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Efficacy and Safety of Durvalumab Plus Tremelimumab in Hepatocellular Carcinoma Patients With Portal Vein Thrombosis and High Tumor Burden: A Multicenter Retrospective Analysis

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ABSTRACT

Aims: This study aimed to evaluate the therapeutic efficacy of durvalumab and tremelimumab (Dur/Tre) in patients with hepatocellular carcinoma (HCC) who had a tumor thrombus in the main portal vein trunk (Vp4) or high tumor burden (HTB).

Methods: A total of 309 patients with BCLC stage B or C HCC who received Dur/Tre between March 2023 and October 2024 were included. HTB was defined as the presence of at least one of the following radiological findings: ≥ 50% liver involvement by HCC, bile duct invasion, or the presence of Vp4.

Results: Both the patients with Vp4 and HTB-positive group had significantly higher proportions of BCLC stage C disease ($p = 0.01$ and 0.007, respectively) and serum DCP levels ≥ 100 mAU/mL ($p = 0.03$ and < 0.001, respectively), and significantly higher neutrophil-to-lymphocyte ratio ($p = 0.04$ and $p = 0.004$, respectively) compared to their respective counterparts. While the objective response rate did not significantly differ between the HTB-positive and HTB-negative groups (21.6% vs. 16.2%, $p = 0.5$), it was significantly higher in patients with Vp4 than in those without (42.9% vs. 15.6%, $p = 0.02$). There were no significant differences in progression-free survival or overall survival (OS) between patients with and without Vp4 ($p = 0.1$ and 0.3, respectively) and nor between the HTB-positive and HTB-negative groups (both $p = 0.3$). Among patients with both Vp4 and HTB, responders had longer OS than non-responders.

Conclusions: Dur/Tre may be a viable treatment option for patients with Vp4 and HTB.

1 | Introduction

Hepatocellular carcinoma (HCC) is the sixth most commonly diagnosed cancer worldwide and the third leading cause of cancer-related death, representing a major global health concern [1]. In recent years, remarkable advances in systemic therapies for advanced HCC have led to the widespread implementation of effective treatment options in clinical practice. The combination of atezolizumab and bevacizumab (Atez/Bev)—a programmed death-ligand 1 (PD-L1) inhibitor and an anti-vascular endothelial growth factor (VEGF) agent, respectively—demonstrated improved progression-free survival (PFS) and overall survival (OS) compared to sorafenib in the IMbrave150 trial [2]. Similarly, the HIMALAYA trial showed that the combination of durvalumab and tremelimumab (Dur/Tre)—a PD-L1 inhibitor and an anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) agent, respectively—achieved superior survival outcomes compared to sorafenib [3]. Furthermore, another pivotal randomized controlled trial (RCT), CheckMate 9DW, reported that the combination of nivolumab and ipilimumab—a PD-1 inhibitor and an anti-CTLA-4 agent, respectively—provided significant survival benefits over lenvatinib or sorafenib in patients with unresectable HCC [4]. Based on these results, recent guidelines recommend immunotherapy as the first-line treatment for patients with advanced HCC [5–7].

In real-world clinical settings, systemic therapy is often administered to patients with a high tumor burden (HTB), such as those with tumor thrombus in the main portal vein trunk (Vp4) or ≥ 50% liver involvement. However, patients with Vp4 were excluded from the HIMALAYA [3] and CheckMate 9DW [4] trials, whereas the REFLECT trial [8]—a phase III non-inferiority RCT comparing lenvatinib with sorafenib—excluded patients with Vp4, ≥ 50% liver involvement, and bile duct invasion. Consequently, the efficacy of molecular targeted agents and immunotherapy in patients with Vp4 and HTB remains inadequately defined. The aim of the present study was to evaluate the therapeutic efficacy of Dur/Tre in patients with Vp4 and HTB.

2 | Methods

2.1 | Patients

Of the 338 patients with HCC who received Dur/Tre at participating Japanese multicenter institutions between March 2023 and October 2024, we excluded those classified as BCLC stage 0 ($n = 5$), stage A ($n = 18$), or stage D ($n = 6$). Consequently, 309 patients with BCLC stage B or C were included in the analysis (Figure S1). Dur/Tre was initiated at the discretion of the attending physician. HCC was diagnosed either histologically or based on characteristic imaging features as defined by the AASLD guidelines, which include arterial phase hyperenhancement followed by washout in the portal venous or delayed phases on dynamic computed tomography (CT) or magnetic resonance imaging (MRI) [9].

The main outcomes of interest in this retrospective analysis were the objective response rate (ORR) and PFS in patients with Vp4. We also examined OS in patients with Vp4, as well as ORR, PFS, and OS in patients with HTB, which was defined as the presence of at least one of the following radiological findings: (1) ≥ 50% liver involvement by HCC, (2) bile duct invasion, or (3) tumor thrombus in the main portal vein trunk (Vp4) [8, 10]. We retrospectively reviewed medical records to obtain clinical data, including treatment course, etiology of liver disease, laboratory findings, and imaging results. Tumor staging was determined based on the BCLC system [11], which accounts for performance status, liver function, and tumor extent. Liver function prior to initiating Dur/Tre therapy was assessed using the Child–Pugh classification. In addition, ALBI scores were calculated following a previously established method [12], and

the liver function was further categorized according to the modified ALBI (mALBI) grading system [13].

