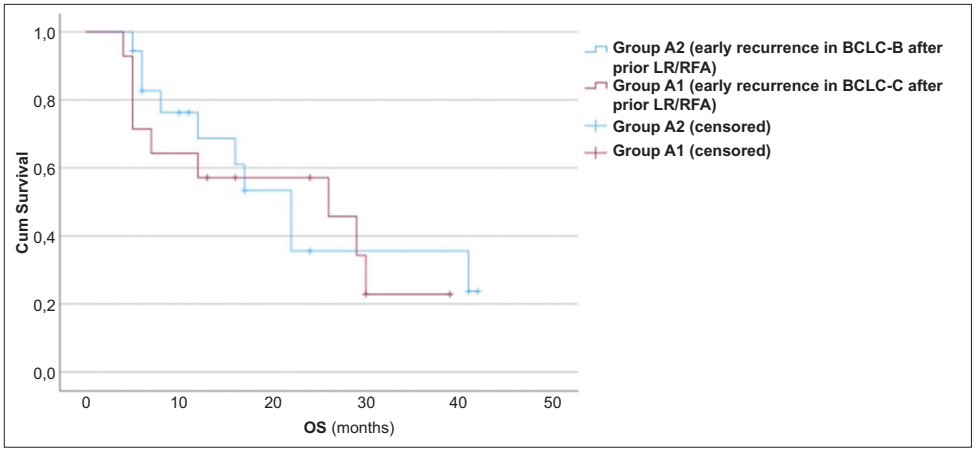

Figure 1 Median OS in groups A1 and A2. Group A1: early recurrence in BCLC-C after prior LR/RFA, Group A2: early recurrence in BCLC-B after prior LR/RFA

OS, overall survival; BCLC, Barcelona Clinic Liver Cancer classification; LR, liver resection; RFA, radiofrequency ablation

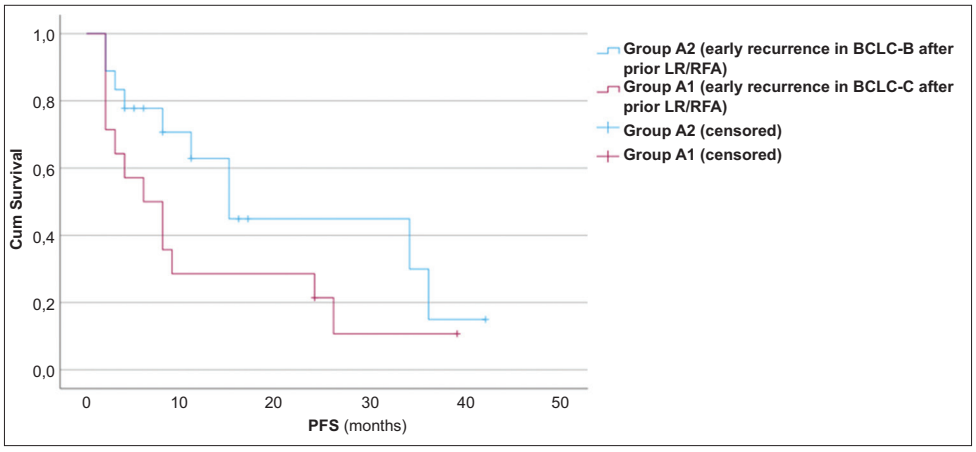

Figure 2 Median PFS in groups A1 and A2. Group A1: early recurrence in BCLC-C after prior LR/RFA, Group A2: early recurrence in BCLC-B after prior LR/RFA

PFS, progression-free survival; BCLC, Barcelona Clinic Liver Cancer classification; LR, liver resection; RFA, radiofrequency ablation

(hazard ratio [HR] 8.3, 95% confidence interval [CI] 1.721-40.137; P=0.008) and PS-1 vs. PS-0 (HR 5.215, 95%CI 1.272-21.384; P=0.022). In addition, median PFS tended to be better in patients who had systemic recurrence compared to initially staged BCLC-C patients (6 vs. 3 months, respectively, P=0.086). In Cox regression analysis for PFS, only ALBI grade showed statistically significant values (HR 7.133, 95%CI 1.817-27.997; P=0.005). In line with the worse survival of group B patients, these patients received a median of 4.5 cycles of immunotherapy, compared to 13.5 cycles in group A1 patients. Interestingly, survival rates for patients in group B were as low as 16.6% in the first year and 0% in the second year.

