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ORIGINAL ARTICLE

Vascular Invasion Within the Resectability Criteria Is a Prognostic Factor in Patients Treated With Atezolizumab and Bevacizumab

Tomomitsu Matono[1] | Toshifumi Tada[2,3] | Takashi Kumada[4] | Atsushi Hiraoka[5] | Masashi Hirooka[6] | Kazuya Kariyama[7] | Joji Tani[8] | Masanori Atsukawa[9] | Koichi Takaguchi[10] | Ei Itobayashi[11] | Shinya Fukunishi[12] | Hiroki Nishikawa[13] | Kazunari Tanaka[14] | Kunihiko Tsuji[14] | Toru Ishikawa[15] | Kazuto Tajiri[16] | Yuichi Koshiyama[17] | Hidenori Toyoda[17] | Chikara Ogawa[18] | Takeshi Hatanaka[19] | Satoru Kakizaki[20] | Kazuhito Kawata[21] | Hideko Ohama[5] | Fujimasa Tada[5] | Kazuhiro Nouso[7] | Asahiro Morishita[8] | Akemi Tsutsui[10] | Takuya Nagano[10] | Norio Itokawa[9] | Tomomi Okubo[9] | Taeang Arai[9] | Takashi Nishimura[12] | Michitaka Imai[15] | Hisashi Kosaka[22] | Atsushi Naganuma[23] | Tomoko Aoki[24] | Hidekatsu Kuroda[25] | Yutaka Yata[26] | Hideyuki Tamai[27] | Takanori Matsuura[2] | Shohei Komatsu[28] | Yoshihide Ueda[29] | Yoshiko Nakamura[6] | Osamu Yoshida[6] | Kosuke Matsui[22] | Shinichiro Nakamura[3] | Hirayuki Enomoto[12] | Masaki Kaibori[22] | Takumi Fukumoto[28] | Yoichi Hiasa[6] | Masatoshi Kudo[24] | on behalf of the Real-life Practice Experts for HCC (RELPEC) Study Group and the Hepatocellular Carcinoma Experts from 48 clinics in Japan (HCC 48) Group

[1]Department of Gastroenterology, Hyogo Prefectural Harima-Himeji General Medical Center, Himeji, Hyogo, Japan | [2]Division of Gastroenterology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan | [3]Department of Gastroenterology, Japanese Red Cross Society Himeji Hospital, Himeji, Hyogo, Japan | [4]Gifu Kyoritsu University, Gifu, Japan | [5]Gastroenterology Center, Ehime Prefectural Central Hospital, Matsuyama, Ehime, Japan | [6]Department of Gastroenterology and Metabology, Ehime University Graduate School of Medicine, Toon, Ehime, Japan | [7]Department of Gastroenterology, Okayama City Hospital, Okayama, Japan | [8]Department of Gastroenterology and Hepatology, Kagawa University, Takamatsu, Kagawa, Japan | [9]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Nippon Medical School, Tokyo, Japan | [10]Department of Hepatology, Kagawa Prefectural Central Hospital, Takamatsu, Kagawa, Japan | [11]Department of Gastroenterology, Asahi General Hospital, Asahi, Chiba, Japan | [12]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Hyogo Medical University, Nishinomiya, Japan | [13]Department of Gastroenterology, Osaka Medical and Pharmaceutical University, Takatsuki, Osaka, Japan | [14]Center of Gastroenterology, Teine Keijinkai Hospital, Sapporo, Hokkaido, Japan | [15]Department of Gastroenterology, Saiseikai Niigata Hospital, Niigata, Japan | [16]Department of Gastroenterology, Toyama University Hospital, Toyama, Japan | [17]Department of Gastroenterology and Hepatology, Ogaki Municipal Hospital, Gifu, Japan | [18]Department of Gastroenterology, Japanese Red Cross Takamatsu Hospital, Takamatsu, Kagawa, Japan | [19]Department of Gastroenterology, Gunma Saiseikai Maebashi Hospital, Maebashi, Gunma, Japan | [20]Department of Clinical Research, NHO Takasaki General Medical Center, Takasaki, Gunma, Japan | [21]Department of Hepatology, Hamamatsu University School of Medicine, Shizuoka, Japan | [22]Department of Surgery, Kansai Medical University, Hirakata, Osaka, Japan | [23]Department of Gastroenterology, NHO Takasaki General Medical Center, Takasaki, Gunma, Japan | [24]Department of Gastroenterology and Hepatology, Kindai University, Higashiosaka, Osaka, Japan | [25]Division of Hepatology, Department of Internal Medicine, Iwate Medical University, Yahaba, Iwate, Japan | [26]Department of Gastroenterology, Hanwa Memorial Hospital, Osaka, Japan | [27]Department of Hepatology, Wakayama Rosai Hospital, Wakayama, Japan | [28]Division of Hepato-Biliary-Pancreatic Surgery, Department of Surgery, Kobe University Graduate School of Medicine, Kobe, Japan | [29]Department of Gastroenterology, Kakogawa Central City Hospital, Kakogawa, Hyogo, Japan

Correspondence: Toshifumi Tada (tadat0627@gmail.com)

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Abbreviations: ALBI, albumin–bilirubin; Atezo, atezolizumab; BCLC, Barcelona Clinic Liver Cancer; Bev, bevacizumab; BR, borderline resectable; BSC, best supportive care; CI, confidence interval; CR, complete response; CT, computed tomography; DCR, disease control rate; ECOG-PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; HCC, hepatocellular carcinoma; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; R, resectable; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease; TACE, transarterial chemoembolization.

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Keywords: ALBI grade | atezolizumab plus bevacizumab | hepatocellular carcinoma | oncological resectability criteria | vascular invasion

ABSTRACT

Background and Aims: To assess the outcomes of patients with hepatocellular carcinoma (HCC) who were treated with atezolizumab plus bevacizumab (Atezo/Bev), categorised by oncological resectability criteria, which reflect tumour burden and extent of disease.

Methods: A cohort of 467 HCC patients who received Atezo/Bev was enrolled. Patients were classified into two groups based on oncological resectability criteria: BR (borderline resectable) 1 ($n = 153$) and BR2 ($n = 314$).

Results: The median progression-free survival (PFS) was 9.0 months in the BR1 group and 6.8 months in the BR2 group ($p = 0.014$). Multivariable analysis identified the following independent prognostic factors for PFS: age ≥ 75 years (hazard ratio [HR], 1.309), albumin–bilirubin (ALBI) grade ≥ 2 (HR, 1.494), neutrophil-to-lymphocyte ratio (NLR) ≥ 3 (HR, 1.289), α-fetoprotein ≥ 100 ng/mL (HR, 1.523) and BR2 classification (HR, 1.360). The median overall survival (OS) was 25.3 months in the BR1 group and 22.3 months in the BR2 group ($p = 0.048$). Multivariable analysis identified the following independent prognostic factors for OS: age ≥ 75 years (HR, 1.522), ALBI grade ≥ 2 (HR, 2.411), NLR ≥ 3 (HR, 1.635), α-fetoprotein ≥ 100 ng/mL (HR, 1.530) and BR2 classification (HR, 1.421). When oncological resectability factors (tumour number and size, vascular invasion and extrahepatic spread) were incorporated into the multivariable analysis, major vascular invasion emerged as a significant predictor of both PFS (HR, 3.188) and OS (HR, 2.650).

Conclusions: In patients with HCC characterised by limited resectability undergoing Atezo/Bev, vascular invasion, in addition to liver function, is a critical prognostic determinant of tumour progression.

1 | Introduction

In 2022, primary liver cancer ranked as the sixth frequently diagnosed malignancy and the third leading cause of cancer-related mortality globally [1]. Approximately 865 000 new cases were reported, resulting in an estimated 757 000 deaths [1]. Hepatocellular carcinoma (HCC) accounts for 75%–85% of primary liver cancer cases, posing a substantial global health challenge [1]. Patients diagnosed with early-stage HCC, as classified by the Barcelona Clinic Liver Cancer (BCLC) staging system [2], are typically eligible for curative interventions, including surgical resection, liver transplantation or locoregional ablation therapies [3]. However, recurrence following curative treatment is common, and tumours frequently progress to an unresectable state, even in individuals with preserved hepatic function. Patients deemed unsuitable for curative therapies generally undergo non-curative treatments, such as transarterial chemoembolization (TACE), radiation therapy or systemic pharmacological interventions [3].