2.2 | Treatment With Dur/Tre

Before initiating Dur/Tre, patients were screened for autoimmune diseases to minimize the risk of immune-mediated adverse events (imAEs). Treatment consisted of a single dose of tremelimumab (300 mg), followed by durvalumab (1500 mg) administered every 4 weeks until disease progression or the occurrence of unacceptable imAEs. To enable early detection of imAEs, patients were followed in outpatient clinics every 1–4 weeks. CT and/or MRI was performed every 6–12 weeks to evaluate disease progression. The tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [14]. Adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE), version 5. PFS was defined as the time from initiation of Dur/Tre to either disease progression or death, whichever occurred first. OS was defined as the time from initiation of Dur/Tre to death from any cause.

2.3 | Statistical Analysis

Continuous variables were summarized as medians with interquartile range (IQRs), and categorical variables were presented as counts and percentages. Group comparisons were performed using the Mann–Whitney *U* test for continuous variables, and either the chi-square test or Fisher's exact test for categorical variables, as appropriate. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. OS was also compared according to tumor response and in subgroup analyses of patients who received Dur/Tre as first-line therapy. Cox proportional hazards regression models were applied to identify prognostic factors. Multivariate analyses for PFS and OS included the following variables: age, sex, mALBI grade (1 or 2a vs. 2b or 3), performance status (0 vs. 1 or 2), treatment setting (first-line vs. later-line), underlying liver disease (viral vs. non-viral), α-fetoprotein (≥ 100 ng/mL vs. < 100 ng/mL), and either presence of Vp4 or HTB. Variables were selected based on clinical relevance and evidence from previous literature. All statistical analyses were conducted using EZR software, version 1.67 (Jichi Medical University Saitama Medical Center) [15].

3 | Results

3.1 | Patient Characteristics in the Entire Cohort

The clinical characteristics of the study cohort are shown in Table 1. The median age was 73.0 years (IQR, 68.0–78.0), and 258 patients (83.5%) were male. Performance status was 0 in 236 patients (76.4%), 1 in 60 patients (19.4%), and 2 in 13 patients (4.2%). The most common underlying liver disease was hepatitis C virus (HCV) infection (n = 90, 29.1%), followed by hepatitis B virus (HBV) infection (n = 55, 17.8%), dual HCV/HBV infection (n = 2, 0.6%), and alcohol-related liver disease (n = 62, 20.1%). BCLC stage was classified as intermediate in 92 patients (29.8%) and advanced in 217 patients (70.2%). The Child–Pugh score was 5 in 121 patients (39.2%), 6 in 122 patients (39.5%), and ≥ 7 in 66 patients (21.4%). The median ALBI score was −2.18 (IQR, −2.56 to −1.83), and the distribution of mALBI grades was as follows: grade 1 in 70 patients (22.7%), grade 2a in 65 (21.0%), grade 2b in 157 (50.8%), and grade 3 in 17 (5.5%). Dur/Tre was administered as first-line therapy in 111 patients (35.9%) and as later-line therapy in 198 patients (64.1%). Among the 198 patients who received Dur/Tre as later-line treatment, 156 (78.8%) had a history of treatment with atezolizumab plus bevacizumab, and 119 (60.1%) had received lenvatinib. Extrahepatic spread (EHS) was observed in 137 patients (44.3%). Vp4, ≥ 50% liver involvement, and bile duct invasion were noted in 14 (4.5%) patients, 26 (8.4%) patients, and 1 (0.3%) patient, respectively.

3.2 | Comparison of Clinical Characteristics and Outcomes Stratified Vp4 Status

As noted above, Vp4 was observed in 14 patients (4.5%) in the entire cohort. We therefore compared clinical characteristics and outcomes according to Vp4 status. Patients with Vp4 had a significantly higher proportion of BCLC advanced stage (p = 0.01) and serum DCP levels ≥ 100 mAU/mL (p = 0.03), as well as a significantly higher neutrophil-to-lymphocyte ratio (NLR; p = 0.04; Table 1).

Tumor responses are summarized in Table 2. The distribution of tumor responses differed significantly between the two groups (p = 0.04). The ORR was 15.6% in patients without Vp4 and 42.9% in those with Vp4, showing a statistically significant difference (p = 0.02). The DCR was 43.7% in patients without Vp4 and 50.0% in those with Vp4, with no significant difference (p = 0.8). During the observation period, PFS events occurred in 226 patients (76.6%) without Vp4 and in 8 patients (57.1%) with Vp4. The median follow-up period was 8.0 months (IQR, 4.3–13.0), and the data cutoff date was February 2025. The median PFS was 3.1 months (95% confidence interval [CI], 2.7–4.0) in patients without Vp4 and 5.5 months (95% CI, 2.8–NA) in those with Vp4, with no significant difference (p = 0.1; Figure 1a). By the end of follow-up, 109 patients (36.9%) without Vp4 and 7 patients (50.0%) with Vp4 had died. The median OS was 15.4 months (95% CI, 13.6–NA) in patients without Vp4 and 12.5 months (95% CI, 4.1–NA) in those with Vp4, also without a statistically significant difference (p = 0.3; Figure 1b). Vp4 status was not found to be an independent predictor of either PFS or OS in the multivariate analyses (Table S1).

Similarly, no significant differences in the frequency or severity of commonly reported immune-related adverse events (imAEs) were found between patients with and without Vp4 (Table S2).

Among the 211 patients without Vp4 and 7 patients with Vp4 who experienced radiological disease progression, 151 (71.6%) and 3 (42.9%) patients, respectively, received post-progression treatment, with no statistically significant difference (p = 0.2).

TABLE 1 | Clinical characteristics of the entire cohort, and comparisons between patients with and without Vp4.

