Real-World Data for Atezolizumab Plus Bevacizumab in Unresectable Hepatocellular Carcinoma: How Does Adherence to the IMbrave150 Trial Inclusion Criteria Impact Prognosis?

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Abstract

Background Atezolizumab plus bevacizumab has recently been approved as a new first-line standard of care for patients with unresectable hepatocellular carcinoma (HCC).

Objective We performed a real-world study to evaluate the impact of the IMbrave150 trial inclusion criteria on the safety and efficacy of treatment outside of clinical trials.

Methods We analyzed patients treated with atezolizumab plus bevacizumab for unresectable HCC from four different countries. No specific inclusion and exclusion criteria were applied, except for the absence of previous systemic therapies for HCC. The entire population was split into two groups according to concordance with the inclusion criteria as reported in the IMbrave150 trial in 'IMbrave150-in' and 'IMbrave150-out' patients, and safety and efficacy in the two groups of patients were evaluated.

Results Overall, 766 patients were included in the analysis: 561/766 (73%) in the 'IMbrave150-in' group and 205/766 (27%) in the 'IMbrave150-out' group. Median overall survival (OS) and median progression-free survival (PFS) were 16.3 versus 14.3 months (hazard ratio [HR] 0.48, 95% confidence interval [CI] 0.35–0.65; $p < 0.0001$] and 8.3 versus 6.0 months (HR 0.79, 95% CI 0.63–0.99; $p = 0.0431$) in 'IMbrave150-in' and 'IMbrave150-out' patients, respectively. Multivariate analysis confirmed that patients included in the 'IMbrave150-in' group had significantly longer OS compared with patients included in the 'IMbrave150-out' group (HR 0.76, 95% CI 0.47–0.97; $p = 0.0195$). In 'IMbrave150-in' patients, the albumin-bilirubin (ALBI) grade was not associated with OS, whereas in 'IMbrave150-out' patients, those with ALBI grade 1 reported a significant benefit in terms of OS compared with those with ALBI grade 2 (16.7 vs. 5.9 months; HR 4.40, 95% CI 2.40–8.08; $p > 0.0001$). No statistically significant differences were reported in the 'IMbrave150-in' and 'IMbrave150-out' groups in terms of safety profile.

Conclusion Adherence to the IMbrave150 trial inclusion criteria favorably impacts the prognosis of patients receiving atezolizumab plus bevacizumab. Among patients who did not meet the IMbrave150 inclusion criteria, those with ALBI grade 1 could benefit from the treatment.

1 Introduction

Hepatocellular carcinoma (HCC) constitutes the sixth most common cancer and the third leading cause of cancer death worldwide [1]. Tyrosine kinase inhibitors (TKIs) had remained the cornerstone of the treatment of advanced and intermediate HCC not suitable for locoregional therapy for many years. Sorafenib was the first TKI approved as first-line therapy, and it remained the only therapeutic option for more than 10 years based on the results of two large randomized controlled trials [2, 3]. The REFLECT trial demonstrated the non-inferiority in terms of overall survival (OS) of another TKI, lenvatinib, compared with sorafenib as a first-line treatment option for unresectable disease, and a superiority of lenvatinib has been highlighted in terms of secondary outcomes, including progression-free survival (PFS), objective response rate (ORR), and time to progression (TTP) [4]. Several real-word retrospective analyses corroborated a possible superiority of lenvatinib in terms of efficacy and tolerability [5–10]. Recently, immunotherapy has proven to be effective in the treatment of unresectable HCC. After disappointing results from randomized controlled trials of immunotherapy as monotherapy [11, 12], significant practice-changing results came from the IMbrave150 trial, which investigated the combination of the anti-programmed death ligand-1 (anti-PD-L1) atezolizumab with the monoclonal antibody directed against the vascular endothelial growth factor (VEGF) bevacizumab [13]. The combination of atezolizumab plus bevacizumab has demonstrated an advantage in terms of OS (19.2 vs. 13.4 months; $p < 0.001$) and PFS (6.9 vs. 4.3 months; $p < 0.001$) over sorafenib as first-line treatment in patients with unresectable HCC. Moreover, this combination showed a significantly higher ORR compared with sorafenib (30% vs. 11.9%; $p < 0.001$). More recently, the phase III HIMALAYA trial reported improved OS with the combination of a single priming dose of the anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) tremelimumab plus the anti-PD-L1 durvalumab compared with sorafenib [14], while the phase III COSMIC-312 trial showed improved PFS with the combination cabozantinib plus atezolizumab over sorafenib, even though no significant benefit was reported in terms of OS [15]. Recently, results from the phase III LEAP-002 trial were presented: no superiority of the combination of lenvatinib plus the anti-PD-1 pembrolizumab was reported in terms of both OS and PFS compared with lenvatinib alone as first-line treatment [16]. Finally, another anti-PD-1 antibody, camrelizumab, has demonstrated to improve survival outcomes when received in combination with the anti-antiangiogenic TKI rivoceranib as first-line treatment in a cohort of patients with unresectable HCC [17]. To date, atezolizumab plus bevacizumab has been approved as a new first-line standard of care for patients with unresectable HCC. Two large network meta-analyses supported the superiority of this combination over TKIs [18, 19], but no real-world data on large number of patients are available. In clinical practice, systemic therapies could be administered to patients who do not exactly match the inclusion criteria of randomized trials, thus investigations in the real-world setting, as well as the evaluation of the impact of adhering to inclusion criteria, are crucial.