Discussion

The atezolizumab–bevacizumab combination is currently the standard of care in patients with advanced HCC (BCLC-C) or in those with diffuse, multinodular, massive intrahepatic disease who are ineligible or unfit for locoregional procedures. Median OS in atezolizumab–bevacizumab treated patients is 19 months according to the registrational IMBRAVE150 study, and approximately 15 months according to real-world data (A-B real study), whereas objective responses are observed in less than a third of treated patients [14,21]. In our small real-life study, median OS was slightly lower compared to other large real-world studies, but was impressively high (22-26 months) in patients who experienced early HCC recurrence with systemic or massive diffuse multinodular intrahepatic disease after resection or ablation with a curative intent. To our knowledge, this is the first study to evaluate the efficacy of atezolizumab–bevacizumab treatment in this special group of patients with unresectable disease, who are not amenable to further locoregional or surgical treatment.

It is well known that early HCC recurrence significantly affects survival rates, so the prevention of recurrence represents a major issue in the management of HCC patients at early

Table 2 Baseline characteristics of patients treated with atezolizumab–bevacizumab who were categorized as advanced BCLC stage (BCLC-C) at initiation of immunotherapy according to prior LR/RFA

Characteristics	Group B Initially BCLC-C stage without prior LR/RFA *(N=24)*		Group A1 Early recurrence in BCLC-C stage after prior LR/RFA *(N=14)*		*P*-value
	N	%	N	%	
Sex					0.171
Male	18	75	13	92.9	
Female	6	25	1	7.1	
Age (mean, SD)	63.7(mean)	12.6 (SD)	65.8 (mean)	7.4 (SD)	0.570
BMI (kg/m^2) (mean, SD)	26.8 (mean)	5.2 (SD)	27.7 (mean)	5.2 (SD)	0.599
Diabetes					0.675
No	17	70.8	9	64.3	
Yes	7	29.2	5	35.7	
Etiology					0.859
Viral	13	54.2	8	57.1	
Non-viral	11	45.8	6	42.9	
ALBI					0.357
Grade 1	10	41.7	8	57.1	
Grade 2	14	58.3	6	42.9	
MVI					0.804
No	11	45.8	7	50	
Yes	13	54.2	7	50	
EHD					0.859
No	11	45.8	6	42.9	
Yes	13	54.2	8	57.1	
PS					0.117
0	6	25	7	50	
1	18	75	7	50	
aFP					0.542
<400	13	54.2	9	64.3	
≥400	11	45.8	5	35.7	
Proliferative					0.357
No	14	58.3	6	42.9	
Yes	10	41.7	8	57.1	
Cirrhosis					0.199
No	7	29.2	7	50	
Yes	17	70.8	7	50	
Varices					0.881
No	16	66.7	9	64.3	
Yes	8	33.3	5	35.7	
mRECIST					0.056
OR	0	0	2	14.3	
SD	4	16.7	0	0	
PD	20	83.3	12	85.7	

BCLC, Barcelona Clinic Liver Cancer classification; LR, liver resection; RFA, radiofrequency ablation; SD, standard deviation; BMI, body mass index; ALBI, albumin–bilirubin; MVI, macrovascular invasion; EHD, extrahepatic disease; PS, performance status; OR, objective response; SD, stable disease, PD; progressive disease

stages of the disease [22]. The atezolizumab–bevacizumab combination treatment as an adjuvant procedure in patients at high risk of recurrence seems to significantly increase recurrence-free survival compared to active surveillance, but data on overall survival are still lacking. Moreover, in the IMBRAVE050 study there was a significant crossover of patients under active surveillance who received atezolizumab–bevacizumab treatment after recurrence confirmation, a factor that could possibly impact overall survival rates [16]. Another significant issue could be the beneficial effect of early treatment