Factors	Entire cohort ($n = 309$)	Patients without Vp4 ($n = 295$)	Patients with Vp4 ($n = 14$)	p-value
Age (years)	73.0 [68.0,78.0]	73.0 [68.0, 78.0]	72.5 [64.3, 76.8]	0.5
Gender, *n* (%)				
Male	258 (83.5)	247 (83.7)	11 (78.6)	0.7
Performance status, *n* (%)				
0	236 (76.4)	227 (76.9)	9 (64.3)	0.3
1	60 (19.4)	56 (19.0)	4 (28.6)	
2	13 (4.2)	12 (4.1)	1 (7.1)	
Underlying liver diseases, *n* (%)				
HCV	90 (29.1)	88 (29.8)	2 (14.3)	0.051
HBV	55 (17.8)	52 (17.6)	3 (21.4)	
HCV plus HBV	2 (0.6)	2 (0.7)	0 (0.0)	
Alcohol	62 (20.1)	62 (21.0)	0 (0.0)	
Others	100 (32.4)	91 (30.8)	9 (64.3)	
Viral-related disease, *n* (%)	147 (47.6)	142 (48.1)	5 (35.7)	0.4
BCLC stage, *n* (%)				
Intermediate	92 (29.8)	92 (31.2)	0 (0.0)	0.01
Advanced	217 (70.2)	203 (68.8)	14 (100.0)	
Child-pugh score, *n* (%)				
5	121 (39.2)	119 (40.3)	2 (14.3)	0.1
6	122 (39.5)	115 (39.0)	7 (50.0)	
≥ 7	66 (21.4)	61 (20.7)	5 (35.7)	
ALBI score	−2.18 [−2.56, −1.83]	−2.19 [−2.57, −1.84]	−1.95 [−2.30, −1.75]	0.09
mALBI grade, *n* (%)				
1	70 (22.7)	69 (23.4)	1 (7.1)	0.2
2a	65 (21.0)	62 (21.0)	3 (21.4)	
2b	157 (50.8)	149 (50.5)	8 (57.1)	
3	17 (5.5)	15 (5.1)	2 (14.3)	
Treatment settings, *n* (%)				
First-linc	111 (35.9)	106 (35.9)	5 (35.7)	1.0
Later-line	198 (64.1)	189 (64.1)	9 (64.3)	
Prior systemic treatments				
Atez/Bev	156 (78.8)	147 (77.8)	9 (100.0)	0.2
LEN	119 (60.1)	114 (60.3)	5 (55.6)	1.0
EHS, *n* (%)				
Presence	137 (44.3)	133 (45.1)	4 (28.6)	0.3
Vp4, *n* (%)				
Presence	14 (4.5)	0 (0.0)	14 (100.0)	< 0.001
Liver involvement				
≥ 50%	26 (8.4)	22 (7.5)	4 (28.6)	0.02
Bile duct invasion				
Presence	1 (0.3)	1 (0.3)	0 (0.0)	1.0
NLR	3.21 [2.06, 5.55]	3.18 [2.02, 5.42]	4.96 [3.23, 9.39]	0.04

(Continues)

TABLE 1 | (Continued)

Factors	Entire cohort (n = 309)	Patients without Vp4 (n = 295)	Patients with Vp4 (n = 14)	p-value
AFP, n (%)				
≥ 100 ng/mL	145 (46.9)	137 (46.4)	8 (57.1)	0.6
DCP, n (%)[a]				
≥ 100 mAU/mL	232 (75.8)	218 (74.7)	14 (100.0)	0.03

Abbreviations: AFP, α-fetoprotein; ALBI score, albumin-bilirubin score; BCLC stage, Barcelona Clinic Liver Cancer stage; DCP, Des-gamma-carboxy prothrombin; EHS, extrahepatic spread; HBV, hepatitis B virus; HCV, hepatitis C virus; mALBI grade, modified albumin-bilirubin grade; NLR, neutrophil to lymphocyte ratio; Vp4, tumor thrombus in the main portal vein trunk.
[a]Missing data for 3 patients.

TABLE 2 | Overall tumor response in the entire cohort and in subgroups according to Vp4 status.

Factors	Overall (n = 309)	Patients without Vp4 (n = 295)	Patients with Vp4 (n = 14)	p-value
Best response, n (%)				0.04
CR	3 (1.0)	3 (1.0)	0 (0.0)	
PR	49 (15.9)	43 (14.6)	6 (42.9)	
SD	84 (27.2)	83 (28.1)	1 (7.1)	
PD	144 (46.6)	139 (47.1)	5 (35.7)	
NE	29 (9.4)	27 (9.2)	2 (14.3)	
ORR (%)	16.8	15.6	42.9	0.02
DCR (%)	44.0	43.7	50.0	0.8

Abbreviations: CR, complete response; DCR, disease control rate; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; Vp4, tumor thrombus in the main portal vein trunk.