Sorafenib was the first molecularly targeted agent developed for patients with unresectable HCC [4, 5]. In 2018, lenvatinib [6], another molecularly targeted agent, was introduced in Japan and has since become the most widely used first-line systemic therapy for HCC. Subsequently, in 2020, the immune checkpoint inhibitor atezolizumab (Atezo) and the anti-vascular endothelial growth factor monoclonal antibody bevacizumab (Bev) were approved in Japan, establishing themselves as standard first-line systemic treatments for HCC [7]. The phase 3 IMbrave150 trial [7] demonstrated that Atezo/Bev therapy provided statistically significant and clinically meaningful improvements in both progression-free survival (PFS) and overall survival (OS) compared to sorafenib in patients with unresectable HCC. More recently, in 2023, durvalumab in combination with tremelimumab was introduced as an initial immunotherapeutic regimen based on the findings of the HIMALAYA trial, further expanding first-line systemic treatment options for HCC [8]. In clinical practice, Atezo/Bev is frequently preferred as the primary systemic therapy for unresectable HCC, particularly in patients at low risk of gastrointestinal bleeding [9], such as those with gastroesophageal varices.

In the BCLC classification commonly utilised in Western nations, the presence of vascular invasion typically precludes surgical resection, with systemic pharmacotherapy being the preferred treatment modality [2]. However, in Japan, surgical intervention may still be considered if the clinical conditions of the patient are favourable [10]. Recently, a Japanese expert consensus introduced oncological resectability criteria for HCC [11]. Notably, these criteria do not incorporate the concept of unresectable tumours, but rather classify borderline resectability into two distinct subgroups, defined from the therapeutic perspective of hepatic resection. Furthermore, the criteria do not account for hepatic functional reserve. Based on these classifications, resectability is categorised into three groups: resectable (R), borderline resectable 1 (BR1) and borderline resectable 2 (BR2). Resectable cases are characterised by a limited tumour burden, with no evidence of macrovascular invasion or extrahepatic dissemination. BR1 denotes intermediate oncological status, in which surgical resection, when integrated into a multidisciplinary treatment strategy, may confer a survival advantage. BR2 encompasses patients with substantial tumour burden or advanced disease, for whom the therapeutic role of surgery remains equivocal and necessitates thorough multidisciplinary assessment.

Importantly, the clinical outcomes of systemic chemotherapy for patients stratified according to these criteria, particularly those classified as BR1 or BR2, remain insufficiently understood.

Summary

- This study assessed the clinical outcomes of patients with HCC treated with Atezo/Bev in a real-world context, categorised according to oncological resectability criteria (BR1 and BR2).
- Multivariable analysis identified oncological resectability criteria, along with ALBI grade, as significant determinants of PFS and OS.
- Among the components of oncological resectability criteria, major vascular invasion was particularly influential in predicting PFS and OS.

Thus, in this study, we evaluated the clinical outcomes of a large cohort of patients classified as BR1 or BR2 who received Atezo/Bev in a real-world setting across multiple Japanese centres. Specifically, we examined the association between each oncological criterion included in the oncological resectability criteria, clinical factors such as liver function and patient outcomes.

2 | Materials and Methods

2.1 | Patients

This study was conducted in strict adherence to the Declaration of Helsinki and received approval from the institutional review boards of all participating centres. Informed consent for this analysis was obtained from patients prior to the approval of the clinical research committee through an opt-out process. Subsequently, written informed consent was acquired from all participants after the committee's approval and before the initiation of treatment.

Between May 2018 and May 2024, a total of 1055 patients with unresectable HCC were treated with Atezo/Bev across 26 institutions in Japan. Of these, 467 met the following inclusion criteria: (1) Child–Pugh class A, (2) Atezo/Bev administered as the first-line systemic therapy, (3) Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0 or 1, (4) BR1 or BR2 classification [11], (5) treatment administered as part of standard clinical practice in a non-trial setting and (6) availability of complete clinical data (Figure 1). Follow-up regarding prognosis was conducted with a data cutoff date of November 15, 2024.

The aetiology of HCC was classified as hepatitis B virus infection in patients who tested positive for hepatitis B surface antigen, and as hepatitis C virus infection in those with detectable hepatitis C virus RNA or a documented history of antiviral therapy.

The initiation of Atezo/Bev therapy was designated as the starting point for follow-up. The endpoint of follow-up was determined as the date of the final clinic visit for patients who survived the observation period, or the date of death for those who succumbed before the conclusion of the observation period.

2.2 | Diagnosis and Treatment of HCC

The diagnosis of HCC was established based on one or more of the following criteria: elevated α-fetoprotein levels (supplementary criterion to typical imaging findings); characteristic imaging findings observed on dynamic computed tomography (CT); gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid–enhanced magnetic resonance imaging; contrast-enhanced ultrasonography; or histopathological findings [12, 13]. The staging of HCC was determined using the BCLC classification system [2].

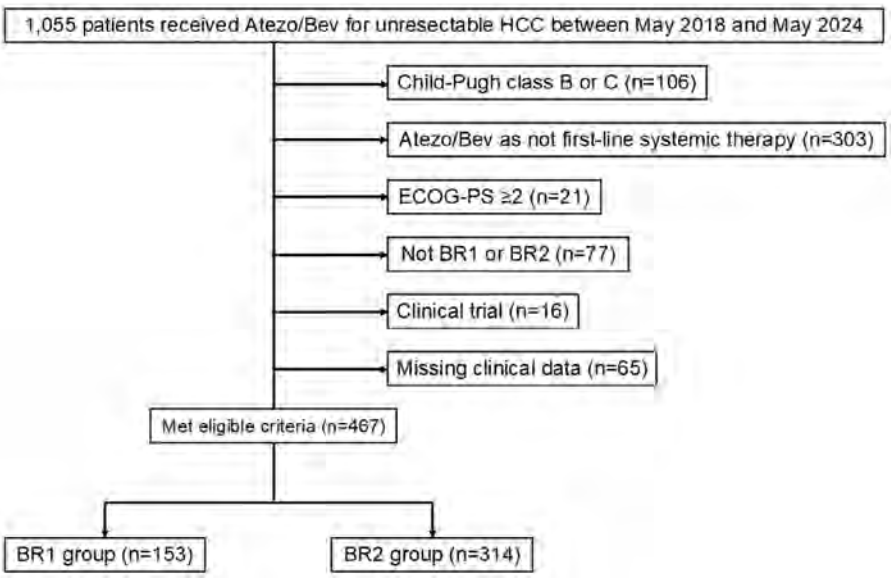

FIGURE 1 | Flowchart of the patient selection process. Atezo/Bev, atezolizumab plus bevacizumab; BR, borderline resectable; ECOG-PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma.

The optimal treatment strategy for each patient with HCC was determined through multidisciplinary collaborations conducted by the cancer board at each participating institution. These discussions adhered to the Japanese clinical practice guidelines for HCC [10, 14].

2.3 | Systemic Therapy With Atezo/Bev

After obtaining written informed consent from all participants, intravenous therapy with Atezo/Bev was initiated. The regimen comprised Atezo (1200 mg) and Bev (15 mg/kg of body weight) administered every 3 weeks [7]. Treatment was discontinued in cases of clinical tumour progression or the occurrence of serious or intolerable adverse events during therapy.

2.4 | Oncological Criteria of Resectability for HCC

The study population was categorised according to the oncological criteria for HCC resectability, as defined in the 2023 Expert Consensus Statement by the Japanese Liver Cancer Association and the Japanese Society of Hepato-Biliary-Pancreatic Surgery.