The aim of the present study was to perform a real-world analysis on a large sample of patients with unresectable HCC who received atezolizumab plus bevacizumab as first-line treatment and to evaluate the impact of the IMbrave150 inclusion and exclusion criteria on treatment safety and efficacy.

2 Materials and Methods

2.1 Study Population and Procedures

The overall population included patients treated with atezolizumab plus bevacizumab as first-line treatment for advanced HCC (Barcelona Clinic Liver Cancer [BCLC]-C) or intermediate HCC (BCLC-B) deemed not eligible for locoregional therapies. Data were retrospectively collected from 45 centers in four different countries (Italy, Germany, Japan, and Republic of Korea). Patients were treated with atezolizumab plus bevacizumab between May 2018 and May 2022. Eligible patients presented a histologically confirmed or clinically confirmed diagnosis of HCC according to the international guidelines and were systemic treatment-naïve. Due to the intent to build a real-world dataset of patients treated with atezolizumab plus bevacizumab, no specific inclusion and exclusion criteria were applied, except for the absence of previous systemic therapies for HCC.

Next, the population was split into two groups according to concordance with the inclusion criteria as reported

in the IMbrave150 trial [11]. In particular, according to the IMbrave150 inclusion criteria, patients with Child–Pugh class A, Eastern Cooperative Oncology Group performance status (ECOG-PS) ≤ 1, albumin >2.8 g/dL, absolute neutrophil count (ANC) ≥1.5 × 10^9/L (1500/μL), lymphocyte count ≥ 0.5 × 10^9/L (1500/μL), platelet count ≥ 75 × 10^9/L (75,000/μL) without transfusion, hemoglobin ≥90 g/L, aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP) ≤5 × upper limit of normal (ULN), serum bilirubin ≤ 3 ×ULN, and serum creatinine ≤ 1.5 × ULN or creatinine clearance ≥ 50 mL/min (calculated using the Cockcroft–Gault formula) were considered as the 'IMbrave150-in' group, whereas all patients who did not meet the criteria of the pivotal trial were regarded as the 'IMbrave150-out' group (electronic supplementary Table).

Baseline characteristics, including sex, age, underlying liver disease, body mass index (BMI), ECOG performance status, liver function classified according to the Child–Pugh class and albumin-bilirubin (ALBI) grade, neutrophil–lymphocyte ratio (NLR), and tumor-specific characteristics, including disease stage according to BCLC classification, presence of portal vein thrombosis, presence of extrahepatic disease, α-fetoprotein (AFP) levels, and subsequent systemic treatments were collected.

ALBI grade was calculated as follows: ($\log_{10}$ bilirubin × 0.66) + (albumin −0.085); the patient-level linear value was then assigned to one of the three prognostic groups named ALBI grades 1–3. The cut-off points for each grade were: less than or equal to − 2.60 (ALBI grade 1), more than − 2.60 to less than or equal to − 1.39 (ALBI grade 2), and more than − 1.39 (ALBI grade 3) [20].

Atezolizumab plus bevacizumab was administered according to the IMbrave150 trial, and all patients received 1200 mg of atezolizumab plus 15 mg/kg of body weight of bevacizumab intravenously every 3 weeks [11]. Treatment response was evaluated by computed tomography or magnetic resonance imaging, and categorized as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) by local review according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

Treatment interruptions were permitted to manage adverse events (AEs). AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 [21].

The present study was approved by the Ethics Committee at each center, complied with the provisions of the Good Clinical Practice guidelines and the Declaration of Helsinki and local laws, and fulfilled the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data.

2.2 Statistical Analysis

Categorical variables were compared using Fisher's exact test, whereas continuous variables were compared using the Student's t-test.

The primary endpoint of the study was OS with atezolizumab plus bevacizumab in 'IMbrave150-in' patients compared with 'IMbrave150-out' patients, while the secondary endpoints were PFS, ORR, and safety of atezolizumab plus bevacizumab in 'IMbrave150-in' and 'IMbrave150-out' patients.