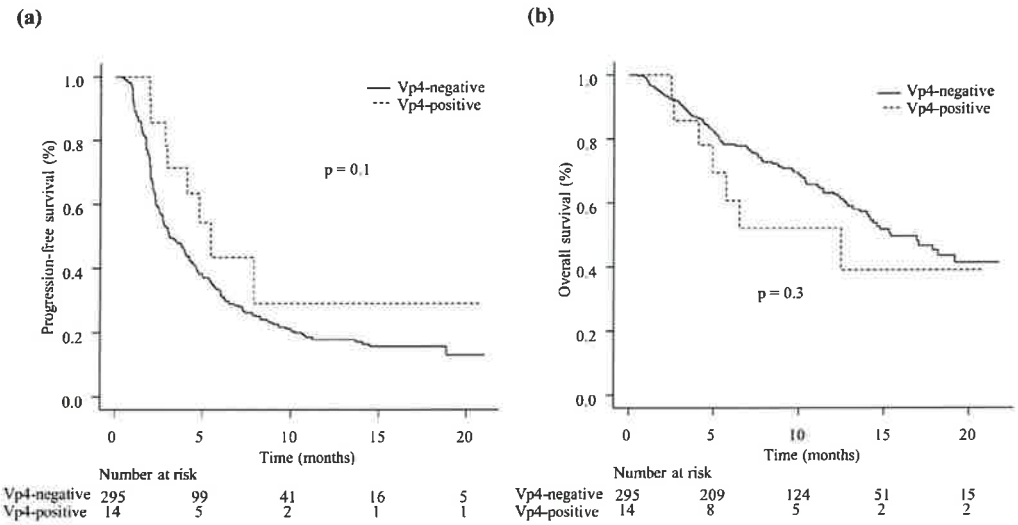

FIGURE 1 | PFS and OS according to Vp4 status. (a) The median PFS was 3.1 months (95% CI, 2.7–4.0) in patients without Vp4 and 5.5 months (95% CI, 2.8–NA) in those with Vp4, with no significant difference (p = 0.1). (b) The median OS was 15.4 months (95% CI, 13.6–NA) in patients without Vp4 and 12.5 months (95% CI, 4.1–NA) in those with Vp4, also without a statistically significant difference (p = 0.3). CI, confidence interval; NA, not applicable; OS, overall survival; PFS, progression-free survival; Vp4, tumor thrombus in the main portal vein trunk.

3.3 | Comparison of Clinical Characteristics and Outcomes Stratified HTB Status

Among the 309 cases, 37 patients (12.0%) were classified as HTB-positive. Although the distribution of underlying liver disease differed significantly between the two groups (p = 0.03), the proportion of viral-related disease was not significantly different (p = 0.4). The HTB-positive group had a significantly higher proportion of patients with advanced BCLC stage (p = 0.007) and serum DCP ≥ 100 mAU/mL (p < 0.001), as well as a significantly higher NLR (p = 0.004; Table 3).

Overall tumor response was described in Table 4. The ORR was 16.2% in the HTB-negative group and 21.6% in the HTB-positive group, with no statistically significant difference (p = 0.5). The DCR was 43.8% and 45.9% in the HTB-negative and HTB-positive groups, respectively, also without a significant difference (p = 0.9).

TABLE 3 | Clinical characteristics according to HTB status.

Factors	Patients without HTB (n = 272)	Patients with HTB (n = 37)	p-value
Age (years)	73.0 [68.0,78.0]	72.0 [64.0,77.0]	0.4
Gender, n (%)			
Male	225 (82.7)	33 (89.2)	0.5
Performance status, n (%)			
0	208 (76.5)	28 (75.7)	0.9
1	52 (19.1)	8 (21.6)	
2	12 (4.4)	1 (2.7)	
Underlying liver diseases, n (%)			
HCV	84 (30.9)	6 (16.2)	0.03
HBV	47 (17.3)	8 (21.6)	
HCV plus HBV	1 (0.4)	1 (2.7)	
Alcohol	58 (21.3)	4 (10.8)	
Others	82 (30.1)	18 (48.6)	
Viral-related disease, n (%)	132 (48.5)	15 (40.5)	0.4
BCLC stage, n (%)			
Intermediate	88 (32.4)	4 (10.8)	0.007
Advanced	184 (67.6)	33 (89.2)	
Child-pugh score, n (%)			
5	109 (40.1)	12 (32.4)	0.4
6	108 (39.7)	14 (37.8)	
≥ 7	55 (20.2)	11 (29.7)	
ALBI score	−2.19 [−2.59, −1.85]	−2.06 [−2.36, −1.76]	0.2
mALBI grade, n (%)			
1	64 (23.5)	6 (16.2)	0.4
2a	58 (21.3)	7 (18.9)	
2b	137 (50.4)	20 (54.1)	
3	13 (4.8)	4 (10.8)	
Treatment settings, n (%)			
First-linc	98 (36.0)	13 (35.1)	1.0
Later-line	174 (64.0)	24 (64.9)	
Prior systemic treatments			
Atez/Bev	136 (78.2)	20 (83.3)	0.8
LEN	102 (58.6)	17 (70.8)	0.3
EHS, n (%)			
Presence	125 (46.0)	12 (32.4)	0.2
Vp4, n (%)			
Presence	0 (0.0)	14 (37.8)	< 0.001
Liver involvement			
≥ 50%	0 (0.0)	26 (70.3)	< 0.001
Bile duct invasion			
Presence	0 (0.0)	1 (2.7)	0.1
NLR	3.09 [1.98, 5.08]	4.68 [2.95, 8.39]	0.004

(Continues)

TABLE 3 | (Continued)

Factors	Patients without HTB (n = 272)	Patients with HTB (n = 37)	p-value
AFP, n (%)			
≥ 100 ng/mL	126 (46.3)	19 (51.4)	0.6
DCP[a], n (%)			
≥ 100 mAU/mL	196 (72.9)	36 (97.3)	< 0.001

Abbreviations: AFP, α-fetoprotein; ALBI score, albumin-bilirubin score; BCLC stage, Barcelona Clinic Liver Cancer stage; DCP, Des-gamma-carboxy prothrombin; EHS, extrahepatic spread; HBV, hepatitis B virus; HCV, hepatitis C virus; HTB, high tumor burden; mALBI grade, modified albumin-bilirubin grade; NLR, neutrophil to lymphocyte ratio; Vp4, tumor thrombus in the main portal vein trunk.
[a]Missing data for 3 patients.