Portal vein tumour thrombus was classified according to the Japanese staging system as follows: Vp4, involvement of the main trunk or contralateral branch; Vp3, involvement of a first-order branch; Vp2, involvement of a second-order branch; and Vp1, involvement of a third-order branch or microscopic invasion [15]. Hepatic vein tumour thrombus was categorised as follows: Vv1, tumour thrombus in the peripheral hepatic vein; Vv2, tumour thrombus in a major hepatic vein; or Vv3, tumour thrombus in the inferior vena cava [15]. Bile duct tumour thrombus was classified as follows: B4, involvement of the common hepatic duct; B3, involvement of first-order branches of the bile duct; B2, involvement of second-order branches of the bile duct; or B1, involvement of peripheral branches of the bile duct [15].

Patients were divided into three groups: R, BR1 and BR2 (Table S1) [11]. Patients classified as R were excluded from the analysis cohort in this study.

The classification of tumour number and size was defined as follows [11]:

i. A solitary lesion (with no size limitation) or multiple lesions, each measuring ≤ 3 cm in diameter, with a maximum of three nodules.
ii. Multiple lesions exceeding the criteria described above but limited to no more than five nodules, each measuring ≤ 5 cm in diameter.
iii. Multiple lesions comprising more than five nodules or lesions exceeding 5 cm in diameter.

The classification of vascular invasion was defined as follows [11]:

i. No macrovascular invasion detected on imaging (Vp0–1, Vv0–1 and B0–1).
ii. Presence of macrovascular invasion (Vp2–3, Vv2 or B2–3).
iii. Major vascular invasion (Vp4, Vv3 or B4).

The classification of extrahepatic spread (EHS) was defined as follows [11]:

i. No evidence of extrahepatic disease.
ii. Localised extrahepatic disease.
iii. Extrahepatic disease that does not meet the criteria for localisation and is classified as BR1.

2.5 | Therapeutic Response

Radiological therapeutic responses were evaluated using the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 [16]. Responses were categorised as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). Whenever feasible, the initial evaluation of therapeutic response was conducted based on dynamic CT imaging performed 6 weeks after initiating Atezo/Bev therapy. Between the sixth week and the sixth month of treatment, dynamic CT assessments were performed every 6 weeks. Beyond the sixth month, assessments were conducted at intervals of 9–12 weeks.

2.6 | Statistical Analysis

Continuous variables are presented as medians with interquartile ranges. PFS was defined as the time period from the initiation of Atezo/Bev treatment to either disease progression or death. OS was defined as the period of time from the initiation of Atezo/Bev treatment to the conclusion of the follow-up period. Cumulative PFS and OS were estimated using the Kaplan–Meier method, and between-group differences were evaluated using the log-rank test with Holm correction. Univariable and multivariable Cox proportional hazards models were employed to calculate hazard ratios (HRs) for survival. Clinical variables previously recognised as risk factors for HCC or as predictors of liver disease prognosis were included in the multivariable analysis [17–21]. Three distinct models were developed for the multivariable analysis. In Model 1, age, sex, HCC aetiology, albumin–bilirubin (ALBI) grade, α-fetoprotein level, neutrophil-to-lymphocyte ratio (NLR) and BR categories were included as covariates. In Model 2, additional factors—tumour number and size categories, vascular invasion categories and EHS categories—were incorporated alongside the covariates used in Model 1 (excluding BR categories). Model 3 (subgroup analysis) included age, sex, tumour number and size categories, vascular invasion categories and EHS categories as covariates. Cutoff values for clinical data were determined based on previous reports regarding the risk or prognosis of HCC [17–21].

Sankey diagrams were constructed to visualise concomitant or subsequent treatments following Atezo/Bev therapy in the BR1 and BR2 groups.

Statistical significance was set at $p < 0.05$. All statistical analyses were conducted using EZR version 1.68 (Saitama Medical

TABLE 1 | Patient characteristics.

	Overall ($n=467$)	BR1 group ($n=153$)	BR2 group ($n=314$)	p
Age[a] (years)	74.0 (69.0–79.0)	74.0 (70.0–79.0)	74.0 (68.3–79.0)	0.445
Sex (female/male)	102/365	33/120	69/245	1.000
ECOG-PS (0/1)	402/65	134/19	268/46	0.571
Body mass index (kg/m^2)	23.7 (21.3–26.4)	23.6 (21.4–26.5)	23.7 (21.2–26.4)	0.631
HCC aetiology (hepatitis B/C/non-B, non-C)	73/164/230	25/61/67	48/103/163	0.225
Albumin (g/dL)[a]	3.9 (3.6–4.2)	3.9 (3.6–4.2)	3.8 (3.6–4.1)	0.514
Total bilirubin (mg/dL)[a]	0.7 (0.6–1.0)	0.7 (0.6–1.0)	0.8 (0.6–1.0)	0.520
Neutrophil count (/μL)[a]	2999 (2290–39.5)	2746 (2234–3449)	3114 (2310–4160)	0.009
Lymphocyte count (/μL)[a]	1302 (175–4390)	1305 (903–1640)	1302 (1008–1640)	0.253
NLR[a]	2.43 (1.68–3.44)	2.48 (1.67–3.32)	2.41 (1.71–3.46)	0.497
Platelet count (/μL)[a]	14.4 (10.9–19.0)	13.3 (10.4–17.3)	15.4 (11.2–20.3)	0.002
Prothrombin time (%)[a]	90 (81–100)	89 (78–100)	92 (82–101)	0.076
α-Fetoprotein (ng/mL)[a]	18.0 (5.1–350.0)	15.3 (4.0–193.0)	20.0 (6.0–466.0)	0.096
Child–Pugh score (5/6)	225/132	110/43	225/89	1.000
ALBI grade (1/2/3)	215/250/2	70/83/0	145/67/2	0.964
BCLC stage (B/C)	223/244	65/68	158/156	0.116
Portal vein invasion (0/1/2/3/4)	369/5/38/30/25	129/1/18/5/0	240/4/20/25/25	<0.001
Hepatic vein invasion (0/1/2/3)	442/6/14/5	148/1/4/0	294/5/10/5	0.460
Bile duct invasion (0/1/2/3/4)	462/0/1/4/0	151/0/1/1/0	311/0/0/3/0	0.399
EHS (yes/no)	118/349	56/97	62/252	<0.001
Follow-up duration[a] (months)	14.3 (7.5–24.0)	15.3 (9.5–22.0)	14.1 (7.1–24.1)	0.255
Initial treatment for HCC				<0.001
Resection	151	57	94	
Locoregional ablation therapy	94	47	47	
TACE	91	28	63	
Atezo/Bev	122	21	101	
Other	9	0	9	

Abbreviations: ALBI, albumin–bilirubin; Atezo/Bev, atezolizumab plus bevacizumab; BCLC, Barcelona Clinic Liver Cancer; BR, borderline resectable; ECOG-PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; HCC, hepatocellular carcinoma; NLR, neutrophil-to-lymphocyte ratio; TACE, transarterial chemoembolization.
[a]Data are expressed as medians (interquartile range).

Center, Jichi Medical University, Saitama, Japan) [22], a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

3 | Results

3.1 | Patient Characteristics

Table 1 summarises the characteristics of the 467 patients analysed in the study. Of these, 102 (21.8%) were women and 365 (78.2%) were men. The median age was 74.0 (69.0–79.0) years. Patients were categorised into BR1 ($n=153$ [32.8%]) and BR2 ($n=314$ [67.2%]) groups. The median follow-up period was 14.3 (7.5–24.0) months. During the follow-up period, disease progression occurred in 307 patients (65.7%) and 213 patients (45.6%) died from all causes.

3.2 | PFS and OS

In this cohort ($n=467$), the median PFS and OS were 7.5 (95% confidence interval [CI], 6.6–9.0) and 22.3 (95% CI, 19.3–26.5) months, respectively.