OS was defined as the time from the start date of atezolizumab plus bevacizumab to the date of death, and PFS was defined as the time from the start date of atezolizumab plus bevacizumab to the date of progression or death or last follow-up, whichever occurred first. OS and PFS were reported as median values expressed in months, with 95% confidence intervals (CIs). ORR was defined as the proportion of patients who achieved a CR or a PR, and disease control rate (DCR) was defined as the proportion of patients who achieved an ORR or an SD. Survival curves were estimated using the product-limit method of Kaplan–Meier. The role of stratification factors was analyzed using log-rank tests. Unadjusted and adjusted hazard ratios (HRs) by baseline characteristics were calculated using the Cox proportional hazards model. A p-value < 0.05 was considered statistically significant. MedCalc® version 16.8.4 was used for statistical analysis.

3 Results

3.1 Study Population

Overall, 766 patients were enrolled in the study. Median age was 71 years (30–94), with a significantly higher proportion of males (80.5 vs. 19.5%). ECOG PS was 0 in 74% of patients. Regarding the underlying liver disease, 46.5% of patients had non-viral etiology, and the vast majority presented a well-preserved liver function at baseline (Child–Pugh class A, 92%; and ALBI grade 1, 91.5%). At the initiation of systemic treatment, 60% of patients had advanced stage disease (BCLC C), 22% had portal vein thrombosis, and 36% had extrahepatic disease. A significant proportion of patients had received previous surgery (35.5%), whereas 20.5% had received radiofrequency ablation and 33% had received at least one transarterial chemoembolization (TACE). 38% of patients received at least one subsequent systemic treatment after progression on atezolizumab plus bevacizumab, with lenvatinib being the most commonly administered second-line therapy (n = 92, 32%), followed by sorafenib (n = 47, 16%), TACE (n = 26, 9%),

and cabozantinib (n = 26, 9%). Only three patients received a subsequent immunotherapy.

After evaluation of the inclusion and exclusion criteria as reported in the IMbrave150 trial, 561/766 (73%) of patients were included in the 'IMbrave150-in' group and 205/766 (27%) were included in the 'IMbrave150-out' group. A significantly higher proportion of patients included in the 'IMbrave150-in' group had received previous surgery. Moreover, a significantly higher proportion of patients in the 'IMbrave150-in' group were treated with a further systemic treatment after progression on atezolizumab plus bevacizumab, compared with those in the 'IMbrave150-out' group (41.5 vs. 27%).

Patient characteristics of the entire cohort, and the 'IMbrave150-in' and 'IMbrave150-out' groups are reported in Table 1.

3.2 Efficacy

In the entire population, median OS (mOS) was 15.7 months (95% CI 14.8–23.9) and median PFS (mPFS) was 7.4 months (95% CI 6.6–8.5). ORR was 25.4%, including CR in 3.3% of patients and PR in 22.1% of patients. DCR was 78.3%.

In the 'IMbrave150-in' group of patients, mOS was 16.3 months (95% CI 14.8–23.9) compared with 14.3 months in the 'IMbrave-out' group (95% CI 8.7–16.8) [HR 0.48, 95% CI 0.35–0.65; $p < 0.0001$] (Fig. 1a). In the 'IMbrave150-in' group, mPFS was 8.3 months compared with 6.0 months in the 'IMbrave150-out' group (HR 0.79, 95% CI 0.63–0.99; $p = 0.0431$) (Fig. 1b). Moreover, patients included in the 'IMbrave150-in' group achieved a higher ORR compared with patients included in the 'IMbrave150-out' group (27.6% vs. 19.2%; $p = 0.02$).

Overall, Child–Pugh class B, BCLC-C, AFP >400 ng/mL, ALBI grade 2, and presence of macrovascular invasion were associated with a significantly shorter mOS in the entire population (Table 2).

Following adjustment for clinical covariates positive in univariate analysis, multivariate analysis confirmed that patients included in the 'IMbrave150-in' group had significantly longer OS compared with patients in the 'IMbrave150-out' group (HR 0.76, 95% CI 0.47–0.97; $p = 0.0195$) (Table 3).

Evaluation of survival outcomes in the entire population according to liver function showed that patients with ALBI grade 1 experienced an mOS of 16.3 months compared with 6.7 months for patients with ALBI grade 2 (HR 7.05, 95% CI 4.05–12.26; $p < 0.0001$), and a PFS of 8.06 months compared with 5.3 months (HR 1.80, 95% CI 1.21–2.68; $p = 0.0035$). According to Child–Pugh class, patients with Child–Pugh class A performed better compared with patients with Child–Pugh class B in terms of OS (16.3 months vs. 5.9 months; HR 10.26, 95% CI 5.43–19.40; $p < 0.0001$) and PFS (7.9 months vs. 5.3 months; HR 1.86, 95% CI 1.20–2.88).