TABLE 4 | Overall tumor response according to HTB status.

Factors	The HTB-negative group (n = 272)	The HTB-positive group (n = 37)	p-value
Best response, n (%)			0.8
CR	3 (1.1)	0 (0.0)	
PR	41 (15.1)	8 (21.6)	
SD	75 (27.6)	9 (24.3)	
PD	128 (47.1)	16 (43.2)	
NE	25 (9.2)	4 (10.8)	
ORR (%)	16.2	21.6	0.5
DCR (%)	43.8	45.9	0.9

Abbreviations: CR, complete response; DCR, disease control rate; HTB, high tumor burden; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response.

During the observation period, PFS events were observed in 209 patients (76.8%) in the HTB-negative group and in 25 patients (67.6%) in the HTB-positive group. The median PFS was 3.1 months (95% CI, 2.7–4.0) in the HTB-negative group and 4.5 months (95% CI, 2.3–6.0) in the HTB-positive group, with no significant difference (p = 0.3; Figure 2a). A total of 100 patients (36.8%) in the HTB-negative group and 16 patients (43.2%) in the HTB-positive group had died by the end of follow-up. The median OS was 15.4 months (95% CI, 14.0–NA) in the HTB-negative group and 12.5 months (95% CI, 6.5–NA) in the HTB-positive group. This difference was not statistically significant (p = 0.3; Figure 2b). HTB status was not identified as an independent predictor of either PFS or OS in the multivariate analyses (Table S3).

The frequency and severity of imAEs were also compared by HTB status. No significant differences in commonly reported imAEs were observed between patients with and without HTB (Table S4).

Following radiological disease progression, 140 of 195 patients (71.8%) in the HTB-negative group and 14 of 23 patients (60.9%) in the HTB-positive group received post-progression treatment, with no significant difference between the groups (p = 0.3).

3.4 | Overall Survival in Patients With Vp4 and HTB According to Tumor Response

Given that the ORR was significantly higher in patients with Vp4 than in those without Vp4 (42.9% vs. 15.6%, p = 0.02) and numerically higher in patients with HTB compared to those without HTB (21.6% vs. 16.2%, p = 0.5), we examined OS in patients with Vp4 and HTB according to tumor response.

Among patients with Vp4 (n = 14), the median OS was not reached in those with PR, with a 1-year survival rate of 75.0% (95% CI, 12.8%–96.1%). Notably, no deaths occurred among patients with SD during the observation period. The median OS was 4.9 months (95% CI, 2.5–NA) in patients with PD and 4.1 months (95% CI, 4.1–NA) in those with NE. Although OS tended to differ according to tumor response, the difference did not reach statistical significance (p = 0.05; Figure 3a). In the SD + PD + NE group, the median OS was 5.3 months (95% CI, 2.5–NA). Patients with PR had significantly better survival than those in the SD + PD + NE group (i.e., patients with SD, PD, or NE; p = 0.04; Figure 3b). Among patients receiving Dur/Tre as first-line treatment, the median PFS was 5.3 months (95% CI, 2.8–7.2) in the Vp4-negative group (n = 106) and 7.9 months (95% CI, 2.8–NA) in the Vp4-positive group (n = 5), with no significant difference between the groups (p = 0.3; Figure S2a). The median OS was not reached in either group. The 1-year OS rates were 71.3% (95% CI, 60.0–79.9) in the Vp4-negative group and 66.7% (95% CI, 27.2–94.5) in the Vp4-positive group, with no statistically significant difference observed (p = 0.8; Figure S2b).

Among the patients with HTB (n = 37), the median OS was not reached in those who achieved PR or SD, with 1-year survival rates of 66.7% (95% CI, 19.5%–90.4%) and 87.5% (95% CI, 38.7%–98.1%), respectively. In contrast, the median OS was 5.8 months (95% CI, 2.6–12.5) in patients with PD, and 7.1 months (95% CI, 4.1–NA) in those with NE. A statistically significant difference in OS was observed according to tumor response (p = 0.005; Figure 3c). The median OS in the SD + PD + NE group was

