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Original article

Transarterial radioembolization versus atezolizumab-bevacizumab for the treatment of hepatocellular carcinoma with portal vein tumor thrombosis

Youngsu Park [a,b,1], Yuri Cho [b,1], Seung Up Kim [c,1], Aryoung Kim [d,e,1], Hyunjae Shin [a], Hyo-Cheol Kim [f], In Joon Lee [g], Gyoung Min Kim [h], Dongho Hyun [i], Yunmi Ko [a], Jeayeon Park [a], Jae Woong Yoon [a], Gyung Sun Lim [a], Moon Haeng Hur [a], Yun Bin Lee [a], Eun Ju Cho [a], Jeong-Hoon Lee [a], Su Jong Yu [a], Jung-Hwan Yoon [a], Jin Wook Chung [f], Dong Hyun Sinn [d], Yoon Jun Kim [a,*]

[a] Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, 03080 Seoul, Republic of Korea
[b] Center for Liver and Pancreatobiliary Cancer, National Cancer Center, 10408 Goyang, Republic of Korea
[c] Department of Internal Medicine and Yonsei Liver Center, Severance Hospital, Yonsei University College of Medicine, 03722 Seoul, Republic of Korea
[d] Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 06351 Seoul, Republic of Korea
[e] Department of Internal Medicine, Inje University Ilsan Paik Hospital, 10380 Goyang, Republic of Korea
[f] Department of Radiology, Seoul National University Hospital, Seoul National University College of Medicine, 03080 Seoul, Republic of Korea
[g] Department of Radiology, National Cancer Center, 10408 Goyang, Republic of Korea
[h] Department of Radiology, Severance Hospital, Yonsei University College of Medicine, 03722 Seoul, Republic of Korea
[i] Department of Radiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 06351 Seoul, Republic of Korea

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ABSTRACT

Purpose: The purpose of this study was to compare transarterial radioembolization (TARE) and atezolizumab plus bevacizumab (Atezo/Bev) in treatment-naïve patients with hepatocellular carcinoma (HCC) and portal vein tumor thrombosis (PVTT) without extrahepatic metastasis.
Material and methods: This multicenter retrospective study evaluated 213 patients initially treated with TARE or Atezo/Bev between 2016 and 2023. The primary outcome was overall survival, and the secondary outcomes were progression-free survival, objective response rate, and safety. Baseline characteristics were adjusted using inverse probability treatment weighting or propensity score matching.
Results: Deaths occurred in 36 out of 125 patients (28.8 %) in the TARE group and 57 out of 88 patients (64.8 %) in the Atezo/Bev group. The median overall survival was significantly longer in the TARE group (27.5 months) than in the Atezo/Bev group (8.6 months) ($P < 0.01$), consistent across analyses before matching (hazard ratio [HR], 0.38; 95% confidence interval [CI]: 0.25–0.58; $P < 0.01$), after inverse probability treatment weighting (HR, 0.49; 95 % CI: 0.28–0.85; $P = 0.01$), and after propensity score matching (HR, 0.40; 95% CI: 0.22–0.74; $P < 0.01$). In the PVTT subgroup involving segmental to lobar branches (Vp1–3), TARE demonstrated prolonged overall survival (HR, 0.36; 95 % CI: 0.20–0.63; $P < 0.01$), with no significant difference in patients with Vp4. The TARE and Atezo/Bev groups exhibited similar progression-free survival. No significant differences in objective response rate were found between TARE group (22.2–30.9 %) and Atezo/Bev group (30.6–30.9 %). Adverse events were less frequent in the TARE group than in the Atezo/Bev group. The incidence of grade ≥ 2 ascites and variceal bleeding were significantly lower in the TARE group (12.0 % and 1.7 %, respectively) than in the Atezo/

Abbreviations: AFP, Alpha-fetoprotein; aHR, Adjusted hazard ratio; ALBI, Albumin-bilirubin; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; Atezo/Bev, Atezolizumab plus Bevacizumab; BMI, Body mass index; CI, Confidence interval; CTCAE, Common Terminology Criteria for Adverse Events version; ECOG, Eastern Cooperative Oncology Group; HAIC, Hepatic artery infusion chemotherapy; HBV, Hepatitis B virus; HCC, Hepatocellular carcinoma; HCV, Hepatitis C virus; HPFS, Hepatic progression-free survival; HR, Hazard ratio; ICI, Immune checkpoint inhibitor; INR, International normalized ratio; IPTW, Inverse probability treatment weighting; NR, Not reached; OR, Odds ratio; ORR, Objective response rate; OS, Overall survival; PFS, Progression-free survival; PIVKA-II, Protein induced by vitamin K absence II; PS, Performance status; PSM, Propensity score matching; PT, Prothrombin time; PV, Portal vein; PVTT, Portal vein tumor thrombosis; REILD, Radioembolization-induced liver disease; TACE, Transarterial chemoembolization; TARE, Transarterial radioembolization.

* Corresponding author.
E-mail address: yoonjun@snu.ac.kr (Y.J. Kim).
[1] These four authors contributed equally to this study as co-first authors.

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Bev group (20.5 % and 8 %, respectively) (both $P < 0.05$). No significant differences in Child–Pugh score aggravation of ≥ 2 were observed between the TARE group (14.4 %) and the Atezo/Bev group (25 %) ($P = 0.08$). *Conclusion:* For patients with preserved liver function and locally advanced HCC involving segmental or lobar PVTT, TARE may be preferable to Atezo/Bev.

1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most commonly diagnosed cancer worldwide and the third leading cause of cancer-related deaths [1]. Even with active surveillance in high-risk populations [2,3], most patients with HCC are diagnosed at an intermediate or advanced stage, according to the Barcelona Clinic Liver Cancer staging [4]. Portal vein tumor thrombosis (PVTT) is an important tumor characteristic in terms of HCC development and patient prognosis, accounting for 10–40 % of the initial presentations of patients with HCC [5]. HCC with PVTT exhibits a median overall survival (OS) of three months without treatment [6] and 4–34 months with treatment [7]. According to Barcelona Clinic Liver Cancer staging, HCC with portal vein invasion is classified as advanced stage, for which systemic therapy is recommended [4,8]. However, recent studies have demonstrated favorable outcomes with transarterial radioembolization (TARE) [9–11], and there is still no consensus on a treatment method for HCC with PVTT [5,7,12].

TARE involves the direct administration of Yttrium-90-labeled microspheres to viable tumors via the hepatic artery [13]. Compared to external beam radiotherapy, this approach enables more continuous radiation release while preserving non-tumor liver tissues. According to various studies, TARE is an effective and safe treatment for patients with unresectable HCC [14–16]. In the SARAH trial, TARE revealed no significant difference in efficacy and safety compared with sorafenib in unresectable HCC [17]. Previous studies have indicated that TARE may serve as an effective treatment option for patients with HCC and PVTT [9,10]. In a recent study, TARE showed superior OS compared to tyrosine kinase inhibitors, with fewer adverse events in patients with HCC and segmental or lobar PVTT [11].

Immunotherapy has become the first-line systemic treatment for advanced-stage HCC. The IMbrave150 trial demonstrated that atezolizumab plus bevacizumab (Atezo/Bev) significantly prolonged survival compared to sorafenib [18,19]. Similarly, the HIMALAYA trial showed that tremelimumab plus durvalumab improved OS compared with sorafenib [20]. Despite these advances, the relative efficacy and safety of TARE versus Atezo/Bev in patients with locally advanced HCC remain uncertain. One study reported no significant difference in effectiveness when comparing TARE and Atezo/Bev indirectly [21]. However, that study had several limitations, including an absence of a head-to-head comparison [17,21,22].

The purpose of this study was to compare TARE and Atezo/Bev in treatment-naïve patients with HCC and PVTT, without extrahepatic metastasis.

2. Materials and methods

2.1. Patients

The medical records of 290 consecutive patients newly diagnosed with HCC and PVTT, who were treated with either TARE or Atezo/Bev at four specialized centers in South Korea (Seoul National University Hospital, National Cancer Center, Severance Hospital, Samsung Medical Center) between January 2016 and June 2023, were retrospectively reviewed (Fig. 1). The institutional review board at each participating hospital approved this study. Data were extracted from the electronic medical records by board-certified physicians using a standardized case report form to ensure consistency across centers. All baseline characteristics, tumor parameters, laboratory results, and treatment details were collected according to predefined definitions agreed upon by all participating institutions. Missing data for continuous variables were imputed using the median value. Patients with advanced HCC and PVTT preserved hepatic function (that is, Child-Pugh class A or B), and those without distant metastases and received TARE or Atezo/Bev were included. Patients with: (*i*), HCC with lymph node or distant metastasis; (*ii*), HCC accompanied by intrahepatic cholangiocarcinoma; (*iii*), a history of malignancy within the past 5 years; (*iv*), a history of liver transplantation; (*v*), a Child–Pugh score of ≥ 10; and (*vi*), an Eastern Cooperative Oncology Group (ECOG) performance status of ≥ 3 were excluded. After applying the exclusion criteria, 213 patients were finally included in the analysis.

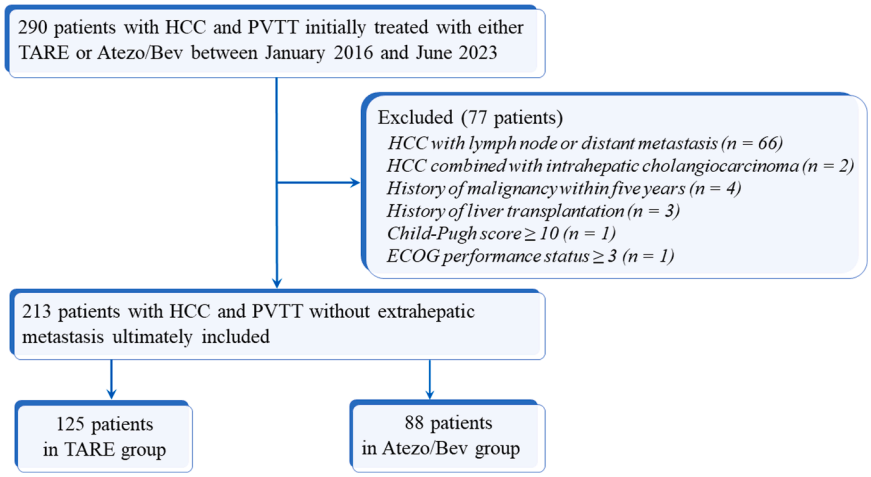

Fig. 1. Study flow chart.
Atezo/Bev indicates atezolizumab plus bevacizumab; ECOG indicates Eastern Cooperative Oncology Group; HCC indicates hepatocellular carcinoma; PVTT indicates portal vein tumor thrombosis; TARE indicates transarterial radioembolization.