We also assessed survival outcomes according to liver function in 'IMbrave150-in' and 'IMbrave150-out' patients. In 'IMbrave150-in' patients, ALBI grade was not associated with OS (HR 2.28, 95% CI 0.97–5.36; $p = 0.0578$) (Fig. 2a). Contrarily, in 'IMbrave150-out' patients, ALBI grade 1 was associated with a significant OS benefit compared with ALBI grade 2 (16.7 months vs. 5.9 months; HR 4.40, 95% CI 2.40–8.08; $p > 0.0001$) (Fig. 2b).

In terms of safety, no statistically significant differences were observed for any AE experienced by patients in the 'IMbrave150-in' and 'IMbrave150-out' groups (Table 4).

4 Discussion

The present study evaluated the survival outcomes and safety profile of atezolizumab plus bevacizumab as a first-line systemic treatment in a real-world multicenter and multinational cohort of Eastern and Western patients with unresectable HCC. We analyzed the impact of adherence on the inclusion criteria as reported in the IMbrave150 trial, thus defining two groups of patients, 'IMbrave150-in' and 'IMbrave150-out'. We showed that patients included in the 'IMbrave150-in' group experienced better survival outcomes compared with those included in the 'IMbrave150-out' group. On the other hand, patients included in the 'IMbrave150-out' group with ALBI grade 1 showed an mOS quite similar to the mOS achieved by patients in the 'IMbrave150-in' group (16.7 months vs. 16.3 months). In other words, in patients who fulfill the inclusion criteria of the IMbrave150 trial, thus including only Child–Pugh class A patients, the ALBI score seems to have no prognostic role. On the contrary, in patients who do not completely meet the IMbrave150 inclusion criteria, the ALBI grade seems to have an impact on survival. This result reinforces the stratification role of ALBI score in patients with unresectable HCC (29, 30), and is consistent with a previous real-world experience that reported the prognostic role of ALBI grade in a cohort of patients with unresectable HCC receiving atezolizumab plus bevacizumab (31).

Recently, D'Alessio and colleagues reported a real-world experience of the use of atezolizumab plus bevacizumab as first-line treatment in a cohort of 216 HCC patients that also included patients not completely adherent to the IMbrave150 inclusion criteria, thus confirming the safety profile and efficacy as reported in the registration trial [22]. Interestingly, survival outcomes were similar to those reported in our analysis.

The mOS shown in the entire population, aswell as those of the 'IMbrave150-in' population, wre both inferior

Table 1 Patient baseline characteristics

Patient characteristics	Whole population [$N = 766$] (%)	IMbrave-IN [$n = 561$] (%)	IMbrave-OUT [$n = 205$] (%)	p-value
Sex				
Male	616 (80.5)	453 (81)	163 (79.5)	0.76
Female	150 (19.5)	108 (19)	42 (20.5)	
Age, years				
≥ 70	470 (61)	341 (61)	129 (63)	0.62
< 70	296 (39)	220 (39)	76 (37)	
Etiology				
HCV	218 (28.5)	156 (28)	62 (30)	0.42
HBV	190 (25)	146 (26)	44 (21.5)	
Non-viral	358 (46.5)	259 (46)	99 (48.5)	
Previous surgery				
Yes	273 (35.5)	220 (39)	53 (26)	**0.0006**
No	493 (64.5)	341 (61)	152 (74)	
Previous RFA				
Yes	157 (20.5)	110 (19.5)	47 (23)	0.60
No	497 (65)	368 (65.5)	129 (63)	
NA	112 (14.5)	83 (15)	29 (14)	
Previous TACE				
Yes	254 (33)	186 (33)	68 (33)	0.97
No	400 (52)	292 (52)	108 (52.5)	
NA	112 (15)	83 (15)	29 (14.5)	
Child–Pugh				
A	707 (92)	561 (100)	146 (71)	< 0.0001
B	59 (8)	0 (0)	59 (29)	
BCLC stage				
B	308 (40)	224 (40)	84 (41)	0.80
C	458 (60)	337 (60)	121 (59)	
BMI				
≥ 25	217 (28)	161 (28.5)	56 (27)	0.52
< 25	480 (62.5)	346 (61.5)	134 (65)	
NA	69 (9.5)	54 (10)	15 (8)	
ECOG PS				
0	569 (74)	431 (77)	138 (67)	**0.009**
≥ 1	197 (26)	130 (23)	67 (33)	
Portal vein thrombosis				
Yes	168 (22)	117 (21)	51 (25)	0.24
No	598 (78)	444 (79)	154 (75)	
AFP				
≥ 400	229 (30)	164 (29)	65 (32)	0.77
< 400	532 (69.5)	393 (70)	139 (67.5)	
NA	5 (0.5)	4 (1)	1 (0.5)	
NLR				
≥ 5	97 (12.5)	52 (9)	45 (22)	**< 0.0001**
< 5	669 (87.5)	509 (91)	160 (78)	
ALBI grade				
1	701 (91.5)	539 (96)	162 (79)	**< 0.0001**
2	65 (8.5)	22 (4)	43 (21)	
EHD				
Yes	275 (36)	206 (37)	69 (33.5)	0.61