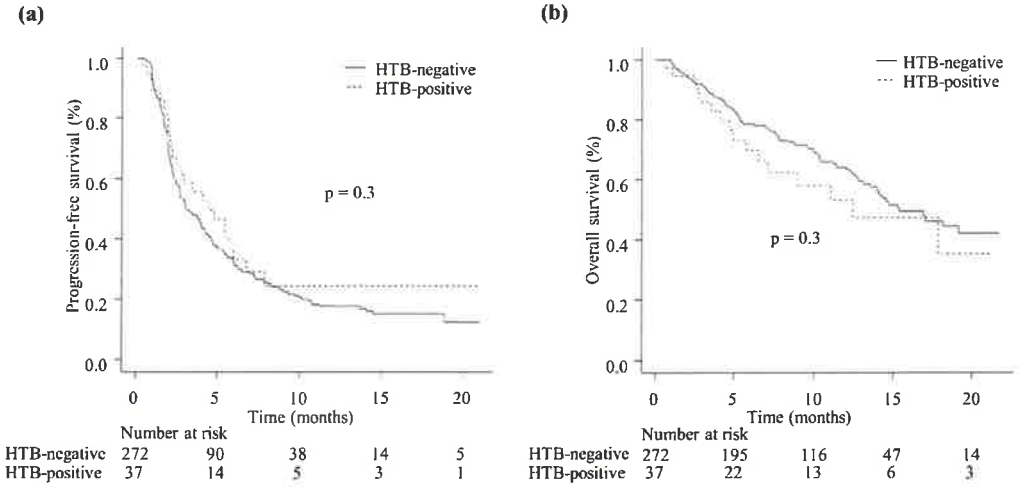

FIGURE 2 | PFS and OS according to HTB status. (a) The median PFS was 3.1 months (95% CI, 2.7–4.0) in the HTB-negative group and 4.5 months (95% CI, 2.3–6.0) in the HTB-positive group, with no significant difference ($p = 0.3$). (b) The median OS was 15.4 months (95% CI, 14.0–NA) in the HTB-negative group and 12.5 months (95% CI, 6.5–NA) in the HTB-positive group. This difference was not statistically significant ($p = 0.3$). CI, confidence interval; HTB, high tumor burden; NA, not applicable; OS, overall survival; PFS, progression-free survival.

12.5 months (95% CI, 4.6–NA). Patients with PR had better survival than those in the SD + PD + NE group, although the difference was not statistically significant ($p = 0.1$; Figure 3d). Among patients receiving Dur/Tre as first-line treatment, the median PFS was 5.3 months (95% CI, 2.7–7.2) in the HTB-negative group ($n = 98$) and 6.8 months (95% CI, 2.3–NA) in the HTB-positive group ($n = 13$), with no significant difference between the groups ($p = 0.5$; Figure S3a). The median OS was not reached in either group. The 1-year OS rates were 68.4% (95% CI, 56.3–77.8) in the HTB-positive group and 60.6% (95% CI, 16.6–87.0) in the HTB-negative group, with no statistically significant difference observed ($p = 0.9$; Figure S3b).

4 | Discussion

We conducted a retrospective multicenter study to evaluate the efficacy of Dur/Tre in patients with Vp4 and HTB. The main findings of this study are that both the patients with Vp4 and HTB-positive group had significantly higher proportions of BCLC stage C disease and serum DCP ≥ 100 mAU/mL, and higher NLR compared to their counterparts. Although ORR did not significantly differ between the HTB-positive and HTB-negative groups, it was significantly higher in patients with Vp4 than in those without ($p = 0.02$). Patients with Vp4 showed a numerically longer PFS compared to those without Vp4 ($p = 0.1$), whereas OS remained similar between the two groups ($p = 0.3$). There were no significant differences in PFS or OS between the HTB-positive and HTB-negative groups. To further explore the impact of treatment response, we assessed OS according to tumor response in patients with Vp4 and HTB. In both groups, patients who achieved PR had longer OS than those with SD, PD, or NE. These findings suggest that Dur/Tre may be a potentially effective treatment option for patients with Vp4 and HTB. To our knowledge, this is the first study to specifically evaluate the efficacy of Dur/Tre in this high-risk population.

HTB, which includes Vp4, bile duct invasion, and/or ≥ 50% liver involvement, has been frequently used as an exclusion criterion in RCTs due to its association with poor prognosis. For example, the REFLECT trial excluded patients with Vp4, bile duct invasion, and ≥ 50% liver involvement [8]. Similarly, the HIMALAYA [3], LEAP-002 [16], and CheckMate 9DW [4] trials excluded patients with Vp4. Furthermore, a post hoc analysis of the IMbrave150 trial reported an ORR of 25%, a median PFS of 5.4 months (95% CI, 4.0–6.9), and a median OS of 7.6 months (95% CI, 6.6–12.8) in patients with HTB treated with Atez/Bev ($n = 64$) [10]. In patients with Vp4 ($n = 48$), the ORR was 23%, the median PFS was 5.4 months (95% CI, 3.5–6.9), and the median OS was 7.6 months (95% CI, 6.0–13.9) [10]. Although the patient background in our study differs substantially from that of the IMbrave150 trial, we believe that the treatment outcomes observed with Dur/Tre in our cohort are broadly comparable to those reported for Atez/Bev in that trial.

The reason why Dur/Tre may exert some therapeutic benefit in patients with Vp4 and HTB remains unclear. A possible explanation is suggested by a recent single-cell analysis of portal vein tumor thrombus (PVTT), a representative feature of Vp4 disease [17]. This study demonstrated that the tumor microenvironment of PVTT is enriched with immunosuppressive $C5aR^+$ tumor-associated macrophages (TAMs), which upregulate PD-L1 and CTLA-4 and suppress $CD8^+$ T cell function [17]. Such an immunosuppressive profile may contribute to the poor prognosis typically seen in patients with Vp4 and HTB. As Dur/Tre targets both PD-L1 and CTLA-4 pathways, dual immune checkpoint blockade could potentially mitigate this immune suppression to some extent. In this context, the unique immune characteristics of PVTT may offer a biological basis for the modest treatment responses observed with Dur/Tre in this high-risk population.

Recently, updated 5-year OS data from the HIMALAYA trial have been reported, showing that long-term survival with Dur/Tre was strongly correlated with overall tumor response [18].