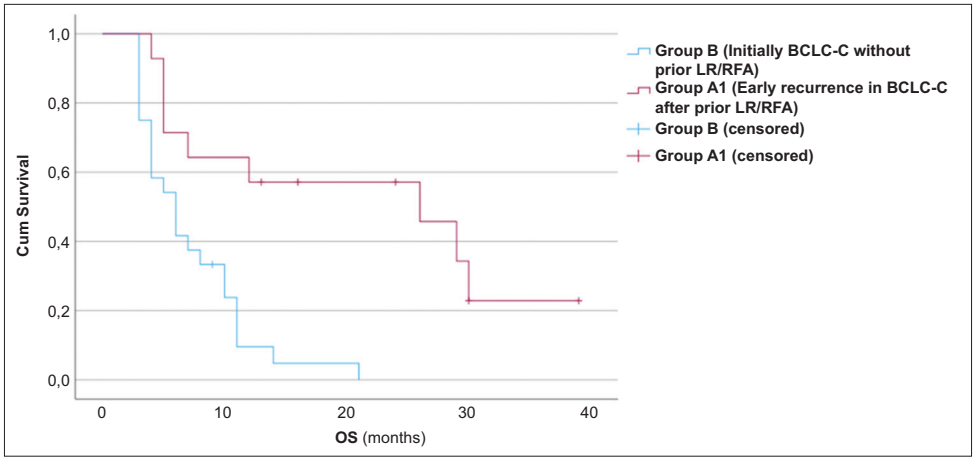

Figure 3 Median OS in groups A1 and B. Group A1: early recurrence in BCLC-C after prior LR/RFA, Group B: initially BCLC-C without prior LR/RFA
OS, overall survival; BCLC, Barcelona Clinic Liver Cancer classification; LR, liver resection; RFA, radiofrequency ablation

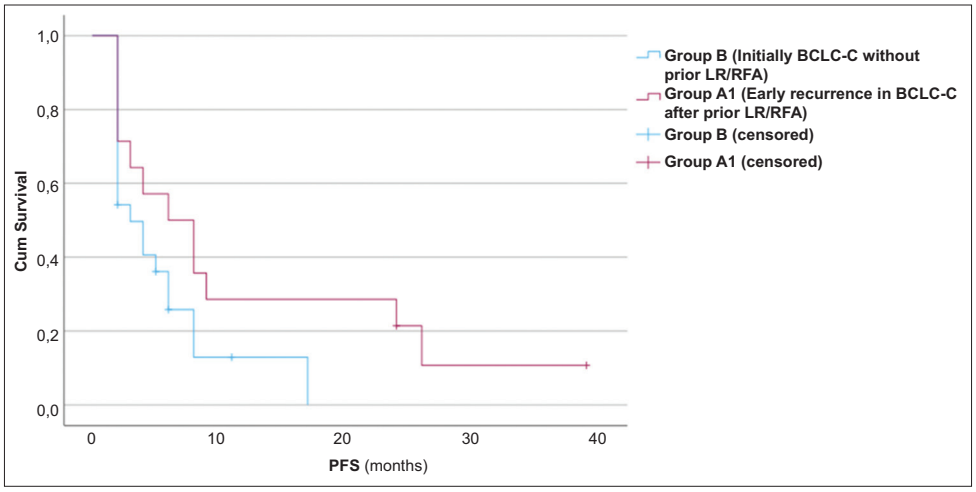

Figure 4 Median PFS in groups A1 and B. Group A1: early recurrence in BCLC-C after prior LR/RFA, Group B: initially BCLC-C without prior LR/RFA
PFS, progression-free survival; BCLC, Barcelona Clinic Liver Cancer classification; LR, liver resection; RFA, radiofrequency ablation

initiation after recurrence confirmation in patients under active surveillance, considering the unknown and possibly unpredicted efficacy of atezolizumab–bevacizumab treatment in recurred patients who received the same combination as adjuvant therapy [23]. It is noteworthy that approximately a third of patients at high risk of recurrence recurred even after atezolizumab–bevacizumab adjuvant therapy, according to the IMBRAVE050 study (100/334 patients, 29.9%), so retreatment of patients who have been previously exposed to immunotherapy could be an issue in our future clinical practice.