Table 1 (continued)

Patient characteristics	Whole population [$N = 766$] (%)	IMbrave-IN [$n = 561$] (%)	IMbrave-OUT [$n = 205$] (%)	p-value
No	490 (64)	354 (63)	136 (66.5)	
NA	1 (0)	1 (0)	0 (0)	
Subsequent therapies				
Yes	289 (38)	233 (41.5)	56 (27)	**0.0003**
No	477 (62)	328 (48.5)	149 (73)	

Bold values indicates the statistically significance

HCV hepatitis C virus, *HBV* hepatitis B virus, *RFA* radiofrequency ablation, *TACE* transarterial chemoembolization, *BCLC* Barcelona Clinic Liver Cancer staging system, *BMI* body mass index, *ECOG PS* Eastern Cooperative Oncology Group performance status, *AFP* α-fetoprotein, *NLR* neutrophil–lymphocyte ratio, *ALBI* albumin-bilirubin, *EHD* extrahepatic disease, *NA* not available

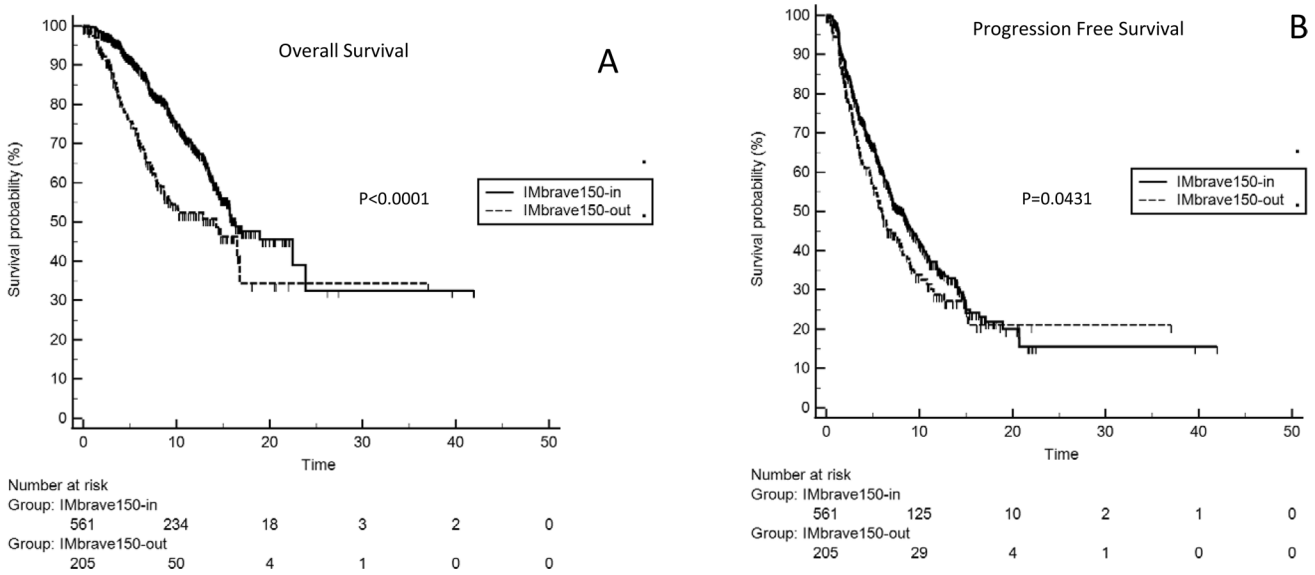

Fig. 1 Kaplan–Meier for **a** overall survival and **b** progression-free survival in patients included in the 'IMbrave150-in' group compared with those included in the 'IMbrave150-out' group

compared with the mOS reported in the updated results of the IMbrave150 trial (15.7 months and 16.3 months vs. 19.2 months, respectively) [11]. These results could be partly explained by the differences in terms of baseline characteristics between our real-world cohort and the Imbrave150 trial population [11]. Indeed, more patients in our cohort presented with impaired liver function. However, patients enrolled in the IMbrave150 trial presented a higher proportion of patients with BCLC-C stage (82% vs. 60%), AFP >400 ng/mL (38% vs. 30%), and extrahepatic disease (63% vs. 36%), which are known negative prognostic factors in the advanced HCC setting. In the HCC field, TKIs (lenvatinib) previously demonstrated to perform better in terms of survival outcomes in real-world context compared with clinical trials [23]. The improved performance of lenvatinib in a real-world setting compared with a randomized clinical trial could be ascribed to the learning curve and the increased expertise in the management of similar TKIs, including sorafenib, cabozantinib, and regorafenib [24]. Contrarily, even if immunotherapy has been used to treat solid tumors for more than 10 years, atezolizumab plus bevacizumab is the first immunotherapy combination approved for HCC, thus meaning that part of the physicians specialized in the treatment of HCC may have approached such treatment for the first time. For this reason, although immunotherapy is generally characterized by a better tolerability profile than TKIs, it is probably necessary to wait for physicians to learn how to manage the AEs associated with this new class of drugs to achieve an improvement in survival outcomes.