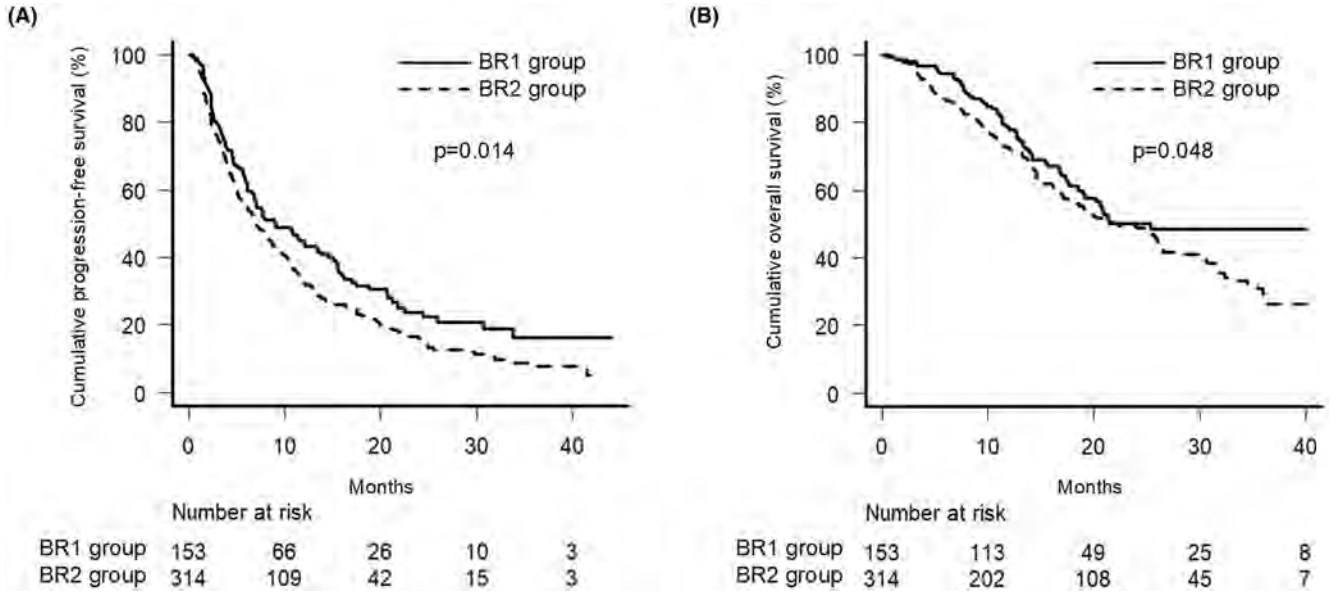

FIGURE 2 | (a) Cumulative PFS curves stratified by BR categories. The cumulative PFS rates at 3, 6, 12 and 18 months were 79.3%, 61.1%, 43.4% and 31.6%, respectively, in the BR1 group (solid line) and 74.8%, 55.2%, 31.8% and 22.8%, respectively, in the BR2 group (dashed line) ($p = 0.014$, log-rank test). (b) Cumulative OS curves stratified by BR categories. The cumulative OS rates at 6, 12, 18 and 24 months were 94.5%, 77.9%, 61.1% and 50.1%, respectively, in the BR1 (solid line), and 86.6%, 72.2%, 56.4% and 49.0%, respectively, in the BR2 group (dashed line) ($p = 0.048$, log-rank test). Atezo/Bev, atezolizumab plus bevacizumab; BR, borderline resectable; OS, overall survival; PFS, progression-free survival.

Figure 2a presents the PFS curves stratified by BR categories. The median PFS for the BR1 and BR2 groups was 9.0 (95% CI, 6.8–13.4) and 6.8 (95% CI, 6.0–8.6) months, respectively ($p = 0.014$).

Figure 2b depicts the OS curves stratified by BR categories. The median OS for the BR1 and BR2 groups was 25.3 (95% CI, 18.9–not achieved) and 22.3 months (95% CI, 18.1–not achieved) respectively ($p = 0.048$).

Figure 3a illustrates the PFS curves stratified by tumour number and size categories, demonstrating no significant differences in PFS among the three groups ($p = 0.065$). Figure 3b shows PFS curves stratified by vascular invasion categories, revealing a significant difference in PFS among the groups ($p < 0.001$). Post hoc comparisons utilising the Holm test identified significant differences in all pairwise comparisons (Table S2). Figure 3c presents PFS curves stratified by EHS categories, showing no significant differences among the groups ($p = 0.063$).

Figure 3d depicts OS curves stratified by tumour number and size categories, with no significant differences in OS observed among the three groups ($p = 0.261$). Figure 3e displays OS curves stratified by vascular invasion categories, revealing a significant difference in OS among the groups ($p < 0.001$). Post hoc analyses using the Holm test identified significant differences across all pairwise comparisons (Table S2). Figure 3f shows OS curves stratified by EHS categories, indicating no significant differences in OS among the groups ($p = 0.106$).

3.3 | Factors Associated With PFS and OS

Multivariable analysis using Model 1 identified the following factors as independently associated with PFS: age ≥ 75 years (HR, 1.309; 95% CI, 1.057–1.622; $p = 0.014$), ALBI grade 2 or 3 (HR, 1.494; 95% CI, 1.201–1.859; $p < 0.001$), NLR ≥ 3 (HR, 1.289; 95% CI, 1.030–1.613; $p = 0.027$), α-fetoprotein ≥ 100 ng/mL (HR, 1.523; 95% CI, 1.214–1.912; $p < 0.001$) and BR2 (HR, 1.360; 95% CI, 1.076–1.718; $p = 0.010$) (Table 2).

Multivariable analysis using Model 2 also identified independent factors associated with PFS: age ≥ 75 years (HR, 1.373; 95% CI, 1.105–1.706; $p = 0.004$), ALBI grade 2 or 3 (HR, 1.432; 95% CI, 1.144–1.792; $p = 0.002$), α-fetoprotein ≥ 100 ng/mL (HR, 1.432; 95% CI, 1.132–1.811; $p = 0.003$), vascular invasion categories iii group (HR, 3.188; 95% CI, 2.051–4.953; $p < 0.001$) and EHS category iii (HR, 1.690; 95% CI, 1.140–2.504; $p = 0.009$) (Table 2).

For OS, multivariable analysis with Model 1 revealed that age ≥ 75 years (HR, 1.522; 95% CI, 1.155–2.007; $p = 0.003$), ALBI grade 2 or 3 (HR, 2.411; 95% CI, 1.802–3.224; $p < 0.001$), NLR ≥ 3 (HR, 1.635; 95% CI, 1.233–2.169; $p < 0.001$), α-fetoprotein ≥ 100 ng/mL (HR, 1.530; 95% CI, 1.152–2.032; $p = 0.003$) and BR2 (HR, 1.421; 95% CI, 1.048–1.927; $p = 0.024$) were independently associated with OS (Table 3). Similarly, multivariable analysis using Model 2 identified age ≥ 75 years (HR, 1.607; 95% CI, 1.213–2.128; $p < 0.001$), ALBI grade 2 or 3 (HR, 2.302; 95% CI, 1.710–3.098; $p < 0.001$), NLR ≥ 3 (HR, 1.610; 95% CI, 1.208–2.145; $p = 0.001$) and vascular invasion category iii (HR, 2.650; 95% CI, 1.541–4.556; $p < 0.001$) as independent factors associated with OS (Table 3).