2.2. Treatments

At each hospital, TARE was conducted by interventional radiologists with over 10 years of experience. Prior to treatment, a simulation procedure was performed using 99mTc-labeled macroaggregated albumin to evaluate lung shunt fraction by lung SPECT [23] and to detect any extrahepatic deposition. Yttrium-90-labeled microspheres (TheraSphere® [glass microspheres, Boston Scientific] or SIR-Spheres® [resin microspheres, Sirtex Medical]) were administered to the target lesions via the hepatic artery, with the microsphere type chosen based on the preference of the interventional radiologists. TARE was conducted in the absence of any technical contraindications such as excessive lung radiation exposure. Regarding TheraSphere®, TARE was performed unless the lung dose exceeded 30 Gy. The lung dose was calculated using the Medical Internal Radiation Dose measurement. For SIR-Spheres®, TARE was performed when the lung dose, determined through a partition model, was below 25 Gy.

In the Atezo/Bev group, patients received 1,200 mg of atezolizumab and 15 mg/kg of bevacizumab every 3 weeks. Dose reduction or discontinuation was decided based on the disease progression or adverse events as evaluated by physicians. Atezo/Bev was contraindicated in patients with a recent history of variceal bleeding, autoimmune diseases, immunosuppressive medication use, or organ transplantation.

2.3. Outcomes and assessment

The primary outcome of this study was OS, defined as the time from the initiation of treatment to either death from all causes or the end of follow-up. Survival data were sourced from electronic health records and the national database maintained by the Ministry of the Interior and Safety of Korea through resident registration numbers. The secondary outcomes were progression-free survival (PFS), hepatic PFS (HPFS), best treatment response, PVTT response, and safety. HPFS was defined as the time from treatment initiation to the first recorded progression within the liver, while overall PFS was defined as the time from treatment initiation to disease progression at any location, including extrahepatic sites, or death from any cause. The best treatment response was evaluated using the modified Response Evaluation Criteria in Solid Tumors guideline [24]. Radiologists evaluated the PVTT response using the following criteria: complete response, resolution of PVTT with revascularization; partial response, a marked reduction in PVTT size and extent; stable disease, no appreciable change; and progressive disease, a notable increase in PVTT size or extent, or the emergence of new PVTT. Adverse events related to treatment were assessed in both groups. Ascites of grade 2 or greater was considered an adverse event, as were newly developed variceal bleeding, hepatic encephalopathy, an increase of $\geq$ 2 points in the Child–Pugh score, radiation pneumonitis, and radiation-induced liver disease (REILD) [25]. Immune checkpoint inhibitor (ICI)-related adverse events were assessed according to the Common Terminology Criteria for Adverse Events version (CTCAE) 5.0.

HCC was diagnosed using either radiological or histological methods in accordance with international guidelines [2,3,26]. PVTT was categorized based on the classification proposed by the Liver Cancer Study Group of Japan as follows: Vp1, tumor thrombus confined to the segmental branches of the portal vein (PV); Vp2, involvement of the second-order branches of the PV; Vp3, involvement of the first-order branches of the PV; and Vp4, involvement of the main trunk and/or the contralateral branches of the PV relative to the primarily affected lobe [27]. Data for each patient were gathered from electronic health records, including details on age, sex, height, body weight, cause of underlying liver disease, ECOG performance status, comorbidities, and laboratory test results.

2.4. Statistical analysis

Categorical variables were expressed as raw numbers and percentages, and continuous variables were expressed as means ± standard deviations (SD) if normally distributed, or as medians, first quartiles (Q1) and third quartiles (Q3) if not normally distributed, as determined by the Shapiro-Wilk test [28]. Categorical and continuous variables were compared using Chi-squared tests and independent t-tests, respectively. The baseline characteristics of the TARE and Atezo/Bev groups were balanced using inverse probability of treatment weighting (IPTW) and propensity score matching (PSM), respectively. OS, PFS, and HPFS were analyzed through the Kaplan–Meier method and compared using the log-rank test. Independent risk factors of progression or survival were examined using the Cox proportional hazards model, with hazard ratio (HR) and 95% confidence interval (CI) reported. Factors related to an increased objective response rate (ORR) were identified using logistic regression, and the odds ratios (OR) were determined. All statistical analyses were conducted using R software (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria), with statistical significance defined as $P < 0.05$.

3. Results

3.1. Baseline characteristics

This study involved 213 patients; 125 (median age 61 [Q1, 52; Q3, 63] years; 100 men) and 88 (median age 62 [Q1, 55; Q3, 69] years; 76 men) patients in the TARE and Atezo/Bev groups, respectively. Median follow up period was 7.9 (Q1, 4.1; Q3, 14.6) months. In the unmatched cohort, the Atezo/Bev group included more patients with ECOG of 1 than in the TARE group (25.0 % *vs*. 11.2 %; $P = 0.01$) (Table 1). The Atezo/Bev group had lower albumin levels, higher aspartate aminotransferase levels, and a greater proportion of patients with an albumin-bilirubin (ALBI) grade of $\geq$ 2 (62.5 % *vs*. 42.4 % in the TARE group) (all $P < 0.05$) (Table 1). The Atezo/Bev group had higher protein induced by vitamin K absence II (PIVKA-II) levels ($P < 0.01$) than the TARE group. The Atezo/Bev group exhibited more frequent ill-defined tumors, larger tumor sizes, and a greater number of tumors (all $P < 0.05$). In the Atezo/Bev group, 55.7 % of the patients had Vp4 PVTT, compared to 25.6 % in the TARE group. After applying IPTW or PSM, the baseline characteristics between the two groups were well-balanced.

Table 2 provides an overview of the TARE treatment. The median absorbed dose and delivered radiation activity in the TARE group was 267.5 Gy (Q1, 150.0; Q3, 315.0) and 4.1 GBq (Q1, 2.7; Q3, 5.0), respectively. The median lung shunt fraction and lung dose were 5.4 % (Q1, 2.9; Q3, 6.6) and 9.8 Gy (Q1, 3.2; Q3, 14.6), respectively. In the TARE group, the median target liver and tumor volumes were 888.5 mL (Q1, 557.3; Q3, 1195.0) and 419.5 mL (Q1, 112.5; Q3, 522.5), respectively.

3.2. Overall survival analysis (primary outcome)

3.2.1. Matched and unmatched cohort

In the unmatched cohort, mortality occurred in 36 patients (28.8 %) receiving TARE and in 57 patients (64.8 %) receiving Atezo/Bev. The TARE group demonstrated a median OS of 27.5 months (Q1, 18.1; Q3, not reached), compared to 8.6 months (Q1, 7.1; Q3, 12.5) in the Atezo/Bev group (Table 3). These results remained consistent after balancing with IPTW or PSM. Fig. 2 illustrates the Kaplan–Meier curves comparing the OS between the treatment groups. The TARE group showed a significantly longer OS than the Atezo/Bev group (log-rank, $P < 0.01$) (Fig. 2). Similar findings were observed in the study cohorts balanced using either IPTW (log-rank, $P < 0.01$) or PSM (log-rank, $P < 0.01$) (Fig. 2).

The multivariable Cox analysis of the unmatched cohort revealed that TARE was an independent variable associated with a reduced mortality risk compared to Atezo/Bev (TARE *vs*. Atezo/Bev: adjusted HR, 0.38; 95 % CI: 0.25–0.58; $P < 0.01$) (Table 4). A Child–Pugh score of B, larger tumor sizes, and bilobar tumor involvement were associated

Table 1
Baseline characteristics of the transarterial radioembolization and atezolizumab/bevacizumab groups.