Of note, 27% of the patients included in our cohort would have been excluded from the IMbrave150 trial. Therefore, we decided to assess the survival outcomes of patients who fulfilled the IMbrave150 inclusion criteria and patients who did not. As expected, we shwed

Table 2 Univariate and multivariate analysis in the whole population

Covariate	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
IMbrave-150 criteria						
Out	1			1		
In	0.48	0.35–0.65	<0.0001	0.49	0.47–0.97	0.0173
Sex						
Male	1			1		
Female	1.26	0.91–1.75	0.1585	1.18	0.90–1.68	0.1872
Age, years						
< 70	1					
> 70	1.17	0.90–1.52	0.2342			
Etiology						
Viral	1					
Non-viral	1.06	0.82–1.37	0.6390			
Child–Pugh						
A	1			1		
B	10.3	5.42–19.4	< 0.0001	1.57	0.95–2.60	0.0789
BCLC						
B	1			1		
C	1.30	1.00–1.69	0.0451	1.25	0.95–1.65	0.1024
AFP						
< 400	1			1		
> 400	2.07	1.55–2.75	< 0.0001	1.78	1.37–2.34	< 0.0001
ALBI						
1	1			1		
2	7.05	4.05–12.3	< 0.0001	2.40	1.60–3.63	< 0.0001
Vascular invasion						
No	1					
Yes	2.02	1.47–2.78	< 0.0001			
ECOG PS						
0	1					
> 0	2.79	0.89–8.77	0.0786			

BCLC Barcelona Clinic Liver Cancer staging system, *ECOG PS* Eastern Cooperative Oncology Group performance status, *AFP* α-fetoprotein, *ALBI* albumin-bilirubin, *HR* hazard ratio, *CI* confidence interval

improved mOS and mPFS in 'IMbrave150-in' patients compared with the 'IMbrave150-out' group. The evaluation of OS in patients receiving first-line treatment should take into account the subsequent anticancer therapies received by the patients. A higher percentage of patients in the 'IMbrave150-in' group received subsequent anticancer therapies (41.4% vs. 27%; $p = 0.0003$), likely due to the more favorable baseline characteristics, and this factor could have had an impact on the observed OS. This observation has to be taken into consideration with attention, since the differences in terms of baseline characteristics between patients receiving a sequential treatment versus those who did not has partially influenced the survival outcomes. In particular, as expected, we observed that a higher proportion of patients who received a subsequent systemic treatment after progression on atezolizumab plus immunotherapy presented a baseline Child–Pugh grade of A, thus eventually contributing to the better survival outcome. In a recently published multicenter study, Sho and colleagues evaluated the efficacy of atezolizumab plus bevacizumab in a cohort of patients who did not meet the inclusion criteria of the IMbrave150 trial, showing similar efficacy in terms of PFS compared with patients who met the inclusion criteria, inconsistently with our results. Differences in terms of sample size and baseline characteristics could explain the different results from our analysis and those from Sho and colleagues. Moreover, the authors reported a significative worsening of liver function during treatment according to ALBI grade in patients who did not meet the inclusion criteria after treatment initiation [25].

Table 3 Univariate and multivariate analysis in the 'IMbrave150-in' and 'IMbrave150-out' patients

Covariate	IMbrave150 IN						IMbrave150 OUT					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Sex												
Male	1						1					
Female	1.13	0.76–1.68	0.5346				1.55	0.87–2.78	0.1372			
Age, years												
< 70	1						1					
> 70	1.25	0.90–1.72	0.1747				1.02	0.65–1.60	0.9398			
Etiology												
Viral	1						1					
Non-viral	1.10	0.80–1.51	0.5398				0.93	0.59–1.44	0.7386			
Child–Pugh												
A							1			1		
B							3.17	1.85–5.46	<0.0001	1.38	0.81–2.37	0.2381
BCLC												
B	1						1			1		
C	1.14	0.83–1.57	0.4222				1.76	1.13–2.75	0.0117	1.65	1.02–2.68	0.0414
AFP												
< 400	1			1			1			1		
> 400	1.88	1.34–2.66	0.0003	1.69	1.23–2.33	0.0014	2.69	1.60–4.52	0.0002	2.54	1.46–4.42	0.0010
ALBI grade												
1	1						1			1		
2	2.28	0.97–5.36	0.0578				4.40	2.40–8.08	<0.0001	1.91	1.20–3.03	0.0063
Vascular invasion												
No	1			1			1					
Yes	2.15	1.45–3.20	0.0001	1.75	1.25–2.47	0.0012	1.67	0.98–2.86	0.0598			
ECOG PS												
0							1					
> 0							1.08	0.45–2.56	0.8618			

BCLC Barcelona Clinic Liver Cancer staging system, *ECOG PS* Eastern Cooperative Oncology Group performance status, *AFP* α-fetoprotein, *ALBI* albumin-bilirubin, *HR* hazard ratio, *CI* confidence interval

In terms of the safety profile, patients in the 'IMbrave150-in' and 'IMbrave150-out' groups showed a similar incidence of AEs of any cause. In addition, by evaluating separately each type of AE, no statistically significant differences were reported between the two groups of patients. No new, unexpected AEs were observed in both patients who matched the Mbrave150 inclusion criteria and those who did not.