3.4 | Therapeutic Response

Table 4 details the therapeutic response rates, with the best radiological response rates as follows: CR, 4.3%; PR, 23.5%; SD, 50.5%; and PD, 21.7%. The overall response rate (ORR) was 27.8% and the disease control rate (DCR) was 78.3%. No significant

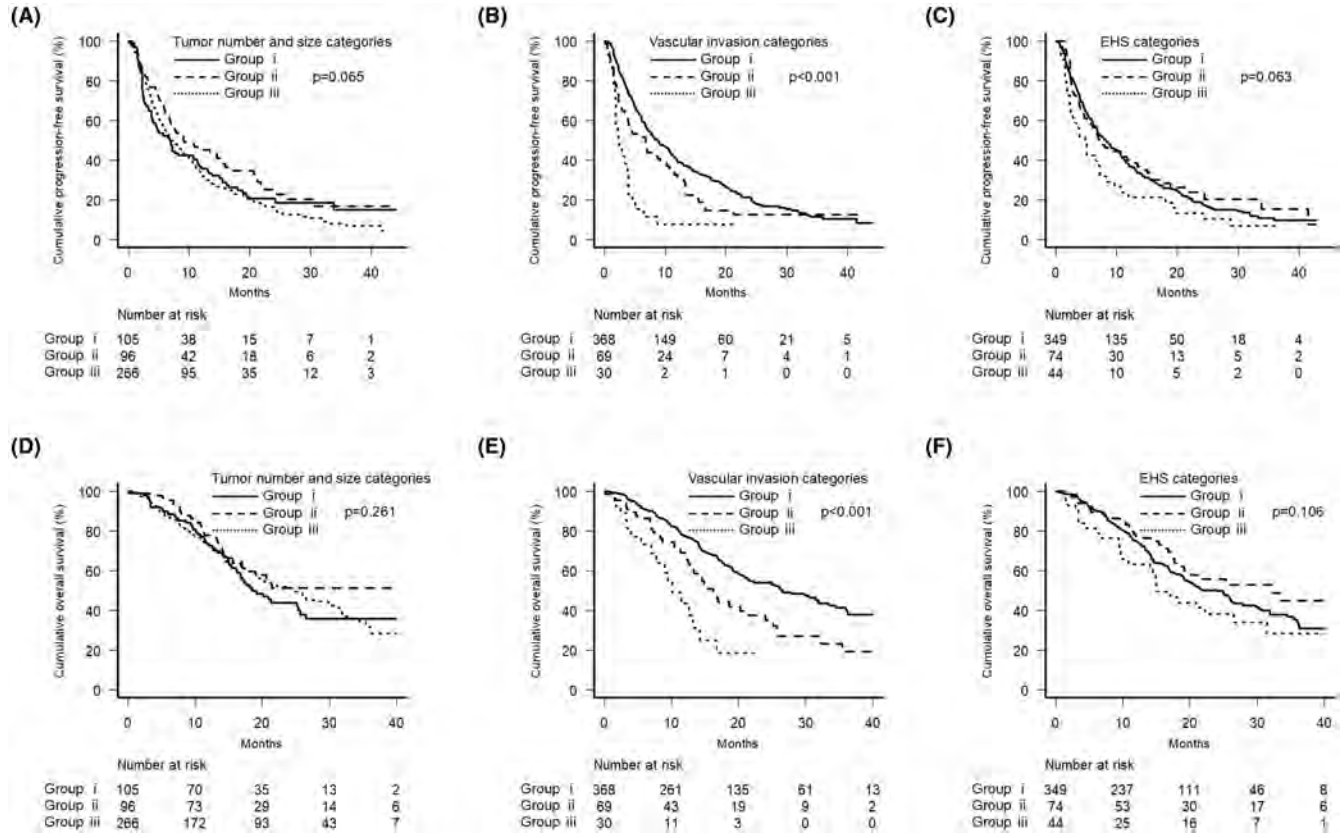

FIGURE 3 | (a) Cumulative PFS curves stratified by tumour number and size categories. The cumulative PFS rates at 3, 6, 12 and 18 months were 67.0%, 52.4%, 35.7% and 24.9%, respectively, in the group i (solid line), 82.3%, 65.0%, 45.4% and 34.8%, respectively, in the group ii (dashed line), and 77.6%, 56.0%, 32.1% and 22.8%, respectively, in the group iii (dotted line) ($p = 0.065$, log-rank test). (b) Cumulative PFS curves stratified by vascular invasion categories. The cumulative PFS rates at 3, 6, 12 and 18 months were 81.0%, 61.3%, 33.8% and 29.5%, respectively, in the group i (solid line), 65.0%, 51.7%, 30.8% and 14.6%, respectively, in the group ii (dashed line), and 42.0%, 15.3%, 7.6% and 7.6%, respectively, in the group iii (dotted line) ($p < 0.001$, log-rank test). (c) Cumulative PFS curves stratified by EHS categories. The cumulative PFS rates at 3, 6, 12 and 18 months were 79.1%, 58.7%, 36.9% and 26.0%, respectively, in the group i (solid line), 72.8%, 58.1%, 38.5% and 28.4%, respectively, in the group ii (dashed line), and 58.9%, 42.4%, 21.2% and 18.6%, respectively, in the group iii (dotted line) ($p = 0.063$, log-rank test). (d) Cumulative OS curves stratified by tumour number and size categories. The cumulative OS rates at 6, 12, 18 and 24 months were 88.6%, 72.6%, 52.5% and 43.9%, respectively, in the group i (solid line), 95.7%, 78.1%, 59.7% and 51.3%, respectively, in the group ii (dashed line), and 87.0%, 73.1%, 59.6% and 51.1%, respectively, in the group iii (dotted line) ($p = 0.261$, log-rank test). (e) Cumulative OS curves stratified by vascular invasion categories. The cumulative OS rates at 6, 12, 18 and 24 months were 90.9%, 77.6%, 63.0% and 54.2%, respectively, in the group i (solid line), 86.2%, 65.8%, 44.1% and 35.0%, respectively, in the group ii (dashed line), and 73.3%, 43.6%, 18.7% and 18.7%, respectively, in the group iii (dotted line) ($p < 0.001$, log-rank test). (f) Cumulative PFS curves stratified by EHS categories. The cumulative OS rates at 6, 12, 18 and 24 months were 90.3%, 74.9%, 58.1% and 49.7%, respectively, in the group i (solid line), 89.6%, 76.5%, 64.0% and 55.7%, respectively, in the group ii (dashed line), and 81.5%, 63.3%,46.8% and 38.3%, respectively, in the group iii (dotted line) ($p = 0.106$, log-rank test). EHS, extrahepatic spread; OS, overall survival; PFS, progression-free survival.

differences in the best radiological response rates were observed between the BR1 and BR2 groups (Table 4).

3.5 | Concomitant or Subsequent Treatments

Figure 4 presents a Sankey diagram illustrating the concomitant or subsequent treatments administered following Atezo/Bev treatment for individual patients in the BR1 ($n = 111$) and BR2 ($n = 250$) cohorts. Conversion therapy (aimed at achieving CR through the addition of local therapies), local therapy (including resection, ablation therapy, TACE or radiotherapy), systemic therapy, and best supportive care (BSC) were employed in 9 (including resection, $n = 1$; 8.1%), 16 (14.4%), 42 (37.8%) and 44 (39.6%) patients in the BR1 cohort, and in 12 (including resection, $n = 1$; 4.8%), 38 (15.2%), 113 (45.2%) and 87 (34.8%) patients in the BR2 cohort ($p = 0.391$).

Moreover, during the follow-up period, surgical intervention for either conversion or tumour reduction was performed in two patients (1.8%) in the BR1 cohort and three patients (1.2%) in the BR2 cohort.

3.6 | Subgroup Analysis

A subgroup analysis was conducted exclusively on patients whose initial treatment for HCC consisted of Atezo/Bev ($n = 122$). Multivariable analysis employing Model 3 identified

TABLE 2 | Multivariable analysis for PFS.