	Unmatched cohort			After IPTW			After PSM		
Variables	TARE (n = 125)	Atezo/Bev (n = 88)	*P*	TARE	Atezo/Bev	*P*	TARE (n = 55)	Atezo/Bev (n = 55)	*P*
Age (year)	61.0 (51.9; 69.0)	62.0 (55.1; 69.0)	0.19	61.4 (53.0; 68.0)	62.0 (55.0; 69.0)	0.71	59.0 (48.0; 66.7)	61.0 (54.5; 67.0)	0.22
Sex			0.31			0.49			0.80
Male	100 (80.0)	76 (86.4)		23 (82.3)	76 (86.4)		45 (81.8)	47 (85.5)	
Female	25 (20.0)	12 (13.6)		5 (17.7)	12 (13.6)		10 (18.2)	8 (14.5)	
Cause of HCC			0.08			0.09			0.67
HBV	93 (74.4)	55 (62.5)		21 (75.6)	55 (62.5)		42 (76.4)	39 (70.9)	
HCV	8 (6.4)	4 (4.6)		1 (4.2)	4 (4.6)		3 (5.4)	2 (3.6)	
Others	24 (19.2)	29 (33.0)		6 (20.2)	29 (32.9)		10 (18.2)	14 (25.5)	
ECOG performance status			0.01			0.28			0.35
0	111 (88.8)	66 (75.0)		23 (83.5)	66 (75.0)		46 (83.6)	41 (74.5)	
1	14 (11.2)	22 (25.0)		5 (16.5)	22 (25.0)		9 (16.4)	14 (25.5)	
Child-Pugh score			0.43			0.66			0.79
A	111 (88.8)	74 (84.1)		23 (81.0)	74 (84.1)		46 (83.6)	48 (87.3)	
B	14 (11.2)	14 (15.9)		5 (19.0)	14 (15.9)		9 (16.4)	7 (12.7)	
ALBI Grade			< 0.01			0.14			0.09
1	72 (57.6)	33 (37.5)		14 (50.0)	33 (37.5)		31 (56.4)	21 (38.2)	
2 or 3	53 (42.4)	55 (62.5)		14 (50.0)	55 (62.5)		24 (43.6)	34 (61.8)	
Albumin (g/dL)	4.1 (3.7; 4.4)	3.9 (3.6; 4.1)	0.02	4.0 (3.6; 4.2)	3.9 (3.6; 4.1)	0.40	4.0 (3.7; 4.4)	3.9 (3.6; 4.1)	0.19
Bilirubin (mg/dL)	0.8 (0.6; 1.2)	1.0 (0.6; 1.4)	0.059	0.9 (0.6; 1.4)	1.0 (0.6; 1.4)	0.75	0.8 (0.6; 1.4)	0.9 (0.6; 1.3)	0.96
AST (U/L)	57.0 (37.0; 81.0)	77.5 (53.0; 128.5)	< 0.01	67.1 (44.5; 89.0)	77.5 (53.0; 128.5)	0.06	62.0 (44.5; 84.5)	78.0 (47.0; 128.5)	0.09
ALT (U/L)	36.0 (23.0; 54.0)	39.0 (26.0; 58.5)	0.29	35.1 (24.0; 52.9)	39.0 (26.0; 58.5)	0.26	34.0 (22.5; 50.0)	38.0 (27.0; 60.5)	0.20
PT (INR)	1.1 (1.0; 1.2)	1.1 (1.0; 1.2)	0.11	1.1 (1.0; 1.2)	1.1 (1.0; 1.2)	0.24	1.1 (1.0; 1.1)	1.1 (1.0; 1.2)	0.17
Creatinine (mg/dL)	0.8 (0.7; 0.9)	0.8 (0.7; 0.9)	0.11	0.8 (0.7; 0.9)	0.8 (0.7; 0.9)	0.27	0.8 (0.7; 0.9)	0.8 (0.6; 0.9)	0.21
Platelet count (× 10^3/μL)	178.0 (127.0; 245.0)	172.5 (125.5; 255.0)	0.81	167.0 (121.0; 224.5)	172.0 (124.0; 250.0)	0.42	158.0 (129.5; 226.0)	181.0 (125.5; 257.5)	0.47
AFP (ng/mL)	1391.9 (46.9; 13277.0)	1872.5 (68.4; 43751.0)	0.47	1648.7 (67.1; 18557.3)	1871.6 (64.2; 42140.5)	0.95	1865.1 (205.6; 29034.0)	1524.0 (42.4; 43751.0)	0.65
PIVKA-II (mAU/mL)	2169.0 (319.5; 10339.5)	10454.0 (2307.5; 51399.0)	< 0.01	4636.5 (707.3; 29395.3)	9131.0 (2296.0; 50610.0)	0.09	4027.0 (599.5; 25757.0)	8783.0 (2367.0; 38246.0)	0.13
Tumor type			< 0.01			0.17			0.09
Well-defined (nodular)	44 (35.2)	11 (13.9)		6 (22.4)	11 (13.9)		18 (32.7)	8 (16.3)	
Ill-defined (infiltrative)	81 (64.8)	68 (86.1)		22 (77.6)	68 (86.1)		37 (67.3)	41 (83.7)	
Tumor size (cm)	9.1 (6.5; 12.0)	10.1 (7.4; 15.0)	0.01	9.9 (7.0; 13.1)	10.1 (7.4; 15.0)	0.28	10.0 (7.8; 13.3)	12.0 (6.8; 15.0)	0.37
Tumor number			< 0.01			0.86			0.74
1	77 (61.6)	36 (40.9)		13 (45.0)	36 (40.9)		29 (52.7)	28 (50.9)	
2	10 (8.0)	7 (8.0)		2 (8.3)	7 (8.0)		3 (5.4)	6 (10.9)	
≥ 3	38 (30.4)	45 (51.1)		13 (46.7)	45 (51.1)		23 (41.9)	21 (38.2)	
Tumor involvement			0.18			0.45			0.85
Unilobar	78 (62.4)	46 (52.3)		13 (46.0)	46 (52.3)		31 (56.4)	33 (60.0)	
Bilobar	47 (37.6)	42 (47.7)		15 (54.0)	42 (47.7)		24 (43.6)	22 (40.0)	
Bile duct invasion	21 (16.8)	13 (14.8)	0.84	5 (18.0)	13 (14.8)	0.59	8 (14.5)	10 (18.2)	0.80
PVTT grade			< 0.01			0.19			0.32
Vp1	25 (20.0)	9 (10.2)		4 (13.2)	9 (10.2)		7 (12.7)	9 (16.4)	
Vp2	21 (16.8)	4 (4.6)		3 (12.4)	4 (4.5)		10 (18.2)	4 (7.3)	
Vp3	47 (37.6)	26 (29.6)		9 (32.2)	26 (29.5)		16 (29.1)	21 (38.2)	
Vp4	32 (25.6)	49 (55.7)		12 (42.1)	49 (55.7)		22 (40.0)	21 (38.2)	

Quantitative variables are expressed as medians followed by first and third quartiles into parentheses. Qualitative variables are expressed as raw numbers followed by percentages into parentheses. AFP indicates alpha fetoprotein; ALBI indicates albumin-bilirubin; ALT indicates alanine aminotransferase; AST indicates aspartate aminotransferase; Atezo/Bev indicates atezolizumab plus bevacizumab; BMI i indicates body mass index; ECOG indicates Eastern Cooperative Oncology Group; HBV indicates hepatitis B virus; HCC indicates hepatocellular carcinoma; HCV indicates hepatitis C virus; INR indicates international normalized ratio; IPTW indicates inverse probability of treatment weighting; PIVKA-II indicates protein induced by vitamin K absence II; PS indicates performance status; PSM indicates propensity score matching; PT indicates prothrombin time; PVTT indicates portal vein tumor thrombosis; TARE indicates transarterial radioembolization.

with an increased mortality risk. Consistent outcomes were replicated in the cohorts using either IPTW (HR, 0.49; 95 % CI: 0.28–0.85; $P = 0.01$) or PSM (HR, 0.40; 95 % CI: 0.22–0.74; $P < 0.01$) (Table 5).

3.2.2. Subgroup analyses

Subgroup analyses according to PVTT level are presented in Fig. 3. In patients with Vp1–3 PVTT (excluding those with Vp4), the TARE group exhibited significantly longer OS (HR, 0.36; 95% CI: 0.20–0.63; $P < 0.01$). However, no difference was found in patients with Vp4 PVTT after IPTW ($P = 0.54$). TARE resulted in extended OS (HR, 0.20; 95% CI: 0.07–0.55; $P < 0.01$) in patients with Vp1 or Vp2 PVTT (Fig. 4).

Across the cohort, 69.6 % (87 out of 125) patients in the TARE group and 33.0 % (29 out of 88) patients in the Atezo/Bev group underwent rescue treatment following disease progression (Table 6). In the TARE group, 36.0 % (45 out of 125) patients underwent systemic therapy, followed by transarterial chemoembolization in 19.3 % (17 out of 125) patients. Of the patients in the TARE group treated with subsequent systemic therapy, 27 received immune checkpoint inhibitors, whose

Table 2
Characteristics of transarterial radioembolization treatments in patients with hepatocellular carcinoma and portal vein thrombosis.

Variable	Value
TARE Microsphere (n=109)	
TARE Therasphere®	54 (49.5)
TARE SIR-Spheres®	55 (50.5)
Mean absorbed dose (Gy) (n = 68)	267.5 (150.0; 315.0)
Radiation activity delivered (GBq) (n = 115)	4.1 (2.7; 5.0)
Lung shunt fraction (%) (n = 120)	5.4 (2.9; 6.6)
Lung dose (Gy) (n = 67)	9.8 (3.2; 14.6)
Total liver volume (mL) (n = 27)	1518.2 (1168.0; 1892.0)
Target liver volume (mL) (n = 74)	888.5 (557.3; 1195.0)
Tumor volume (mL) (n = 30)	419.5 (112.5; 522.5)
Injection level (n = 114)	
Lobar	59 (51.8)
Segmental	55 (48.2)

Quantitative variables are expressed as medians followed by first and third quartiles into parentheses. Qualitative variables are expressed as raw numbers followed by percentages into parentheses. TARE indicates transarterial radioembolization.

median OS was 17.5 (Q1, 17.0; Q3, not reached) months. Moreover, 10.4 % (13 out of 125) patients received curative treatment, including nine with surgical resection and four with liver transplantation, with no differences in HR for mortality (HR, 0.16; 95% CI: 0.02–1.20; $P = 0.08$) by comparison with those who did not receive curative treatment. In the Atezo/Bev group, 27.3% (24 of 88) and 3.4% (3 of 88) were subsequently treated with systemic treatment and radiotherapy, respectively; one patient underwent curative treatment, which was surgical resection. The TARE group continued to demonstrate longer OS compared to the Atezo/Bev group (median, 8.3 months; Q1, 6.6; Q3, 11.8) after IPTW, even after excluding 14 patients who underwent subsequent curative treatment (median, 19.9 months; Q1, 16.3; Q3, not reached) (Fig. 5).

3.3. Progression-free survival, hepatic progression-free survival, best treatment response, and portal vein tumor thrombosis response (secondary outcomes)

After applying IPTW, no significant differences were observed in PFS between the TARE group (median, 4.5 months; Q1, 2.6; Q3, 6.8) and the Atezo/Bev group (median, 6.1 months; Q1, 4.1; Q3, 8.1) (log-rank, $P =$

Table 3
Primary and secondary outcomes in unmatched and matched cohorts.

Outcomes	Unmatched cohort			After IPTW			After PSM		
	TARE (n = 125)	Atezo/Bev (n = 88)	*P*	TARE	Atezo/Bev	*P*	TARE (n = 55)	Atezo/Bev (n = 55)	*P*
OS (month)	27.5 (18.1; NR)	8.6 (7.1; 12.5)	< 0.01	25.9 (17.0; NR)	8.6 (7.1; 12.5)	0.01	NR (17.5; NR)	9.5 (7.1; 14.9)	< 0.01
PFS (month)	4.9 (3.4; 7.8)	6.1 (4.1; 8.1)	1.00	4.5 (2.7; 6.8)	6.1 (4.1; 8.1)	0.24	4.9 (2.7; 7.0)	6.0 (3.7; 9.9)	0.68
HPFS (month)	4.9 (3.6; 7.4)	6.3 (4.1; 7.4)	0.39	4.9 (3.3; 6.8)	6.3 (4.1; 7.4)	0.65	4.9 (2.9; 7.2)	6.4 (3.5; 9.2)	0.90
Best response			0.16			0.64			0.31
Complete response	10 (8.0)	2 (2.3)		1 (3.6)	2 (2.3)		4 (7.3)	1 (1.8)	
Partial response	33 (26.4)	21 (23.9)		5 (18.6)	21 (23.9)		13 (23.6)	16 (29.1)	
Stable disease	56 (44.8)	38 (43.1)		15 (51.8)	38 (43.1)		26 (47.2)	19 (34.5)	
Progressive disease	26 (20.8)	27 (30.7)		7 (26.1)	27 (30.7)		12 (21.8)	19 (34.5)	
Objective response rate	43 (34.4)	23 (26.1)	0.26	6 (22.2)	19 (30.6)	0.55	17 (30.9)	17 (30.9)	1.00
Disease control rate	99 (79.2)	61 (69.3)	0.14	21 (73.9)	38 (61.3)	0.57	43 (78.2)	36 (65.5)	0.20
PVTT response			0.09			0.82			0.31
Complete response	13 (10.5)	3 (3.4)		2 (5.3)	3 (3.4)		6 (10.9)	2 (3.6)	
Partial response	28 (22.6)	21 (23.9)		7 (26.0)	21 (23.9)		8 (14.5)	13 (23.6)	
Stable disease	63 (50.8)	40 (45.5)		14 (49.4)	40 (45.5)		31 (56.3)	25 (45.4)	
Progressive disease	20 (16.1)	24 (27.2)		5 (19.3)	24 (27.2)		10 (18.2)	15 (27.3)	
Rescue treatment	87 (75.0)	29 (37.7)	< 0.01	19 (70.4)	28 (36.4)	< 0.01	36 (72.0)	19 (38.0)	< 0.01

Quantitative variables are expressed as medians followed by first and third quartiles into parentheses. Qualitative variables are expressed as raw numbers followed by percentages into parentheses. Atezo/Bev indicates atezolizumab plus bevacizumab; HPFS indicates hepatic progression-free survival; IPTW indicates inverse probability of treatment weighting; NR indicates not reached; OS indicates overall survival; PFS indicates progression-free survival; PSM indicates propensity score matching; PVTT indicates portal vein tumor thrombosis; TARE indicates transarterial radioembolization.