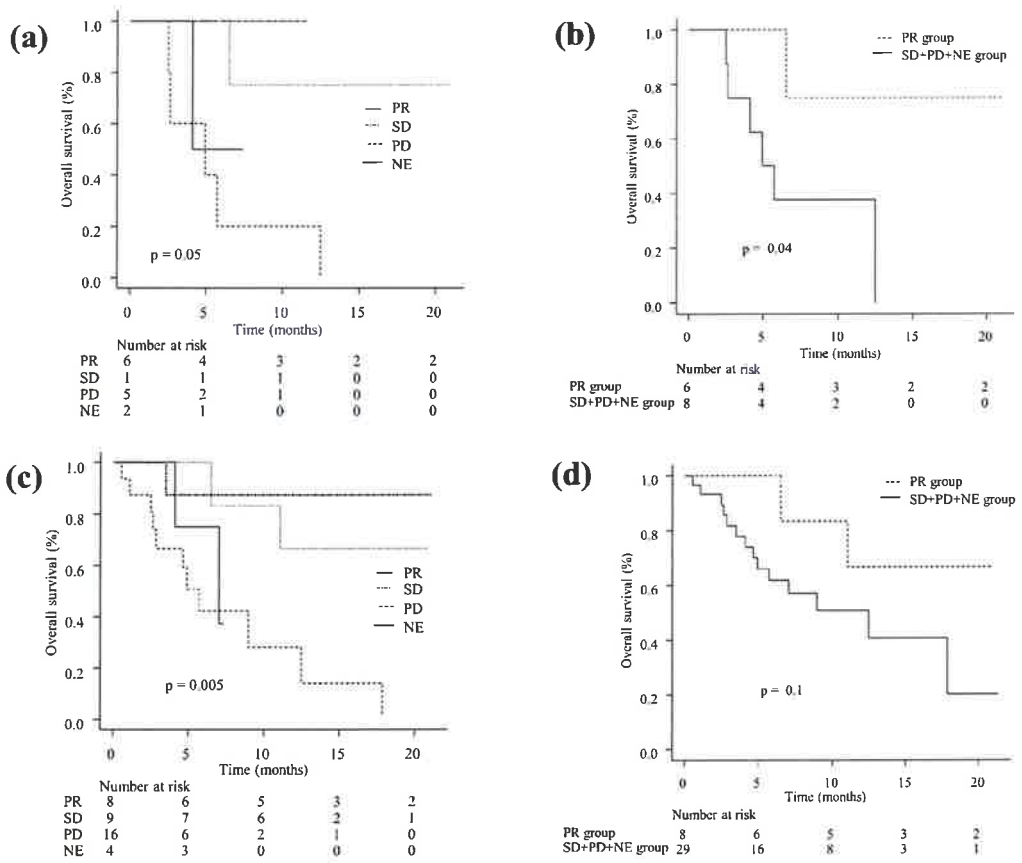

FIGURE 3 | OS in patients with Vp4 and HTB according to tumor response. (a) Among patients with Vp4, the median OS was not reached in those with PR, with a 1-year survival rate of 75.0% (95% CI, 12.8%–96.1%). Notably, no deaths occurred among patients with SD during the observation period. The median OS was 4.9 months (95% CI, 2.5–NA) in patients with PD and 4.1 months (95% CI, 4.1–NA) in those with NE. Although OS tended to differ according to tumor response, the difference did not reach statistical significance (p = 0.05). (b) Among patients with Vp4 classified as SD + PD + NE, the median OS was 5.3 months (95% CI, 2.5–NA). Patients with PR had significantly better survival than those in the SD + PD + NE group (p = 0.04). (c) Among patients with HTB, the median OS was not reached in those who achieved PR or SD, with 1-year survival rates of 66.7% (95% CI, 19.5%–90.4%) and 87.5% (95% CI, 38.7%–98.1%), respectively. In contrast, the median OS was 5.8 months (95% CI, 2.6–12.5) in patients with PD, and 7.1 months (95% CI, 4.1–NA) in those who were NE. A statistically significant difference in OS was observed according to tumor response (p = 0.005). (d) The median OS in the SD + PD + NE group (i.e., patients with SD, PD, or NE). was 12.5 months (95% CI, 4.6–NA). Patients with PR had better survival than those in the SD + PD + NE group, although the difference was not statistically significant (p = 0.1). CI, confidence interval; HTB, high tumor burden; NA, not applicable; NE, not evaluable; OS, overall survival; PR, partial response; PD, progressive disease; SD, stable disease; Vp4, tumor thrombus in the main portal vein trunk.

However, the impact of tumor response on OS remains unclear in patients with Vp4 and HTB because patients with Vp4 were excluded from the HIMALAYA trial, and the efficacy of Dur/Tre in patients with HTB has not been reported. In the present study, patients achieving ORR had better survival than non-responders among those with Vp4, and OS was significantly stratified by overall tumor response in patients with HTB. The absence of statistically significant differences among tumor response groups in patients with Vp4 and between responders and nonresponders in patients with HTB may be attributable to insufficient statistical power. Further studies with larger cohorts and longer follow-up are warranted to validate these findings. Although achieving ORR may be associated with prolonged OS, lack of response may indicate a poorer prognosis, particularly in patients with Vp4 and HTB. Therefore, early evaluation of treatment response is crucial. Changes in tumor markers such as AFP and DCP may serve as early indicators of tumor response [19]. Accordingly, monitoring dynamic changes in tumor marker levels may be essential for predicting treatment response to Dur/Tre, particularly in patients with Vp4 and HTB.

Previous studies have reported that elevated serum DCP levels are associated with aggressive tumor biology, such as large tumor size and the presence of vascular invasion [20–22]. These findings are consistent with the present results, which demonstrated higher serum DCP levels in patients with Vp4 and in those with HTB.