	Model 1			Model 2		
	HR	**95% CI**	***p***	**HR**	**95% CI**	***p***
Age (years)						
<75 (*n* = 251)	1			1		
≥75 (*n* = 216)	1.309	1.057–1.622	0.014	1.373	1.105–1.706	0.004
Sex						
Male (*n* = 365)	1			1		
Female (*n* = 102)	1.085	0.838–1.405	0.534	1.143	0.882–1.481	0.312
HCC aetiology						
Viral (*n* = 237)	1			1		
Non-B, non-C (*n* = 230)	0.922	0.740–1.149	0.469	0.926	0.739–1.160	0.503
ALBI grade						
1 (*n* = 215)	1			1		
2 or 3 (*n* = 253)	1.494	1.201–1.859	<0.001	1.432	1.144–1.792	0.002
NLR						
<3 (*n* = 306)	1			1		
≥3 (*n* = 155)	1.289	1.030–1.613	0.027	1.246	0.991–1.567	0.060
α-Fetoprotein (ng/mL)						
<100 (*n* = 307)	1			1		
≥100 (*n* = 158)	1.523	1.214–1.912	<0.001	1.432	1.132–1.811	0.003
BR categories						
BR1 (*n* = 153)	1					
BR2 (*n* = 314)	1.360	1.076–1.718	0.010			
Tumour number and size categories						
Group i (*n* = 105)				1		
Group ii (*n* = 96)				0.949	0.641–1.407	0.796
Group iii (*n* = 256)				1.257	0.902–1.751	0.177
Vascular invasion categories						
Group i (*n* = 368)				1		
Group ii (*n* = 69)				1.258	0.898–1.761	0.186
Group iii (*n* = 30)				3.188	2.051–4.953	<0.001
EHS categories						
Group i (*n* = 349)				1		
Group ii (*n* = 74)				1.000	0.708–1.413	0.999
Group iii (*n* = 44)				1.690	1.140–2.504	0.009

Abbreviations: ALBI, albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer; BR, borderline resectable; CI, confidence interval; EHS, extrahepatic spread; HCC, hepatocellular carcinoma; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; PFS, progression-free survival.

the following independent factors associated with OS: female sex (HR, 0.476; 95% CI, 0.234–0.967; $p = 0.040$), ALBI grade 2 or 3 (HR, 2.234; 95% CI, 1.200–4.157; $p = 0.011$), tumour number and size categorised as group iii (HR, 2.496; 95% CI, 1.058–5.887; $p = 0.037$) and vascular invasion categorised as group iii (HR, 8.359; 95% CI, 3.453–20.230; $p < 0.001$) (Table S3). Figure S1 illustrates the OS curves stratified by vascular invasion categories, demonstrating a statistically significant difference in OS across the groups ($p < 0.001$). Post hoc analysis using the Holm test revealed significant differences

TABLE 3 | Multivariable analysis for OS.

	Model 1			Model 2		
	HR	**95% CI**	***p***	**HR**	**95% CI**	***p***
Age (years)						
< 75 ($n = 251$)	1			1		
≥ 75 ($n = 216$)	1.522	1.155–2.007	0.003	1.607	1.213–2.128	< 0.001
Sex						
Male ($n = 365$)	1			1		
Female ($n = 102$)	1.251	0.891–1.757	0.196	1.249	0.889–1.755	0.200
HCC aetiology						
Viral ($n = 237$)	1			1		
Non-B, non-C ($n = 230$)	0.950	0.719–1.254	0.715	0.969	0.734–1.279	0.823
ALBI grade						
1 ($n = 215$)	1			1		
2 or 3 ($n = 253$)	2.411	1.802–3.224	< 0.001	2.302	1.710–3.098	< 0.001
NLR						
< 3 ($n = 306$)	1			1		
≥ 3 ($n = 155$)	1.635	1.233–2.169	< 0.001	1.610	1.208–2.145	0.001
α-Fetoprotein (ng/mL)						
< 100 ($n = 307$)	1			1		
≥ 100 ($n = 158$)	1.530	1.152–2.032	0.003	1.345	0.999–1.810	0.051
BR categories						
BR1 ($n = 153$)	1					
BR2 ($n = 314$)	1.421	1.048–1.927	0.024			
Tumour number and size categories						
Group i ($n = 105$)				1		
Group ii ($n = 96$)				0.704	0.428–1.158	0.166
Group iii ($n = 256$)				0.946	0.629–1.422	0.790
Vascular invasion categories						
Group i ($n = 368$)				1		
Group ii ($n = 69$)				1.316	0.874–1.983	0.188
Group iii ($n = 30$)				2.650	1.541–4.556	< 0.001
EHS categories						
Group i ($n = 349$)				1		
Group ii ($n = 74$)				0.803	0.509–1.269	0.348
Group iii ($n = 44$)				1.504	0.946–2.391	0.085

Abbreviations: ALBI, albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer; BR, borderline resectable; CI, confidence interval; EHS, extrahepatic spread; HCC, hepatocellular carcinoma; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival.

between groups i and iii, as well as between groups ii and iii (Table S4).

In patients initially treated with Atezo/Bev for HCC, who exhibited portal vein invasion without hepatic vein or bile duct invasion and no evidence of EHS ($n = 84$), the PFS was 21.7 months (95% CI: 7.3–not achieved) in BR1 and 8.1 months (95% CI: 5.1–11.1) in BR2 ($p = 0.052$) (Figure S1a). The OS was not achieved (95% CI: 15.5–not achieved) in BR1 and 21.8 months (95% CI: 14.1–36.2) in BR2 ($p = 0.086$) (Figure S1b).

4 | Discussion

In this multicentre study, patients with unresectable HCC who were treated with Atezo/Bev and met the inclusion criteria for BR1 exhibited a more favourable prognosis than those classified as BR2. Multivariable analysis adjusted for age, sex, HCC aetiology, ALBI grade, α-fetoprotein level, NLR and BR category as covariates (Model 1) revealed that age ≥ 75 years, ALBI grade 2 or 3, NLR ≥ 3, α-fetoprotein ≥ 100 ng/mL, and BR2 were independently associated with both poor PFS and poor OS. Furthermore, an additional multivariable analysis (Model 2), incorporating tumour number and size, vascular invasion category and EHS category as additional covariates, revealed that in addition to the significant variables identified in Model 1—age, ALBI grade, NLR and α-fetoprotein—the vascular invasion category iii group and EHS category iii group were independently associated with poor PFS. Regarding OS, in addition to age, ALBI grade, and NLR, the vascular invasion category iii group was independently associated with poor OS. Moreover, in the Kaplan–Meier analysis of PFS and OS, multiple comparisons of vascular invasion categories revealed significant differences among all groups. Conversely, when evaluating tumour number and size, as well as EHS categories, no significant differences were detected in the Kaplan–Meier method using the log-rank test for PFS and OS. These findings suggest that among patients with HCC classified as BR1 or BR2 who received Atezo/Bev treatment, vascular invasion category is a particularly critical prognostic factor in the oncological criteria for HCC resectability. Our findings suggest that even among a cohort with preserved liver function according to Child–Pugh classification A, our prognosis is influenced not only by resectability but also by liver function, with ALBI grade serving as an independent prognostic factor.

TABLE 4 | Therapeutic response.

	Overall ($n = 467$)	BR1 group ($n = 153$)	BR2 group ($n = 314$)	p
CR	19 (4.3%)	8 (5.5%)	11 (3.7%)	0.773
PR	104 (23.5%)	35 (24.1%)	69 (23.2%)	
SD	223 (50.5%)	73 (50.3%)	150 (50.5%)	
PD	96 (21.7%)	29 (20.0%)	67 (22.6%)	
ORR	27.8%	29.7%	26.8%	0.572
DCR	78.3%	80.0%	77.5%	0.623

Abbreviations: BR, borderline resectable; CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Kawamura et al. [23] examined the prognosis of 156 patients with HCC presenting with intrahepatic target nodules. These patients were classified into three groups based on oncological criteria for resectability (R, BR1 or BR2) and had initially undergone systemic therapy with either Lenvatinib ($n = 118$) or Atezo/Bev ($n = 58$). Their findings revealed that patients classified as R and BR1 exhibited significantly better OS compared to those in the BR2 group (R vs. BR2, $p = 0.012$; BR1 vs. BR2, $p = 0.004$). However, no significant difference in OS was observed between the R and BR1 groups ($p = 1.000$), despite BR1 patients exhibiting a significantly worse oncological profile. Furthermore, the study highlighted that among patients with advanced HCC and intrahepatic target nodules, those classified as BR1 represent a favourable subgroup for treatment with a combination of systemic sequential therapy involving two or more agents and locoregional treatment. Although our study included only patients classified as BR1 and BR2, both PFS and OS were significantly superior in the BR1 group. However, analysis using the Sankey diagram indicated no significant differences in concomitant or subsequent therapies between BR1 and BR2. Compared to the study by Kawamura et al. [23], the strength of our study lies in the exclusive use of a single systemic therapy regimen (i.e., Atezo/Bev) to evaluate the prognosis of a large cohort

FIGURE 4 | Sankey diagram depicting concomitant or subsequent treatments. In the BR1 cohort ($n = 111$), 9 (8.1%), 1 (0.9%), 12 (10.8%), 2 (1.8%), 6 (5.4%), 3 (2.7%), 32 (28.8%), 1 (0.9%), 0 (0.0%) and 44 (39.6%) patients received conversion therapy, ablation therapy, TACE, radiotherapy, Dur/Tre, sorafenib, lenvatinib, ramucirumab, cabozantinib and BSC as concomitant or subsequent treatments during or after Atezo/Bev therapy. In the BR2 cohort ($n = 250$), 12 (4.8%), 2 (0.8%), 1 (0.4%), 29 (11.6%), 6 (2.4%), 9 (3.6%), 7 (2.8%), 87 (34.8%), 7 (2.8%), 3 (1.2%) and 87 (34.8%) patients received these treatments. Atezo/Bev, atezolizumab plus bevacizumab; BSC, best supportive care; Dur/Tre, durvalumab plus tremelimumab; TACE, transarterial chemoembolization.

of patients with unresectable HCC ($n = 467$) (112 patients classified as BR1 or BR2 who received Atezo/Bev as their initial treatment). This analysis was conducted not only based on BR1 and BR2 classifications under oncological criteria for resectability but also considering specific oncological components.