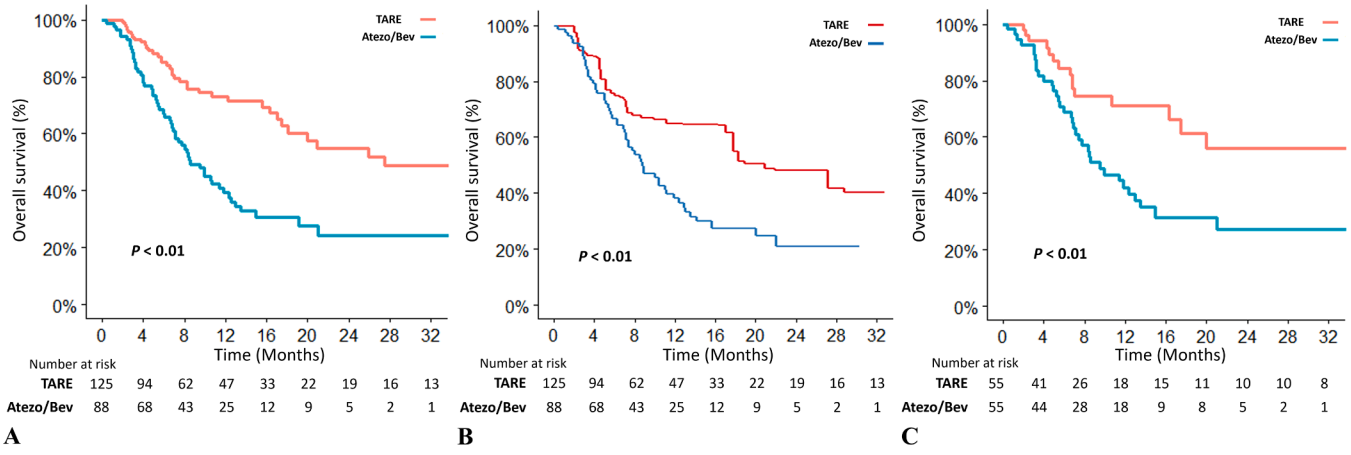

Fig. 2. Graphs show overall survival in the unmatched cohort (A) and matched cohorts after applying inverse probability of treatment weighting (B) and propensity score matching (C). Atezo/Bev indicates atezolizumab plus bevacizumab; IPTW indicates inverse probability of treatment weighting; PSM indicates propensity score matching; TARE indicates transarterial radioembolization.

Table 4
Results of univariable and multivariable Cox analyses in the unmatched cohort.

Characteristic	OS				PFS				HPFS			
	Univariable		Multivariable		Univariable		Multivariable		Univariable		Multivariable	
	HR (95 % CI)	*P*	aHR (95 % CI)	*P*	HR (95 % CI)	*P*	aHR (95 % CI)	*P*	HR (95 % CI)	*P*	aHR (95 % CI)	*P*
TARE *vs.* Atezo/Bev	0.38 (0.25–0.58)	< 0.01	0.48 (0.31–0.74)	< 0.01	1.00 (0.73–1.38)	1.00	1.20 (0.86–1.68)	0.29	0.87 (0.63–1.20)	0.39	1.05 (0.75–1.48)	0.77
Male *vs.* Female	1.41 (0.78–2.56)	0.25			1.03 (0.67–1.57)	0.91			1.05 (0.69–1.61)	0.81		
Age (year)	1.00 (0.99–1.02)	0.69			0.99 (0.97–1.00)	0.03	0.99 (0.98–1.00)	0.16	0.98 (0.97–1.00)	0.01	0.99 (0.97–1.00)	0.07
ECOG PS 1 vs. 0	1.78 (1.07–2.96)	0.03			1.33 (0.87–2.02)	0.18			1.45 (0.96–2.19)	0.08		
Child-Pugh score B *vs.* A	2.42 (1.40–4.20)	< 0.01	2.35 (1.34–4.12)	< 0.01	1.42 (0.88–2.29)	0.15			1.42 (0.88–2.28)	0.15		
Tumor type Ill-defined (infiltrative) *vs.* Well-defined (nodular)	1.65 (1.02–2.66)	0.04			1.40 (0.97–2.02)	0.07			1.30 (0.90-1.88)	0.16		
Tumor size, cm	1.11 (1.05–1.16)	< 0.01	1.08 (1.03–1.14)	< 0.01	1.09 (1.05–1.13)	< 0.01	1.07 (1.03–1.12)	< 0.01	1.10 (1.05–1.14)	< 0.01	1.07 (1.03–1.12)	< 0.01
Tumor number		0.02				0.08				0.04		
1	[reference]				[reference]				[reference]			
2	1.56 (0.70–3.49)				0.98 (0.51–1.90)				0.92 (0.48–1.79)			
≥ 3	1.88 (1.22–2.89)				1.45 (1.04–2.01)				1.51 (1.08–2.10)			
Tumor involvement (bilobar vs. unilobar)	2.05 (1.36–3.10)	< 0.01	1.76 (1.15–2.68)	< 0.01	1.59 (1.15–2.19)	< 0.01	1.51 (1.08–2.13)	0.02	1.64 (1.19–2.26)	< 0.01	1.49 (1.07–2.10)	0.02
PVTT grade		< 0.01				0.01				< 0.01		
Vp1	[reference]				[reference]				[reference]			
Vp2	1.36 (0.51–3.63)				1.66 (0.86–3.19)				1.70 (0.87–3.34)			
Vp3	2.27 (1.05–6.87)				1.89 (1.10–3.28)				1.97 (1.12–3.44)			
Vp4	3.21 (1.50–6.87)				2.31 (1.35–3.97)				2.52 (1.45–4.37)			
Albumin (g/dL)	0.48 (0.32–0.72)	< 0.01			0.86 (0.62–1.19)	0.36			0.77 (0.57–1.06)	0.11		
Bilirubin (mg/dL)	1.63 (1.21–2.18)	< 0.01			1.31 (1.04–1.65)	0.02			1.29 (1.02–1.64)	0.04		
PT (INR)	1.48 (0.61–3.61)	0.38			5.02 (1.94–13.0)	< 0.01			7.34 (2.27–23.8)	< 0.01		

aHR indicates adjusted hazard ratio; Atezo/Bev indicates atezolizumab plus bevacizumab; CI indicates confidence interval; ECOG indicates Eastern Cooperative Oncology Group; HPFS indicates hepatic progression-free survival; HR indicates hazard ratio; INR indicates international normalized ratio; OS indicates overall survival; PFS indicates progression-free survival; PS indicates performance status; PT indicates prothrombin time; PVTT indicates portal vein tumor thrombosis; TARE indicates transarterial radioembolization.

0.24) (Fig. 6). In the matched cohort with IPTW, the HPFS in the TARE group (median, 4.8 months; Q1, 3.3; Q3, 7.2) was not different from that in the Atezo/Bev group (median, 6.3 months; Q1, 4.1; Q3, 7.4) (log-rank $P = 0.65$) (Fig. 7). Similar results were reaffirmed after PSM (Figs. 6 and 7). Subgroup analyses based on the PVTT level using IPTW or PSM showed no significant differences between the two groups regarding PFS and HPFS (Fig. 8 and 9).

With respect to the best treatment and PVTT responses, the TARE group show no significant differences compared with the Atezo/Bev group (Table 3). The ORR of the TARE group was 22.2 % and 30.9 % in the matched cohorts adjusted for IPTW or PSM, respectively; however, that of the Atezo/Bev group was 30.6 % and 30.9 % ($P = 0.55$ and $P > 0.99$, respectively). Logistic regression analysis indicated that the likelihood of ORR did not differ significantly between TARE and Atezo/Bev (OR, 0.75; 95 % CI: 0.34–1.66; $P = 0.49$) (Table 7). In the matched cohorts using IPTW or PSM, the PVTT response in the two groups did not differ significantly. The ORR of PVTT was 25.4–31.3 % in the TARE group and 27.2–27.3 % in the Atezo/Bev group, after IPTW or PSM.

3.4. Safety assessment

The incidence of treatment-related adverse events was significantly lower in the TARE group compared to the Atezo/Bev group (Table 8). Grade ≥2 ascites was more frequently observed in the Atezo/Bev group (20.5 %) than in the TARE group (12.0 %) ($P = 0.02$). Variceal bleeding was more frequently observed in the Atezo/Bev group (8.0%) than in the TARE group (1.7%) ($P = 0.04$). No significant differences in Child–Pugh score aggravation of ≥ 2 were observed between the Atezo/Bev group (25 %) and the TARE group (14.4 %) ($P = 0.08$). Radiation pneumonitis occurred in three (2.7%) patients and radioembolization-induced liver disease in eight (6.4 %) patients of the TARE group. Immune checkpoint inhibitor-related adverse events were observed in 30 patients (34.1 %) in the Atezo/Bev group, although 22 (25.0 %) were grade 1 or 2.

4. Discussion

In this multicenter cohort study, TARE demonstrated significantly longer OS and fewer adverse events than Atezo/Bev in patients with HCC and PVTT, with the most evident advantage in the Vp1–3 PVTT

Table 5
Results of univariable Cox analyses in the matched cohort applying inverse probability of treatment weighting or propensity score matching.