Early HCC recurrence after LR or RFA with curative intent results in lower survival rates compared to patients with late recurrence, and of course those without recurrence. Moreover, 3-year survival rate was approximately 71% in patients with early intrahepatic recurrence following resection, managed mainly with locoregional treatments, according to a large study [24], whereas data concerning patients with extrahepatic recurrence are scarce. A recent study suggests that postoperative adjuvant transarterial chemoembolization plus immunotherapy offers survival benefit in patients with huge HCC (above 10 cm in diameter) following resection [25]. Our previous experience confirmed that median OS was only 9 months in patients treated with tyrosine kinase inhibitors who showed disease recurrence in advanced stages following LR or RFA [26]. An interesting result of the present study is the comparable high median OS (22-26 months) in patients with disease recurrence, irrespective of the pattern of recurrence (diffuse intrahepatic or extrahepatic), despite the relatively low objective response rates observed (33.3% and 14.3%, respectively). It is important to note that most of these patients were non-cirrhotic (20/32, 62.5%) and without clinically significant portal hypertension (25/32, 78.1%), as confirmed by absence of varices in upper gastrointestinal endoscopy, baseline characteristics that could significantly influence overall survival. On the other hand, the high median PFS observed especially in patients with advanced extrahepatic recurrent disease (15 months) suggests that early initiation of atezolizumab–bevacizumab combination

treatment could have an important impact on disease control in these patients. We are eagerly awaiting the overall survival rates in patients included in the IMBRAVE050 study and other large-scale studies to confirm our preliminary results.

HCC is considered as an inflammation-related cancer type, as most of cases result from prolonged and unresolved chronic liver injury of various etiologies and develop on a cirrhotic or significantly fibrotic background [27]. Several studies have suggested that liver fibrosis and cirrhosis negatively impact the tumor microenvironment through various mechanisms, and limit immunosurveillance, resulting in tumor invasion and progression [27-29]. The beneficial reshaping of the tumor microenvironment with prior locoregional or surgical therapy has been suggested in many recently published studies, and trials evaluating combinations of these procedures with immunotherapy are already ongoing [28]. The significant survival benefit observed in our group of patients with advanced HCC after early recurrence following resection or ablation, compared to patients initially diagnosed and equally managed in the advanced BCLC-C stage, could be partially explained by the possible effect of prior surgical/locoregional treatment on tumor microenvironment reshaping and a shift towards an immune-friendly environment before the initiation of immunotherapy. This result should be further re-evaluated in large scale, prospectively designed studies, considering the relatively small sample size of our study population and the retrospective nature of the study, although the 2 groups were comparable according to all the clinical, biochemical and histological parameters that could negatively affect survival, as shown in Table 2.

The BCLC classification categorizes HCC patients with EHD, MVI and/or impaired PS in the BCLC-C stage, implying a short median OS (less than 8 months) in untreated patients. The initial BCLC staging system was proposed to categorize mainly cirrhotic patients with concurrent HCC, and the prognosis of these patients categorized in the advanced stage was poor, especially in the absence of effective systemic treatments at that time. Nowadays, the BCLC staging system is used in the vast majority of registrational trials that evaluate the efficacy of systemic treatment for advanced unresectable HCC, irrespective of the cirrhotic/non-cirrhotic status and the progression pattern of HCC to advanced stage, especially in previously resected or ablated patients, who frequently present acceptable liver function and absence of clinically significant portal hypertension. The median survival observed in patients initially staged as BCLC-C and treated with atezolizumab–bevacizumab combination treatment was very low (6 months) and significantly lower compared to that observed in patients who recurred to the advanced stage following LR or RFA (26 months), according to the results of our study. Despite the numerically higher number of cirrhotic patients in the first group (71% vs. 50%) the 2 groups were comparable as regards all baseline parameters evaluated, especially those that could negatively influence survival rates (MVI, EHD, ALBI grade, presence of varices, proliferative histological status). In this respect, the BCLC staging system may not be the ideal system for restaging patients with EHD recurrence and/or MVI following treatment with a curative intent, as the prognosis of these patients seems to differ significantly from those initially diagnosed in the advanced stage [30]. The great heterogeneity of BCLC-C patients, regarding the pattern of progression to the advanced stage, may have had an impact on the median OS outcomes observed [31]. Future trials should probably separate patients with advanced HCC according to the pattern of progression to the advanced stage and previous non-systemic therapies offered, as the survival curves of these subpopulations seem to differ significantly from one another [32].