Although not evaluated in this cohort, incorporating the CRAFITY score [18] and the α-FAtE model [24] previously reported by our group into the oncological criteria for resectability as prognostic indicators for patients receiving Atezo/Bev may offer greater utility in guiding treatment selection and prognostication across different BR categories.

Major vascular invasion has been associated with a younger age at diagnosis, the presence of symptoms, poorer ECOG-PS, impaired liver function, elevated α-fetoprotein levels and larger HCCs, as analysed in a cohort of 4774 patients with HCC, in which the prevalence of major vascular invasion was 11.1% [25]. Furthermore, an increased incidence of major vascular invasion has been correlated with deteriorated ECOG-PS, ascites, and more severe hepatic dysfunction [25]. A systematic review encompassing 54 studies, including 6187 patients with HCC treated with immune checkpoint inhibitors, suggested that the presence of EHS may be indicative of a reduced ORR (odds ratio: 0.77; 95% CI: 0.63–0.96), although it may not significantly impact PFS (multivariable analysis: HR: 1.27; 95% CI: 0.70–2.31) or OS (multivariable analysis: HR: 1.23; 95% CI: 0.70–2.16) [26]. Moreover, the presence of major vascular invasion may not significantly influence ORR (odds ratio: 0.84; 95% CI: 0.64–1.10) but has been shown to be predictive of inferior PFS (multivariable analysis: HR: 1.75; 95% CI: 1.07–2.84) and OS (multivariable analysis: HR: 2.03; 95% CI: 1.31–3.14) [26]. In the present study, we demonstrated that among the newly proposed components of the oncological resectability classification, vascular invasion is the most critical prognostic factor in patients with HCC undergoing treatment with Atezo/Bev.

The Child–Pugh classification system comprises five parameters: serum albumin, total bilirubin, prothrombin time, ascites and encephalopathy [27]. Widely employed for assessing hepatic function, this system has been incorporated into the HCC staging framework [2]. However, its reliance on the subjective evaluation of encephalopathy and ascites presents inherent limitations. Furthermore, serum albumin levels are closely associated with the severity of ascites [27]. Notably, the Child–Pugh classification system was originally designed for patients with cirrhosis and is not specifically tailored for those with HCC. In contrast, the ALBI grade [28]—a more recently developed, objective metric for evaluating liver function—exclusively considers serum albumin and total bilirubin levels. The ALBI grade has demonstrated superior prognostic accuracy compared to both the Child–Pugh classification [29, 30] and the liver damage classification system in patients with HCC [31]. Although the present study cohort comprised only patients with preserved hepatic function, classified as Child–Pugh A, findings indicate that prognosis is influenced not only by tumour progression but also by ALBI grade. These results underscore the necessity of accounting for hepatic reserve at the treatment initiation to optimise the prognosis of patients with HCC undergoing Atezo/Bev therapy.

This study has certain limitations, most notably its reliance on a hospital-based population and its retrospective design. Although the investigation included patients with unresectable HCC who underwent Atezo/Bev treatment across multiple centres in Japan, future prospective studies should endeavour to incorporate a larger and more nationally representative patient cohort, complemented by extended follow-up periods. Another limitation stems from the multicentre nature of our cohort, which may have introduced variability based on the discretion of individual centres and attending physicians, particularly concerning concomitant or subsequent treatments involving Atezo/Bev.

In conclusion, among HCC patients with a low probability of surgical resection (i.e., those classified as BR1 or BR2) undergoing Atezo/Bev treatment, vascular invasion serves as a critical prognostic factor for tumour progression. Moreover, beyond tumour progression, preserved liver function also plays a pivotal role in determining the prognosis of patients treated with Atezo/Bev. Further studies are required to confirm these findings in other patient populations.

Author Contributions

Toshifumi Tada, Atsushi Hiraoka and Takashi Kumada conceived the study and participated in its design and coordination. Tomomitsu Matono, Toshifumi Tada, Atsushi Hiraoka, Masashi Hirooka, Kazuya Kariyama, Joji Tani, Masanori Atsukawa, Koichi Takaguchi, Ei Itobayashi, Shinya Fukunishi, Hiroki Nishikawa, Kazunari Tanaka, Kunihiko Tsuji, Toru Ishikawa, Kazuto Tajiri, Yuichi Koshiyama, Hidenori Toyoda, Chikara Ogawa, Takeshi Hatanaka, Satoru Kakizaki, Kazuhito Kawata, Hideko Ohama, Fujimasa Tada, Kazuhiro Nouso, Asahiro Morishita, Akemi Tsutsui, Takuya Nagano, Norio Itokawa, Tomomi Okubo, Taeang Arai, Takashi Nishimura, Michitaka Imai, Hisashi Kosaka, Atsushi Naganuma, Tomoko Aoki, Hidekatsu Kuroda, Yutaka Yata, Hideyuki Tamai, Takanori Matsuura, Shohei Komatsu, Yoshihide Ueda, Yoshiko Nakamura, Osamu Yoshida, Kosuke Matsui, Shinichiro Nakamura, Hirayuki Enomoto, Masaki Kaibori, Takumi Fukumoto and Yoichi Hiasa performed data curation. Toshifumi Tada carried out statistical analysis and interpretation. Tomomitsu Matono, Toshifumi Tada and Atsushi Hiraoka drafted the manuscript. Takashi Kumada Masatoshi Kudo supervised all tasks related to this manuscript. All authors read and approved the final version of this manuscript.

Ethics Statement

The study protocol conformed to the ethical guidelines of the Declaration of Helsinki. The study was approved by the institutional ethics review committee of NHO Takasaki General Medical Center (approval number: TGMC2024-003; date of decision: 2024/04/24).

Consent

Written informed consent was obtained from each patient before study enrollment.

Conflicts of Interest

Toshifumi Tada: lecture fees from AbbVie, AstraZeneca, Eisai and Chugai. Atsushi Hiraoka: lecture fees from Eisai, Bayer, Eli Lilly and Otsuka. Hidenori Toyoda: lecture fees from AbbVie, Eisai, Gilead, Terumo and Bayer. Masatoshi Kudo: advisory role at Eisai, Ono, MSD, Bristol-Myers Squibb and Roche; lecture fees from Eisai, Bayer, MSD, Bristol-Myers Squibb, Eli Lilly and EA Pharma; and research funding from Gilead Sciences, Taiho, Sumitomo Dainippon Pharma, Takeda,

Otsuka, EA Pharma, AbbVie and Eisai. None of the other authors have potential conflicts of interest to declare.

Data Availability Statement

The datasets are available from the corresponding author upon reasonable request.

References

1. F. Bray, M. Laversanne, H. Sung, et al., "Global Cancer Statistics 2022: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries," *CA: A Cancer Journal for Clinicians* 74 (2024): 229–263.

2. J. M. Llovet, C. Brú, and J. Bruix, "Prognosis of Hepatocellular Carcinoma: The BCLC Staging Classification," *Seminars in Liver Disease* 19 (1999): 329–338.