Variable	OS				PFS				HPFS			
	After IPTW		After PSM		After IPTW		After PSM		After IPTW		After PSM	
	HR (95 % CI)	*P*	HR (95 % CI)	*P*	HR (95 % CI)	*P*	HR (95 % CI)	*P*	HR (95 % CI)	*P*	HR (95% CI)	*P*
TARE *vs.* Atezo/Bev	0.49 (0.28–0.85)	0.01	0.40 (0.22–0.74)	< 0.01	1.28 (0.85–1.92)	0.24	1.10 (0.71–1.69)	0.68	1.10 (0.73–1.64)	0.65	0.97 (0.63–1.50)	0.90
Male vs. Female	0.80 (0.38–1.67)	0.55	1.31 (0.58–2.93)	0.52	0.73 (0.39–1.35)	0.31	1.03 (0.57–1.88)	0.92	0.68 (0.42–1.10)	0.12	1.09 (0.60–1.98)	0.77
Age (year)	0.99 (0.97–1.02)	0.56	1.00 (0.98–1.03)	0.90	0.98 (0.96–1.00)	0.04	0.98 (0.96–1.00)	0.052	0.98 (0.96–1.00)	0.04	0.98 (0.96–1.00)	0.07
ECOG PS 1 vs. 0	1.35 (0.79–2.31)	0.27	1.45 (0.75–2.78)	0.27	1.17 (0.71–1.91)	0.54	1.25 (0.74–2.11)	0.41	1.25 (0.75–2.09)	0.39	1.40 (0.83–2.36)	0.21
Child-Pugh score B *vs.* A	2.25 (1.13–3.90)	< 0.01	3.21 (1.55–6.67)	< 0.01	1.58 (0.95–2.64)	0.08	1.58 (0.85–2.95)	0.15	1.54 (0.88–2.72)	0.13	1.64 (0.88–3.06)	0.12
Tumor type Ill-defined (infiltrative) *vs.* Well-defined (nodular)	1.68 (0.92–3.07)	0.09	2.07 (1.01–4.27)	0.048	1.26 (0.80–2.00)	0.32	1.30 (0.78–2.18)	0.31	1.28 (0.80-2.06)	0.30	1.29 (0.77-2.16)	0.33
Tumor size (cm)	1.06 (0.99–1.12)	0.09	1.05 (0.98–1.13)	0.13	1.07 (1.02–1.12)	< 0.01	1.07 (1.02–1.13)	< 0.01	1.06 (1.01–1.11)	0.01	1.07 (1.02–1.13)	< 0.01
Tumor number		0.18		0.10		0.79		0.37		0.50		0.17
1	[reference]		[reference]		[reference]		[reference]		[reference]		[reference]	
2	1.66 (0.81–3.40)		2.29 (0.98–5.38)		1.02 (0.51–2.08)	0.95	1.01 (0.45–2.26)		0.93 (0.47–1.84)		1.01 (0.45–2.26)	
≥ 3	1.48 (0.91–2.39)		1.63 (0.90–2.95)		1.15 (0.76–1.74)	0.50	1.38 (0.87–2.18)		1.24 (0.83–1.84)		1.53 (0.97–2.41)	
Tumor involvement (bilobar *vs.* unilobar)	1.60 (1.02–2.51)	0.04	1.98 (1.14–3.45)	0.02	1.37 (0.92–2.03)	0.12	1.53 (0.99–2.37)	0.056	1.47 (1.00–2.17)	0.048	1.64 (1.06–2.54)	0.03
PVTT grade		0.28		0.15		0.11		0.03		0.09		0.02
Vp1	[reference]		[reference]		[reference]		[reference]		[reference]		[reference]	
Vp2	0.75 (0.24–2.30)		0.52 (0.13–2.01)		1.19 (0.47–2.99)		1.77 (0.70–4.48)		1.55 (0.65–3.71)		1.74 (0.68–4.43)	
Vp3	1.32 (0.58–3.01)		1.53 (0.64–3.66)		1.86 (0.88–3.92)		2.30 (1.04–5.08)		2.04 (0.96–4.32)		2.28 (1.04–5.02)	
Vp4	1.67 (0.77–3.62)		1.62 (0.69–3.82)		2.13 (1.06–4.28)		2.86 (1.32–6.16)		2.39 (1.16–4.92)		2.96 (1.37–6.39)	
Albumin (g/dL)	0.60 (0.40–0.92)	0.02	0.57 (0.3–1.00)	0.05	0.88 (0.58–1.32)	0.52	0.96 (0.62–1.50)	0.86	0.85 (0.57–1.25)	0.41	0.88 (0.57–1.34)	0.54
Bilirubin (mg/dL)	1.51 (1.21–1.89)	< 0.01	1.59 (1.10–2.30)	0.01	1.25 (1.01–1.54)	0.04	1.21 (0.88–1.65)	0.23	1.27 (1.03–1.57)	0.02	1.27 (0.94–1.72)	0.12
PT (INR)	2.71 (0.73–10.1)	0.14	3.77 (0.35–41.2)	0.28	2.78 (0.48–16.2)	0.26	1.75 (0.26–11.6)	0.56	1.49 (0.26–8.56)	0.66	1.48 (0.22–10.0)	0.69

Atezo/Bev indicates atezolizumab plus bevacizumab; CI indicates confidence interval; ECOG indicates Eastern Cooperative Oncology Group; HPFS indicates hepatic progression-free survival; HR indicates hazard ratio; INR indicates international normalized ratio; IPTW indicates inverse probability of treatment weighting; OS indicates overall survival; PFS indicates progression-free survival; PS indicates performance status; PSM indicates propensity score matching; PT indicates prothrombin time; PVTT indicates portal vein tumor thrombosis; TARE indicates transarterial radioembolization.

subgroups. PFS and ORR did not differ significantly between both groups. The TARE group experienced significantly fewer treatment-related adverse events than the Atezo/Bev group, suggesting that TARE may be a preferred initial therapeutic option for locally advanced HCC. To our knowledge, this study provides the first head-to-head comparison of TARE and Atezo/Bev as initial treatments for patients with HCC and PVTT. Robustness was ensured by balancing the baseline characteristics with IPTW and PSM with sensitivity analyses. Moreover, the analyses were extended to include Vp4 invasion, which was excluded in a previous study that compared TARE and tyrosine kinase inhibitors [11].

The prolonged OS of TARE over Atezo/Bev may be attributed to several factors. First, the lower incidence of adverse events in the TARE group likely preserved liver function, enabling more rescue treatments. In contrast, the Atezo/Bev group experienced more adverse events and fewer rescues. Over 50 % of patients in the TARE group received subsequent systemic therapy, including 27 patients treated with immune checkpoint inhibitors, demonstrating a median OS of 17.5 months. This may have contributed to the longer OS observed in the TARE group. Second, the median OS in our Atezo/Bev cohort was 8.6 months, markedly shorter than the 19.2 months reported in IMbrave150 [19]. This discrepancy is likely attributable to poorer baseline liver function and more advanced PVTT in our population. Consistent with this, the AB-real study and other real-world series have shown that patients with ALBI grade 2 experience significantly shorter OS (median, 9.6–10 months) than those with grade 1 (median, 22.5 months to not reached) [29,30]. In our study, 15.9 % of patients were Child–Pugh class B and 62.5 % were ALBI grade 2, whereas IMbrave150 enrolled only Child–Pugh class A patients. These differences in baseline liver reserve likely account for the inferior OS observed in our study. Moreover, our study exclusively included patients with PVTT, with 55.7 % classified as Vp4, compared to 38 % with macrovascular invasion in IMbrave150. In alignment with our findings, the AB-real study reported a median OS of 10 months in patients with PVTT [29]. Third, in this study, TARE delivered greater median radiation activity (4.1 GBq) and mean absorbed dose (267.5 Gy) than in previous studies. A recent study reported prolonged OS with TARE compared to tyrosine kinase inhibitors [11], possibly due to the greater delivered radiation activity (median, 3.6 GBq) and mean absorbed dose (median, 208.0 Gy), while the SARAH trial and the SIRveNIB trial with lower median delivered radiation