Although no statistically significant differences in PFS or OS were observed between patients with and without Vp4, or between HTB-positive and HTB-negative groups, there was a trend toward shorter OS in patients with Vp4 and those with HTB, despite their numerically longer PFS. This apparent discrepancy may be partly explained by differences in the receipt of post-

progression treatment following disease progression (Vp4: 71.6% vs. 42.9%; HTB: 71.8% vs. 60.9%). In patients with Vp4 and HTB, liver function and performance status may be more likely to deteriorate after progression, limiting eligibility for further treatment and potentially resulting in shorter post-progression survival.

Some limitations were associated with the present study. First, this study was a retrospective multicenter study. Second, the number of patients was limited particularly in patients with Vp4 and HTB. Accordingly, larger cohort with longer observation period might affect the present results. Third, radiological assessments were not conducted in approximately 10% of patients and were thus classified as NE. This lack of evaluation may have influenced the interpretation of efficacy outcomes such as ORR and PFS. Fourth, although this study compared the efficacy and safety of Dur/Tre between patients with and without Vp4 or HTB, the results do not provide sufficient evidence to guide treatment selection specifically for patients with Vp4 or HTB, as no direct comparison was made with alternative standard regimens. To address this issue, future studies comparing Dur/Tre with other treatment options, such as Atez/Bev, in patients with Vp4 and HTB are warranted to better inform optimal treatment strategies for this population.

Despite their poor expected prognosis, patients with Vp4 or HTB showed clinical outcomes that were not inferior to those of patients without these features. Accordingly, Dur/Tre may be a viable treatment option for this high-risk population.

Ethics Statement

The entire research proposal has received approval from the Institutional Ethics Committee of Takasaki General Medical Center (Approval Number 2024-03). Subsequently, with formal approval, the study was conducted with a retrospective analysis of database records in compliance with clinical research guidelines outlined by the Ministry of Health and Welfare of Japan. All procedures were carried out in accordance with the Declaration of Helsinki. Informed consent: Written informed consent was obtained from all patients before treatment and this study received ethical approval for use of an opt-out methodology.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

Research involving recombinant DNA: N/A.

Conflicts of Interest

Atsushi Hiraoka received lecture fees from Eli Lilly, AstraZeneca, and Chugai. Toshifumi Tada received lecture fees from AbbVie, Eisai, and Chugai. Satoru Kakizaki received lecture frees from AbbVie. Hidenori Toyoda received lecture fees from Eisai, Chugai, Takeda, Terumo, AbbVie, Gilead, Fujifilm WAKO, Abott, Kowa, AstraZeneca, and Bayer. Kazuhiro Kawata received lecture fee from AbbVie. Hidekatsu Kuroda received lecture fee from Eisai. Shohei Komatsu received lecture fees from Chugai. Kazuhiro Nouso received lecture fees from AbbVie, Aska Pharmaceutical, AstraZeneca, Bayer, Century Medical, Chugai, Covidien, Eisai, Gilead, Kowa, Lilly, and Otsuka; and received research funding from CureApp, Denka, Fuji film, and Medtronic. Masatoshi Kudo received honoraria from Chugai, Eisai, AstraZeneca, received research funding from Eisai, GE Healthcare, Otsuka, Taiho, and received advisory consulting fee from Chugai, Roche, Eisai, and AstraZeneca. Toshifumi Tada, Masanori Atsukawa, Hidekatsu Kuroda, and Masaki Kaibori are editorial board members of Hepatology Research. The other authors declare no conflicts of interest associated with this study.

Data Availability Statement

All data associated with the present study will be available from the corresponding author upon reasonable request.

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Supporting Information

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

Supporting Information S1: hepr70033-sup-0001-suppl-data.xlsx. **Figure S1**: Patient selection process. BCLC stage, Barcelona Clinic Liver Cancer stage; Dur/Tre, combination of durvalumab and tremelimumab; HCC, hepatocellular carcinoma. **Figure S2**: (a) Among patients receiving Dur/Tre as first-line treatment, the median PFS was 5.3 months (95% CI, 2.8–7.2) in the Vp4-negative group (n=106) and 7.9 months (95% CI, 2.8–NA) in the Vp4-positive group (n=5), with no statistically difference between the groups (p = 0.3). (b) The median OS was not reached in either group. The 1-year OS rates were 71.3% (95% CI, 60.0–79.9) in the Vp4-negative group and 66.7% (95% CI, 27.2–94.5) in the Vp4-positive group, with no statistically significant difference observed (p = 0.8). CI, confidence interval; Dur/Tre, combination of durvalumab and tremelimumab; OS, overall survival; PFS, progression-free survival; Vp4, tumor thrombus in the main portal vein trunk. **Figure S3**: (a) Among patients receiving Dur/Tre as first-line treatment, the median PFS was 5.3 months (95% CI, 2.7–7.2) in the HTB-negative group (n=98) and 6.8 months (95% CI, 2.8–NA) in the HTB-positive group (n=13), with no statistically difference between the groups (p = 0.5). (b) The median OS was not reached in either group. The 1-year OS rates were 68.4% (95% CI, 56.3–77.8) in the HTB-positive group and 60.6% (95% CI, 16.6–87.0) in the HTB-negative group, with no statistically significant difference observed (p = 0.9). CI, confidence interval; Dur/Tre, combination of durvalumab and tremelimumab; HTB, high tumor burden; NA, not applicable; OS, overall survival; PFS, progression-free survival.