3. J. M. Llovet, A. Villanueva, J. A. Marrero, et al., "Trial Design and Endpoints in Hepatocellular Carcinoma: AASLD Consensus Conference," *Hepatology* 73 (2021): 158–191.

4. J. M. Llovet, S. Ricci, V. Mazzaferro, et al., "Sorafenib in Advanced Hepatocellular Carcinoma," *New England Journal of Medicine* 359, no. 4 (2008): 378–390.

5. A. L. Cheng, Y. K. Kang, Z. Chen, et al., "Efficacy and Safety of Sorafenib in Patients in the Asia-Pacific Region With Advanced Hepatocellular Carcinoma: A Phase III Randomised, Double-Blind, Placebo-Controlled Trial," *Lancet Oncology* 10 (2009): 25–34.

6. M. Kudo, R. S. Finn, S. Qin, et al., "Lenvatinib Versus Sorafenib in First-Line Treatment of Patients With Unresectable Hepatocellular Carcinoma: A Randomised Phase 3 Non-Inferiority Trial," *Lancet* 391 (2018): 1163–1173.

7. R. S. Finn, S. Qin, M. Ikeda, et al., "Atezolizumab Plus Bevacizumab in Unresectable Hepatocellular Carcinoma," *New England Journal of Medicine* 382 (2020): 1894–1905.

8. G. K. Abou-Alfa, G. Lau, M. Kudo, et al., "Tremelimumab Plus Durvalumab in Unresectable Hepatocellular Carcinoma," *NEJM Evidence* 1 (2022): EVIDoa2100070.

9. A. G. Singal, J. M. Llovet, M. Yarchoan, et al., "AASLD Practice Guidance on Prevention, Diagnosis, and Treatment of Hepatocellular Carcinoma," *Hepatology* 78 (2023): 1922–1965.

10. M. Kudo, Y. Kawamura, K. Hasegawa, et al., "Management of Hepatocellular Carcinoma in Japan: JSH Consensus Statements and Recommendations 2021 Update," *Liver Cancer* 10 (2021): 181–223.

11. K. Akahoshi, J. Shindoh, M. Tanabe, et al., "Oncological Resectability Criteria for Hepatocellular Carcinoma in the Era of Novel Systemic Therapies: The Japan Liver Cancer Association and Japanese Society of Hepato-Biliary-Pancreatic Surgery Expert Consensus Statement 2023," *Liver Cancer* 13 (2024): 1–11.

12. J. Bruix and M. Sherman, "Management of Hepatocellular Carcinoma," *Hepatology* 42 (2005): 1208–1236.

13. J. Bruix and M. Sherman, "Management of Hepatocellular Carcinoma: An Update," *Hepatology* 53 (2011): 1020–1022.

14. K. Hasegawa, N. Takemura, T. Yamashita, et al., "Clinical Practice Guidelines for Hepatocellular Carcinoma: The Japan Society of Hepatology 2021 Version (5th JSH-HCC Guidelines)," *Hepatology Research* 53 (2023): 383–390.

15. M. Kudo, M. Kitano, T. Sakurai, and N. Nishida, "General Rules for the Clinical and Pathological Study of Primary Liver Cancer, Nationwide Follow-Up Survey and Clinical Practice Guidelines: The Outstanding Achievements of the Liver Cancer Study Group of Japan," *Digestive Diseases* 33 (2015): 765–770.

16. National Cancer Institute, "Protocol Development Cancer Therapy," 2025, https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm-ctc_40.

17. T. Tada, T. Kumada, A. Hiraoka, et al., "New Prognostic System Based on Inflammation and Liver Function Predicts Prognosis in Patients With Advanced Unresectable Hepatocellular Carcinoma Treated With Atezolizumab Plus Bevacizumab: A Validation Study," *Cancer Medicine* 12 (2023): 6980–6993.

18. T. Hatanaka, S. Kakizaki, A. Hiraoka, et al., "Prognostic Impact of C-Reactive Protein and Alpha-Fetoprotein in Immunotherapy Score in Hepatocellular Carcinoma Patients Treated With Atezolizumab Plus Bevacizumab: A Multicenter Retrospective Study," *Hepatology International* 16 (2022): 1150–1160.

19. T. Tanaka, A. Hiraoka, T. Tada, et al., "Therapeutic Efficacy of Atezolizumab Plus Bevacizumab Treatment for Unresectable Hepatocellular Carcinoma in Patients With Child-Pugh Class A or B Liver Function in Real-World Clinical Practice," *Hepatology Research* 52 (2022): 773–783.

20. T. Tada, T. Kumada, A. Hiraoka, et al., "Neutrophil-Lymphocyte Ratio Predicts Early Outcomes in Patients With Unresectable Hepatocellular Carcinoma Treated With Atezolizumab Plus Bevacizumab: A Multicenter Analysis," *European Journal of Gastroenterology & Hepatology* 34 (2022): 698–706.

21. A. Hiraoka, K. Michitaka, T. Kumada, et al., "Validation and Potential of Albumin-Bilirubin Grade and Prognostication in a Nationwide Survey of 46,681 Hepatocellular Carcinoma Patients in Japan: The Need for a More Detailed Evaluation of Hepatic Function," *Liver Cancer* 6 (2017): 325–336.

22. Y. Kanda, "Investigation of the Freely Available Easy-to-Use Software 'EZR' for Medical Statistics," *Bone Marrow Transplantation* 48 (2013): 452–458.

23. Y. Kawamura, N. Akuta, J. Shindoh, et al., "Newly Established Borderline Resectable 1 (BR1) Category Is One of the Favorable Candidates for Selecting the Use of Multidisciplinary Combination Therapy in Patients With Advanced Hepatocellular Carcinoma Treated With Systemic Therapy," *Hepatology Research* 55 (2025): 275–282.

24. F. Rossari, T. Tada, G. Suda, et al., "α-FAtE: A New Predictive Score of Response to Atezolizumab Plus Bevacizumab for Unresectable Hepatocellular Carcinoma," *International Journal of Cancer* 154 (2024): 1043–1056.

25. M. Guarino, A. Cucchetti, G. Pontillo, et al., "Pattern of Macrovascular Invasion in Hepatocellular Carcinoma," *European Journal of Clinical Investigation* 51 (2021): e13542.

26. C. L. Han, B. W. Tian, L. J. Yan, et al., "Efficacy and Safety of Immune Checkpoint Inhibitors for Hepatocellular Carcinoma Patients With Macrovascular Invasion or Extrahepatic Spread: A Systematic Review and Meta-Analysis of 54 Studies With 6187 Hepatocellular Carcinoma Patients," *Cancer Immunology, Immunotherapy* 72 (2023): 1957–1969.

27. R. N. Pugh, I. M. Murray-Lyon, J. L. Dawson, M. C. Pietroni, and R. Williams, "Transection of the Oesophagus for Bleeding Oesophageal Varices," *British Journal of Surgery* 60 (1973): 646–649.

28. P. J. Johnson, S. Berhane, C. Kagebayashi, et al., "Assessment of Liver Function in Patients With Hepatocellular Carcinoma: A New Evidence-Based Approach: The ALBI Grade," *Journal of Clinical Oncology* 33 (2015): 550–558.

29. J. A. Marrero, L. M. Kulik, C. B. Sirlin, et al., "Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases," *Hepatology* 68 (2018): 723–750.

30. T. Tada, T. Kumada, H. Toyoda, et al., "Impact of Albumin-Bilirubin Grade on Survival in Patients With Hepatocellular Carcinoma Who

Received Sorafenib: An Analysis Using Time-Dependent Receiver Operating Characteristic," *Journal of Gastroenterology and Hepatology* 34 (2019): 1066–1073.

31. A. Hiraoka, T. Kumada, M. Kudo, et al., "Albumin-Bilirubin (ALBI) Grade as Part of the Evidence-Based Clinical Practice Guideline for HCC of the Japan Society of Hepatology: A Comparison With the Liver Damage and Child-Pugh Classifications," *Liver Cancer* 6 (2017): 204–215.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.