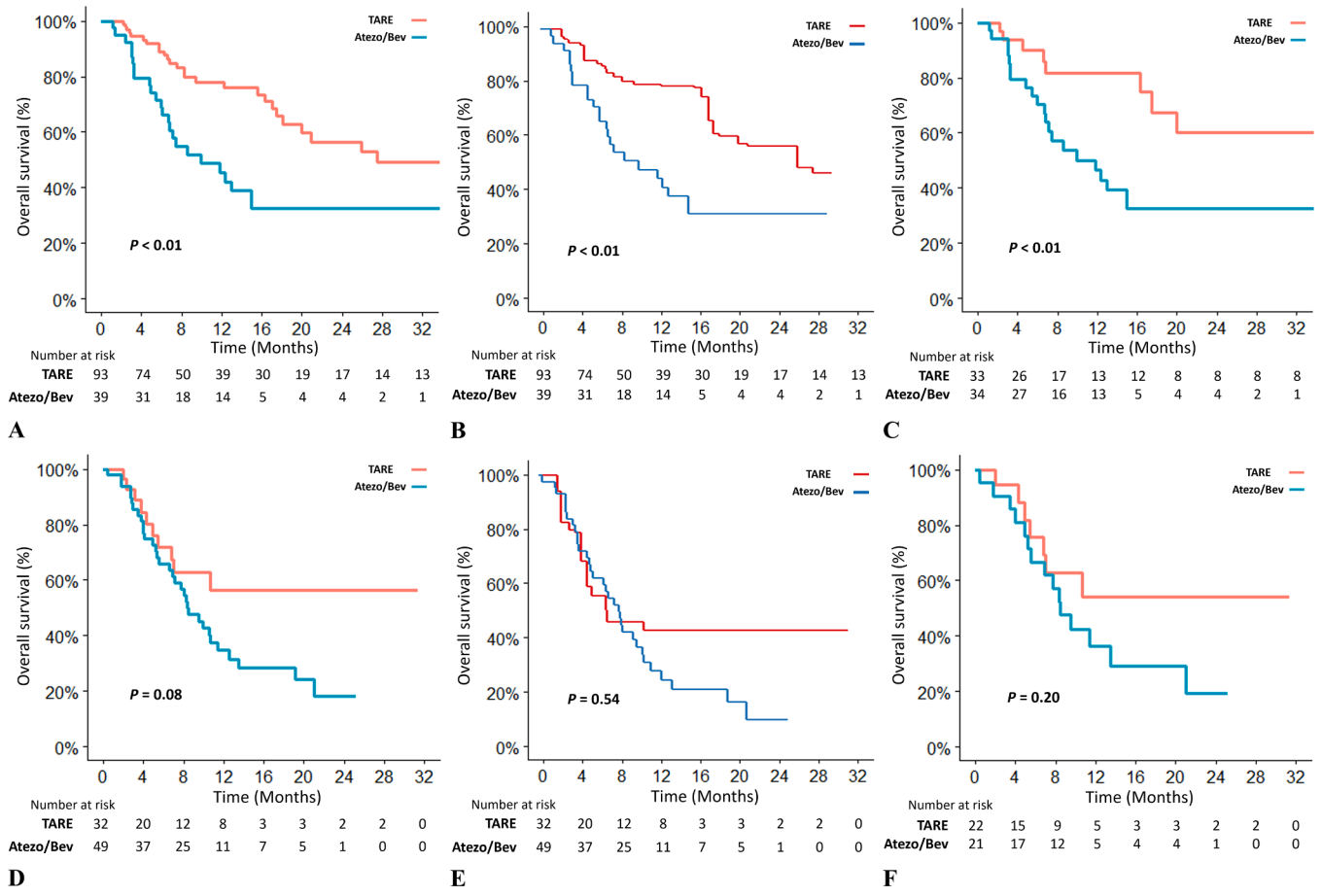

Fig. 3. Graphs show subgroup analyses of overall survival in patients with Vp1–3 level and Vp4 level of portal vein tumor thrombosis. **A**, Vp1–3 subgroup in unmatched cohort; **B**, Vp1–3 subgroup in inverse probability of treatment weighting cohort; **C**, Vp1–3 subgroup in propensity score matching cohort; **D**, Vp4 subgroup in unmatched cohort; **E**, Vp4 subgroup in inverse probability of treatment weighting cohort; and **F**, Vp4 subgroup in propensity score matching cohort. Atezo/Bev indicates atezolizumab plus bevacizumab; IPTW indicates inverse probability of treatment weighting; PSM indicates propensity score matching; PVTT indicates portal vein tumor thrombosis; TARE indicates transarterial radioembolization.

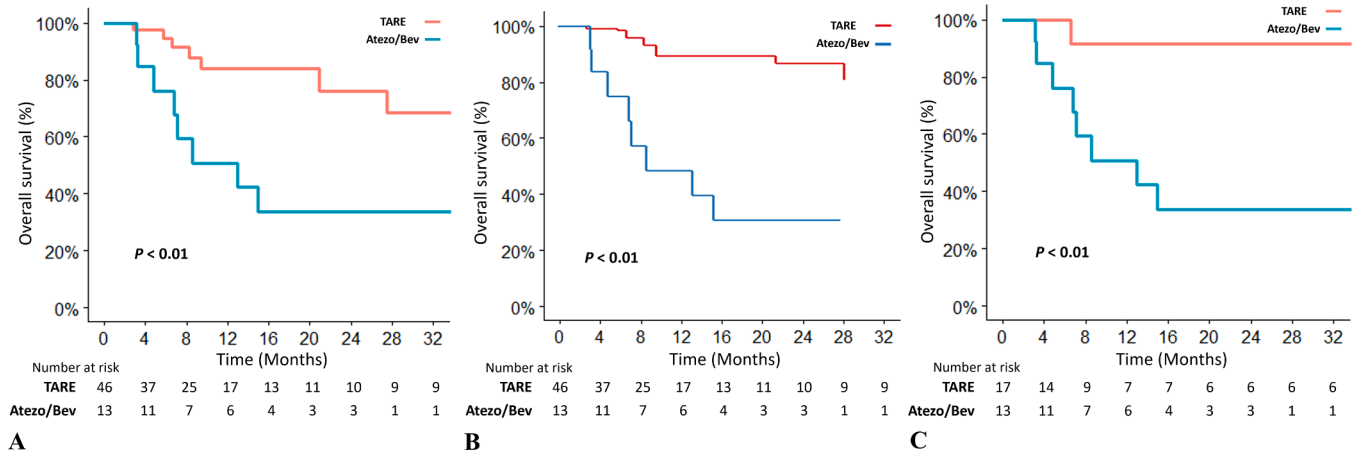

Fig. 4. Graphs show subgroup analyses of overall survival in patients with Vp1–2 level of portal vein tumor thrombosis. **A**, Vp1–2 subgroup in unmatched cohort; **B**, Vp1–2 subgroup in inverse probability of treatment weighting cohort; **C**, Vp1–2 subgroup in propensity score matching cohort. Atezo/Bev indicates atezolizumab plus bevacizumab; IPTW indicates inverse probability of treatment weighting; PSM indicates propensity score matching; PVTT indicates portal vein tumor thrombosis; TARE indicates transarterial radioembolization.

activity (SARAH trial, 1.4 GBq and SIRveNIB trial, 1.6 GBq) showed no significant differences [17,31]. Similarly, DOSISPHERE-01 trial indicated that mean absorbed doses > 205 Gy improve tumor response in patients with locally advanced HCC [32]. Lastly, pre-treatment lung shunt function assessment in TARE-treated patients allowed the exclusion of high lung shunt function cases, a known risk factor for mortality [33], possibly contributing to the improved OS.

Similar PFS was observed in both groups, with prolonged OS noted

Table 6
Subsequent treatment strategies after disease progression.

Subsequent treatment strategies	TARE (n = 87)	Atezo/Bev (n = 29)
TACE	17 (19.3)	2 (6.1)
TARE	2 (2.3)	0 (0.0)
Radiation therapy	5 (5.7)	3 (9.1)
Resection	9 (10.2)	1 (3.0)
Liver transplantation	4 (4.5)	0 (0.0)
Systemic therapy	45 (51.1)	24 (72.7)
Atezo/Bev	20 (23.0)	-
Durvalumab	7 (8.0)	0 (0.0)
Lenvatinib	10 (11.5)	6 (20.7)
Sorafenib	8 (9.2)	16 (55.2)
Atezolizumab plus lenvatinib	0 (0.0)	1 (3.0)
Pembrolizumab plus regorafenib	0 (0.0)	1 (3.0)
HAIC	2 (2.3)	0 (0.0)
Systemic therapy + radiation therapy	3 (3.4)	2 (6.1)
Nivolumab plus radiation therapy	2 (2.3)	0 (0.0)
Sorafenib plus radiation therapy	0 (0.0)	2 (6.1)
Concurrent chemotherapy plus radiation therapy	1 (1.1)	0 (0.0)
Others	1 (1.1)	1 (3.0)

only in the TARE group, which warrants further discussion. TARE is considered locoregional. However, it demonstrated superior OS even in the context of potential distant micrometastasis with PVTT [34,35], presumably due to an abscopal effect from the prolonged radiation associated with TARE [36]. In addition, the variability in responses to TARE highlights the importance of predictive assessment. European guidelines recommend evaluating technetium-99 m macroaggregated albumin uptake at the PVTT before using TARE to assess treatment outcomes [37,38]. Given the higher rate of curative treatment following TARE (10.4 %) and a numerically longer, albeit nonsignificant, survival (HR, 0.16), preliminary assessment and corresponding treatment strategies could improve prognosis. Furthermore, our study's promising results over previous TARE-related studies [17,31] may reflect the advancements in personalized dosimetry and interventional techniques [32].

Despite these encouraging findings, this study has some limitations. First, as this study was retrospective, selection bias and confounding factors may have influenced the outcomes. In this multicenter setting, the allocation of TARE or Atezo/Bev was not determined by uniform criteria but rather varied across institutions, physicians and individual patients. To mitigate this, treatment-naïve patients with preserved liver function were selectively included at each center according to

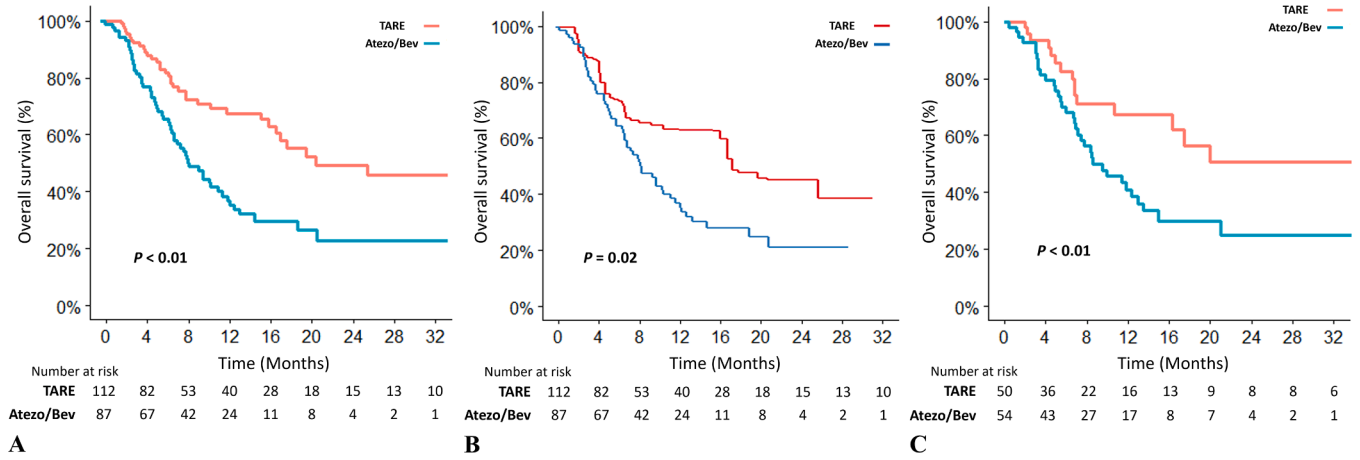

Fig. 5. Graphs show subgroup analyses of overall survival in patients excluding those who received subsequent curative treatment. **A**, Unmatched cohort; **B**, inverse probability of treatment weighting cohort; and **C**, propensity score matching cohort.
Atezo/Bev indicates atezolizumab plus bevacizumab; IPTW indicates inverse probability of treatment weighting; PSM indicates propensity score matching; TARE indicates transarterial radioembolization.