As expected, 70.8% of HCC patients initially diagnosed and treated at the BCLC-C stage were cirrhotic, and 75% presented with impaired performance status (PS-1), compared to 50% of HCC patients who recurred to BCLC-C stage following LR/RFA, for both parameters, as presented in Table 2. Despite the statistically non-significant differences observed, it is well known that liver disease severity drives survival in patients with advanced HCC [33], whereas PS-1 status (vs. PS-0) was significantly correlated with worse survival in the multivariate analysis, among the whole group of BCLC-C HCC patients treated with atezolizumab–bevacizumab. Symptomatic disease and/or cirrhotic background, as well as the presence of MVI, significantly impact survival, in contrast to mild symptomatic or asymptomatic extrahepatic disease/metastasis (lung, bone, lymph nodes, adrenal, etc.), especially in the context of a non-cirrhotic liver background, despite the current categorization of all these patients in the advanced BCLC-C stage in the literature.

The current study has some limitations that should be mentioned. The 3 groups of our study each had a small number of patients, which could possibly lead to biases, combined with the retrospective analysis of the data. In our study, we observed that almost half of the patients (27/56, 48.2%) were categorized as non-cirrhotic, which is in contrast to the quite high proportion (approximately 80%) of cirrhosis presence in HCC patients that is traditionally reported [34]. This could be a result of the altering epidemiology of HCC, as more and more patients with metabolic associated fatty liver disease, which tends to be the leading cause of chronic liver disease in western countries, are diagnosed with HCC in non-cirrhotic livers [35]. Furthermore, the study was conducted in a single HCC referral center of an Oncology Hospital, where the percentage of cirrhotic patients with HCC may be lower than those expected from other hepatology departments that surveilled cirrhotic patients for HCC.

In conclusion, early initiation of atezolizumab–bevacizumab combination treatment, after recurrence diagnosis following therapy with a curative intent, could result in high survival rates, irrespective of the pattern of recurrence. Restaging these patients according to BCLC staging system does not correlate with an accurate prognosis, as they respond significantly better to currently proposed first-line systemic therapeutic approaches, compared to classic patients who are initially diagnosed and treated in the advanced stages.

Summary Box

What is already known:

- Early diffuse intrahepatic or extrahepatic recurrence of hepatocellular carcinoma (HCC) after resection or ablation limits survival benefit
- Patients with extrahepatic HCC recurrence or macrovascular invasion after resection or ablation, as well as patients who presented with the same features initially, are currently categorized as Barcelona Clinic Liver Cancer (BCLC)-C and all treated with systemic treatment
- Atezolizumab-bevacizumab efficacy in BCLC-C stage has not been studied separately in patients who progressed to this stage after early recurrence following resection or ablation

What the new findings are:

- Atezolizumab–bevacizumab treatment after early HCC recurrence, could significantly extend survival rates, irrespective of the pattern of progression
- Patients treated with atezolizumab–bevacizumab, initially diagnosed in the BCLC-C stage, seem to have impressively worse survival than those who migrated to BCLC-C as a result of early recurrence after surgery or ablation
- The BCLC algorithm probably does not accurately predict clinical outcomes of previously resected or ablated HCC patients with early disease recurrence to the advanced stages

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