The present analysis presents several limitations. First, the retrospective nature of the work could not exclude the presence of selection bias. Nevertheless, patients have been enrolled consecutively at each center in order to minimize this kind of bias. Second, the lack of independent review of treatment responses could have affected the results, particularly in the evaluation of PFS. Third, data regarding the presence of esophagogastric varices at baseline as well as the occurrence of bleeding events during treatment were not considered, which could be considered a limitation due to the relevance of the management of such events in patients receiving atezolizumab plus bevacizumab. Finally, the two groups of patients ('IMbrave150-in' and 'IMbrave150-out') presented different sample sizes and different baseline characteristics. Nevertheless, a multivariate analysis including the clinical covariates associated with survival outcomes at univariate analysis has been performed to minimize the risk of bias. The strength of our analysis derives from the large sample size of patients treated with atezolizumab plus bevacizumab. Of note, patients included in the study were both European and Asian, thus increasing the representativeness of our cohort.

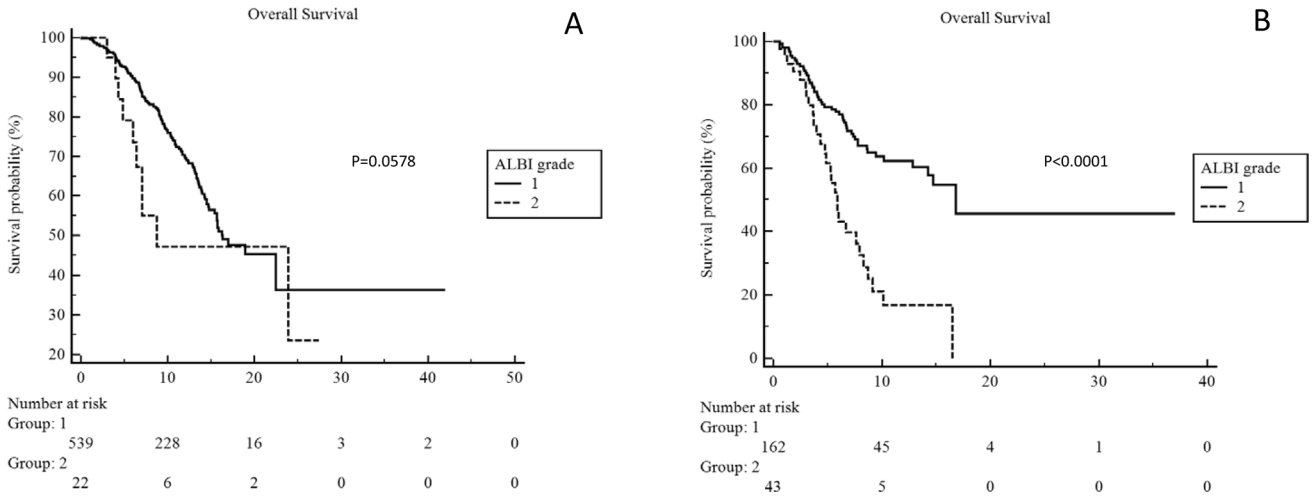

Fig. 2 Kaplan–Meier for overall survival in patients included in the **a** 'IMbrave150-in' and **b** 'IMbrave150-out' groups according to the ALBI score. *ALBI* albumin-bilirubin

Table 4 Adverse events experienced in 'IMbrave150-in' and 'IMbrave150-out' patients

Adverse events	IMbrave150-in [n = 561] (%)	IMbrave150-out [n = 205] (%)	p-Value
Cutaneous toxicities			
Yes	12 (2)	1 (0.5)	0.20
No	549 (98)	204 (99.5)	
Diarrhea			0.75
Yes	39 (7)	16 (8)	
No	522 (93)	189 (92)	
Hypertension			
Yes	142 (25)	43 (21)	0.25
No	419 (75)	162 (79)	
Fatigue			
Yes	143 (25.5)	49 (24)	0.71
No	418 (74.5)	156 (76)	
Decreased appetite			
Yes	124 (22)	49 (24)	0.63
No	437 (78)	156 (76)	
Hypothyroidism			
Yes	30 (5)	6 (3)	0.18
No	531 (95)	199 (97)	
Other immune-related toxicities			
Yes	44 (8)	20 (10)	
No	517 (92)	185 (90)	0.38