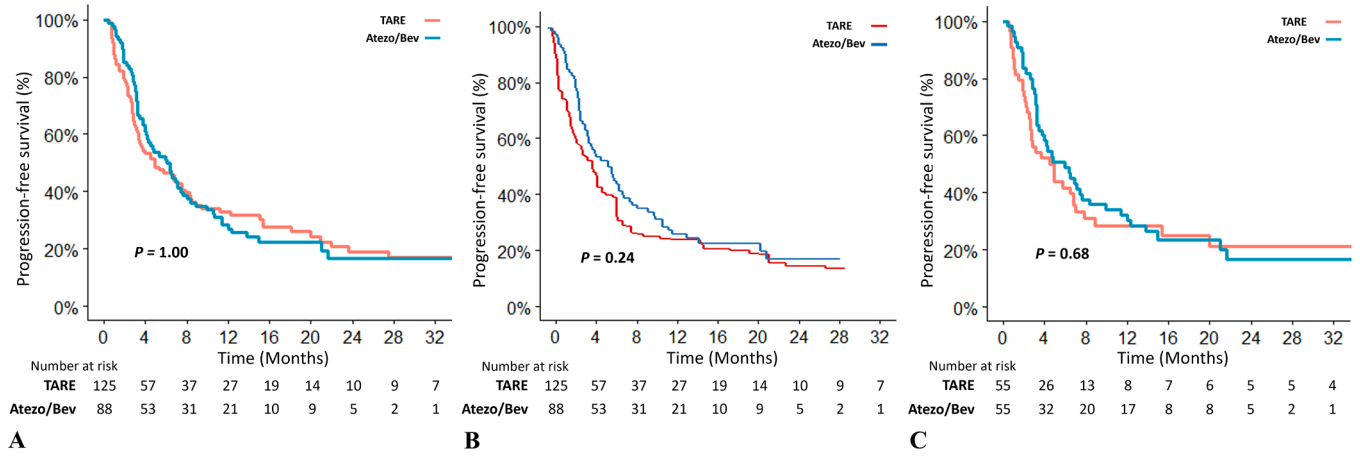

Fig. 6. Graphs show progression-free survival of the unmatched cohort (A) and matched cohorts applying inverse probability of treatment weighting (B) and propensity score matching (C). Atezo/Bev indicates atezolizumab plus bevacizumab; IPTW indicates inverse probability of treatment weighting; PSM indicates propensity score matching; TARE indicates transarterial radioembolization.

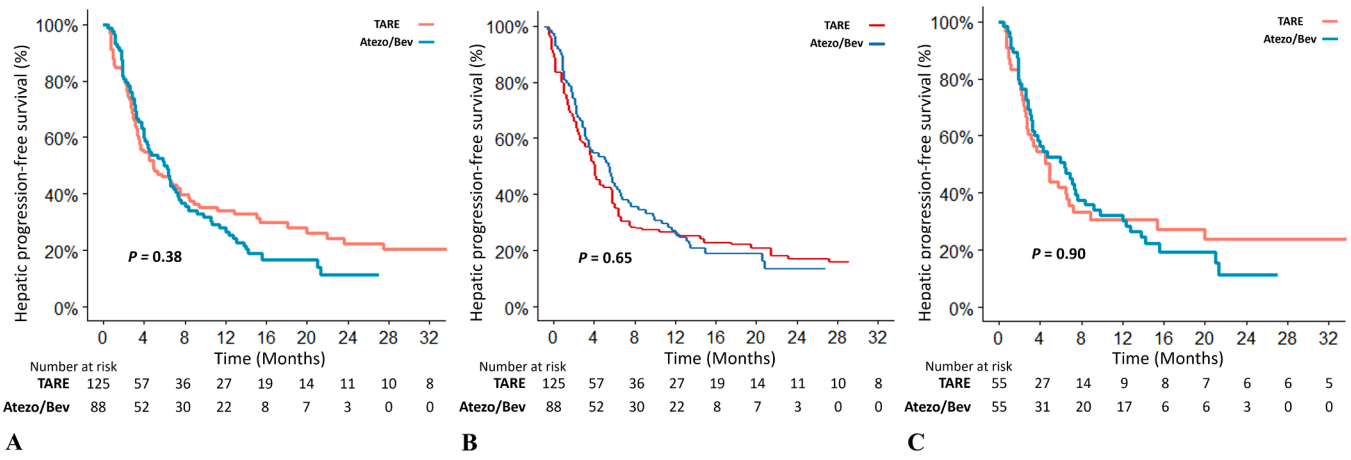

Fig. 7. Graphs show hepatic progression-free survival of the unmatched cohort (A) and matched cohorts applying inverse probability of treatment weighting (B) and propensity score matching (C). Atezo/Bev indicates atezolizumab plus bevacizumab; IPTW indicates inverse probability of treatment weighting; PSM indicates propensity score matching; TARE indicates transarterial radioembolization.

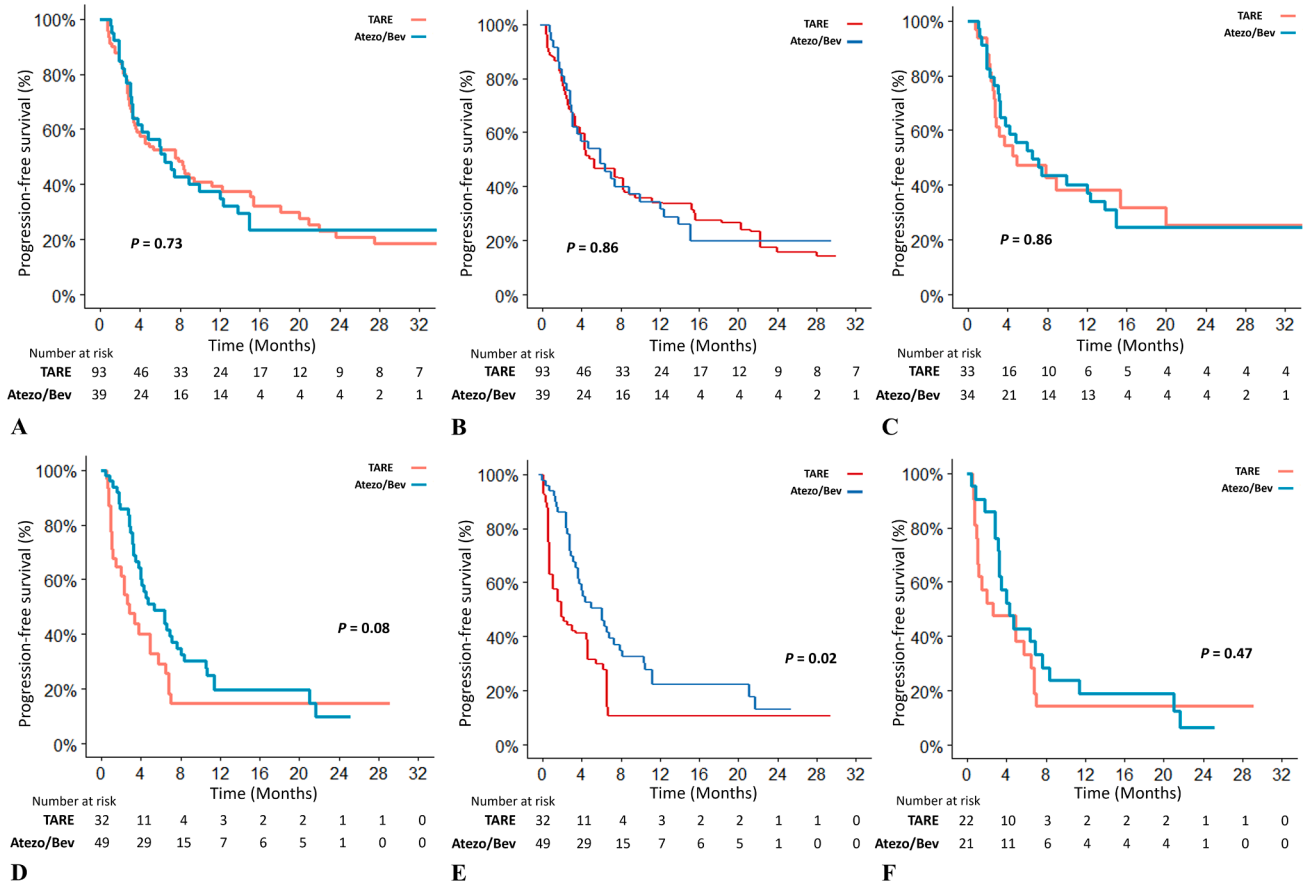

Fig. 8. Graphs show subgroup analyses of progression-free survival based on portal vein tumor thrombosis level. **A**, Vp1–3 subgroup in unmatched cohort; **B**, Vp1–3 subgroup in inverse probability of treatment weighting cohort; **C**, Vp1–3 subgroup in propensity score matching cohort; **D**, Vp4 subgroup in unmatched cohort; **E**, Vp4 subgroup in inverse probability of treatment weighting cohort; and **F**, Vp4 subgroup in propensity score matching cohort. Atezo/Bev indicates atezolizumab plus bevacizumab; IPTW indicates inverse probability of treatment weighting; PSM indicates propensity score matching; PVTT indicates portal vein tumor thrombosis; TARE indicates transarterial radioembolization.

predefined criteria, and IPTW and PSM analyses were applied to reduce potential bias and improve the comparability of baseline characteristics between treatment groups. Second, the baseline characteristics were nevertheless not perfectly balanced, as the Atezo/Bev group had a higher proportion of patients with impaired liver function and poorer performance status. Furthermore, the Atezo/Bev group had higher PIVKA-II levels and comprised more patients with extensive tumor burden and more patients in the Vp4 subgroup. This imbalance may reflect a preference for systemic therapy in patients with more aggressive HCC. However, even in the matched cohort, these differences were minimized, and the survival advantage of TARE remained consistent. Third, safety and adverse events were collected by reviewing medical

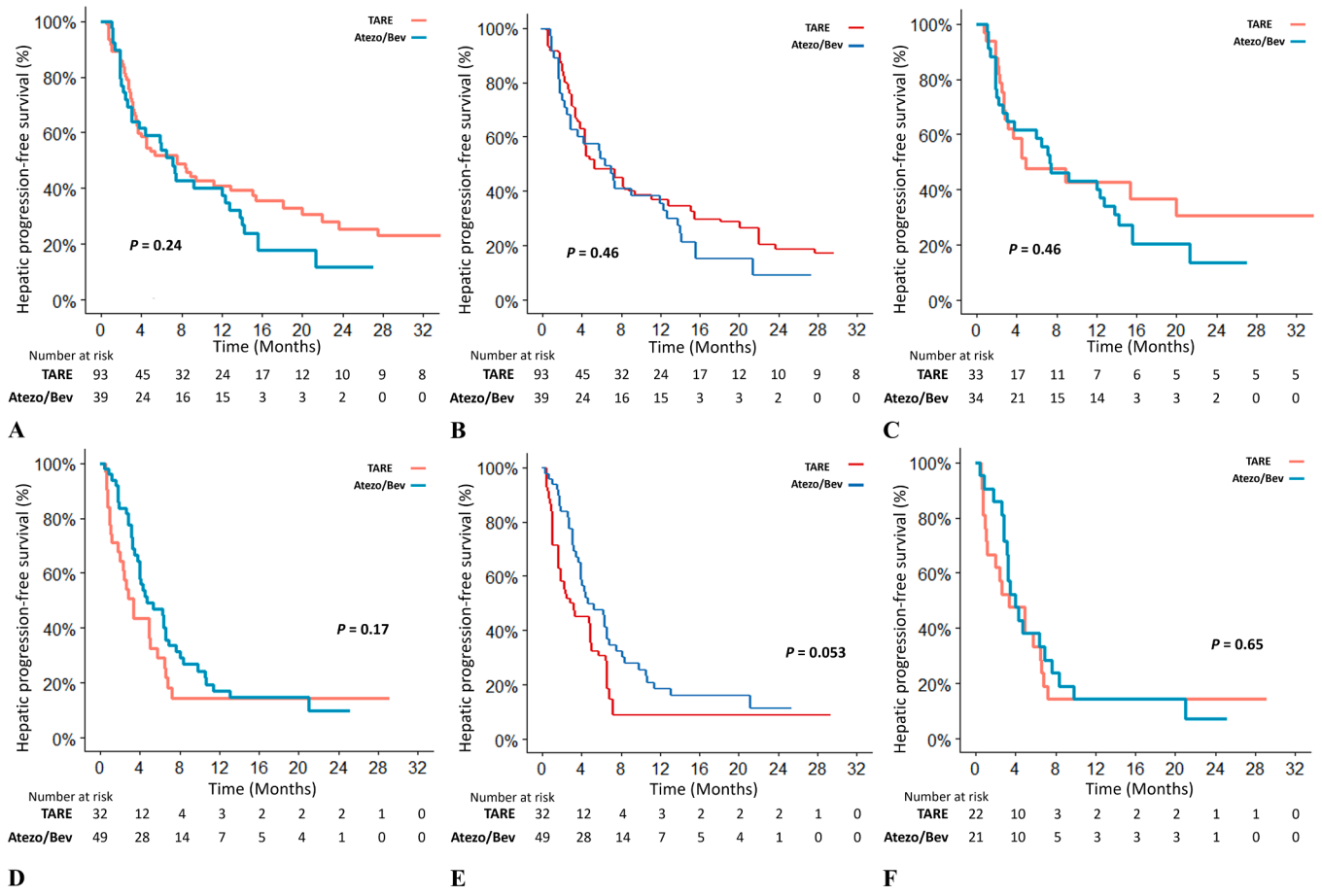

Fig. 9. Graphs show subgroup analyses of hepatic progression-free survival based on portal vein tumor thrombosis level. **A**, Vp1–3 subgroup in unmatched cohort; **B**, Vp1–3 subgroup in inverse probability of treatment weighting cohort; **C**, Vp1–3 subgroup in propensity score matching cohort; **D**, Vp4 subgroup in unmatched cohort; **E**, Vp4 subgroup in inverse probability of treatment weighting cohort; and **F**, Vp4 subgroup in propensity score matching cohort. Atezo/Bev indicates atezolizumab plus bevacizumab; IPTW indicates inverse probability of treatment weighting; PSM indicates propensity score matching; PVTT indicates portal vein tumor thrombosis; TARE indicates transarterial radioembolization.

records and classified according to the CTCAE 5.0; therefore, some events, particularly grade 1–2 adverse events, may have been underreported. Finally, most patients in this study had hepatitis B virus (HBV) infection, which may limit the generalizability of the findings to non-HBV populations.

In conclusion, TARE was associated with longer OS and fewer adverse events than Atezo/Bev in patients with HCC and PVTT without extrahepatic metastasis, particularly in the Vp1–3 subgroup. The PFS and ORR were not significantly different between the two groups. Given the poorer liver function and higher tumor burden in the Atezo/Bev group, these findings should be interpreted cautiously, as subsequent treatment could have contributed to the prolonged OS. In appropriately selected patients with preserved liver function and segmental or lobar PVTT, TARE may offer a preferable therapeutic option.

CRediT authorship contribution statement

Yoon Jun Kim had full access to all of the data of this study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Youngsu Park, Yuri Cho and Hyunjae Shin collected the data and performed the data analysis and interpretation. Aryoung Kim, and Seung Up Kim collected the data. Hyo-Cheol Kim, In Joon Lee, Gyoung Min Kim, Dongho Hyun, Yunmi Ko, Jae Woong Yoon, Gyung Sun Lim, Moon Haeng Hur, Yun Bin Lee, Eun Ju Cho, Jeong-Hoon Lee, Su Jong Yu, Jung-Hwan Yoon, Jin Wook Chung, and Dong Hyun Sinn collected and reviewed the data. Youngsu Park, Yuri Cho, Hyunjae Shin, and Yoon Jun Kim wrote the manuscript with comments from all the authors.

Human and rights

The authors declare that the work described was performed in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patients.

Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

Declaration of competing interest

Dr. Seung Up Kim has served as an advisory committee member Gilead Sciences, Bayer, Eisai, and Novo Nordisk. He is a speaker for Gilead Sciences, GSK, Bayer, Eisai, Abbive, EchoSens, MSD, Eisai, Otsuka, and Bristol-Myers Squibb. He reports receiving research grants from Abbive, Bristol-Myers Squibb, and Gilead. Dr. Yun Bin Lee reports receiving research grants from Samjin Pharmaceuticals and Yuhan

Table 7
Results of logistic regression analysis of objective response.

Variable	Unmatched cohort		After IPTW		After PSM	
	OR (95 % CI)	*P*	OR (95 % CI)	*P*	OR (95 % CI)	*P*
TARE vs. Atezo/Bev	0.75 (0.34–1.66)	0.49	0.67 (0.18–2.2)	0.52	1.49 (0.49–4.7)	0.48
Female vs. Male	1.33 (0.54–2.56)	0.55	6.03 (1.1–64.0)	0.07	1.46 (0.39–6.3)	0.59
Age (year)	1.02 (0.99–1.05)	0.28	1.01 (0.96–1.1)	0.80	1.03 (0.98–1.1)	0.29
ECOG PS						
0	[reference]		[reference]		[reference]	
1	2.27 (0.78–6.58)	0.13	1.39 (0.35–5.3)	0.63	2.08 (0.52–8.3)	0.29
Child-Pugh score						
A	[reference]		[reference]		[reference]	
B	0.48 (0.10–2.08)	0.35	0.19 (0.02–1.5)	0.14	0.15 (0.01–1.3)	0.11
Tumor type						
Well-defined (nodular)	[reference]		[reference]		[reference]	
Ill-defined (infiltrative)	0.68 (0.46–1.00)	0.052	0.68 (0.35–1.3)	0.25	0.64 (0.36–1.1)	0.12
Tumor size (cm)	0.89 (0.80–0.98)	0.03	0.91 (0.79–1.0)	0.18	0.87 (0.75–1.0)	0.08
Tumor number						
1	[reference]		[reference]		[reference]	
2	2.03 (0.61–7.17)	0.26	1.57 (0.25–9.6)	0.62	1.30 (0.2–8.8)	0.78
≥ 3	0.27 (0.11–0.66)	< 0.01	0.5 (0.15–1.6)	0.24	0.34 (0.09–1.1)	0.08
Tumor involvement						
Bilobar	[reference]		[reference]		[reference]	
Unilobar	1.17 (0.51–2.70)	0.71	1.14 (0.36–3.6)	0.82	1.11 (0.33–3.8)	0.86
PVTT grade						
Vp1	[reference]		[reference]		[reference]	
Vp2	0.92 (0.28–2.99)	0.89	1.23 (0.12–12.0)	0.86	0.31 (0.04–1.8)	0.21
Vp3	1.17 (0.44–3.16)	0.75	0.95 (0.17–5.7)	0.96	0.92 (0.19–4.5)	0.91
Vp4	0.37 (0.12–1.06)	0.06	0.43 (0.08–2.4)	0.33	0.21 (0.04–1.0)	0.06
Albumin (g/dL)	1.18 (0.50–2.69)	0.70	0.6 (0.15–2.2)	0.46	0.61 (0.15–2.3)	0.48
Bilirubin (mg/dL)	1.01 (0.47–2.13)	0.98	0.93 (0.33–2.5)	0.89	1.4 (0.47–4.2)	0.54
PT (INR)	0.54 (0.02–5.36)	0.66	0.5 (0.0–110.0)	0.81	0.34 (0.0–110.0)	0.71

Atezo/Bev indicates atezolizumab plus bevacizumab; CI indicates confidence interval; ECOG indicates Eastern Cooperative Oncology Group; OR indicates odds ratio; INR indicates international normalized ratio; IPTW indicates inverse probability of treatment weighting; PS indicates performance status; PSM indicates propensity score matching; PT indicates prothrombin time; PVTT indicates portal vein tumor thrombosis; TARE indicates transarterial radioembolization.
Data are expressed as raw numbers followed by percentages into parentheses. Atezo/Bev, atezolizumab plus bevacizumab; HAIC, hepatic artery infusion chemotherapy; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

Table 8
Treatment-related adverse events.

Adverse event type	TARE (n = 125)	Atezo/Bev (n = 88)	*P*
Ascites of grade 2 or greater	15 (12.0)	18 (20.5)	0.02
Variceal bleeding	2 (1.7)	7 (8.0)	0.04
Hepatic encephalopathy	3 (2.5)	2 (2.3)	1.00
Increased Child-Pugh score by 2 or greater	18 (14.4)	22 (25.0)	0.08
Radiation pneumonitis	3 (2.7)	N.A.	-
REILD	8 (6.4)	N.A.	-
ICI-related adverse events	N.A.	30 (34.1)	-
Grade 1 or 2	N.A.	22 (25.0)	-
Grade 3	N.A.	8 (9.1)	-

Data are expressed as raw numbers followed by percentages into parentheses. Atezo/Bev indicates atezolizumab plus bevacizumab; ICI indicates immune checkpoint inhibitor; N.A. indicates not applicable; REILD indicates radioembolization-induced liver disease; TARE indicates transarterial radioembolization.

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