5 Conclusion

Our real-world study on a large sample of patients with unresectable HCC receiving atezolizumab plus bevacizumab as first-line treatment showed that patients enrolled in accordance with the IMbrave150 trial inclusion criteria achieved longer OS and PFS compared with those who did not match the inclusion criteria reported in the prospective trial. Nevertheless, patients who do not match theIMbrave150 trial inclusion criteria and with ALBI grade

could experience a significant benefit in terms of OS from treatment with atezolizumab plus bevacizumab, similar to patients who meet the inclusion criteria of the prospective trial. No significant differences in terms of AEs have been observed between the two groups of patients. An improvement in both clinical and investigational settings is crucial. In clinical practice, physicians need to improve the expertise in immunotherapy drugs, mainly in the management of AEs, while in the investigational setting, further studies focused on the best sequential treatment after progression on atezolizumab plus bevacizumab are needed to improve clinical outcomes.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11523-023-00953-x.

Declarations

Funding No external funding was used in the preparation of this manuscript.

Conflicts of interest Lorenza Rimassa reports receiving consulting fees from Amgen, ArQule, AstraZeneca, Basilea, Bayer, BMS, Celgene, Eisai, Exelixis, Genenta, Hengrui, Incyte, Ipsen, IQVIA, Lilly, MSD, Nerviano Medical Sciences, Roche, Sanofi, Servier, Taiho Oncology, and Zymeworks; lecture fees from AbbVie, Amgen, Bayer, Eisai, Gilead, Incyte, Ipsen, Lilly, Merck Serono, Roche, Sanofi, and Servier; travel expenses from AstraZeneca; and institutional research funding from Agios, ARMO BioSciences, AstraZeneca, BeiGene, Eisai, Exelixis, Fibrogen, Incyte, Ipsen, Lilly, MSD, Nerviano Medical Sciences, Roche, and Zymeworks. Tiziana Pressiani has received consulting fees from Bayer, Ipsen, and IQVIA, and institutional research funding from Bayer, Lilly, and Roche. Fabian Finkelmeier has received travel support from Ipsen, and speaker's fees from AbbVie, MSD, Ipsen, Eisai, and Fresenius. Mario Scartozzi has received grants and personal fees from MERCK, MSD, Servier, Eisai, and Amgen. Andrea Casadei-Gardini has received grants and personal fees from MSD, Eisai, and Bayer, and is an advisor for MSD, Eisai, Bayer, Bristol-Myers Squibb, AstraZeneca, and GSK. Margherita Rimini, Mara Persano , Toshifumi Tada, Goki Suda, Shigeo Shimose, Masatoshi Kudo, Jaekyung Cheon, Ho Yeong Lim, José Presa, Gianluca Masi, Changhoon Yoo, Sara Lonardi, Fabio Piscaglia, Takashi Kumada, Naoya Sakamoto, Hideki Iwamoto, Tomoko Aoki, Hong Jae Chon, Vera Himmelsbach, Margarida Montes, Caterina Vivaldi, Caterina Soldà, Atsushi Hiraoka, Takuya Sho, Takashi Niizeki, Naoshi Nishida, Christoph Steup, Masashi Hirooka, Kazuya Kariyama, Joji Tani, Masanori Atsukawa, Koichi Takaguchi, Ei Itobayashi, Shinya Fukunishi, Kunihiko Tsuji, Toru Ishikawa, Kazuto Tajiri, Hironori Ochi, Satoshi Yasuda, Hidenori Toyoda, Chikara Ogawa, Takashi Nishimura, Takeshi Hatanaka, Satoru Kakizaki, Noritomo Shimada, Kazuhito Kawata, Fujimasa Tada, Hideko Ohama, Kazuhiro Nouso, Asahiro Morishita, Akemi Tsutsui, Takuya Nagano, Norio Itokawa, Tomomi Okubo, Taeang Arai, Michitaka Imai, Hisashi Kosaka, Atsushi Naganuma, Yohei Koizumi, Shinichiro Nakamura, Masaki Kaibori, Hiroko Iijima, Yoichi Hiasa, Valentina Burgio, and Stefano Cascinu declare they have no conflicts of interest that might be relevant to the contents of this manuscript.

Ethics approval The Ethical Review Board of each Institutional Hospital approved the present study. This study was performed in line with the principles of the Declaration of Helsinki.

Consent to participate Written informed consent for treatment was obtained for all patients.

Consent for publication Not applicable.

Data availability statement Data available on request from the authors.

Code availability Not applicable.

Authors' contributions Conception and design: ACG, MR. Acquisition of data (acquired and managed patients): All authors. Analysis and interpretation of data: ACG, MR. Writing, review, and/or revision of the manuscript: ACG, MR. Final approval of the manuscript: All authors.

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