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Higher Absolute Lymphocyte Counts and Lower Des-γ-Carboxyprothrombin Levels After Treatment Initiation Are Associated With the Clinical Efficacy of Tremelimumab Plus Durvalumab Combination Therapy for Hepatocellular Carcinoma

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ABSTRACT

Background and Aims: Tremelimumab plus durvalumab (Dur/Tre) combination therapy is now a first-line systemic therapy for advanced hepatocellular carcinoma (HCC). Because systemic therapy is not effective in some patients, it is clinically important to identify factors that could predict the response to treatment at an early stage. We investigated the factors associated with the response to Dur/Tre for advanced HCC in a clinical setting.

Methods: Seventy patients (median age 74 years; 61 men) who received Dur/Tre between March 2023 and September 2024 were analyzed. We examined the factors associated with the treatment response, including pretreatment factors and factors early in treatment.

Results: The median treatment duration was 77.5 (interquartile range [IQR] 28–187) days. The overall response and disease control rates were 25.8% and 58.1%, respectively. The median (IQR) progression-free survival (PFS) and overall survival (OS) were 82 (61–133) and 415 (337–NA) days, respectively. Multivariable analysis revealed that higher absolute lymphocyte count (ALC) and lower des-γ-carboxyprothrombin (DCP) levels were significantly associated with PFS. Receiver operating characteristic curve analysis showed that the cutoff value for ALC after 4 weeks of treatment in relation to clinical efficacy was 1125/mm^3. A log-rank test using the Kaplan–Meier method showed that OS was significantly longer in patients with ALC above the cutoff and in patients whose DCP levels decreased after starting treatment.

Conclusion: Higher ALC and lower DCP levels after treatment initiation were associated with the clinical efficacy of Dur/Tre for advanced HCC.

1 | Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death worldwide, and its incidence continues to rise [1, 2]. There have been major advances in drug therapy for advanced HCC in recent years. Tremelimumab plus durvalumab (Dur/Tre) combination therapy is now considered the treatment of choice, along with atezolizumab plus bevacizumab (Atz/Bev), in the recent guidelines from the American Association for the Study of Liver Diseases and the American Society of Clinical Oncology [3, 4]. A global study of Dur/Tre, which included several Asian countries other than Japan, showed that the combination therapy significantly prolonged overall survival (OS) compared with sorafenib [5]. More recently, a 4-year follow-up analysis also demonstrated that the OS was significantly extended by Dur/Tre compared with sorafenib [6]. However, the overall response rate (ORR) and progression-free survival (PFS) of Dur/Tre in the HIMALAYA trial were 20.1% and 3.78 months, respectively, which are not sufficient. Second-line therapies based on tyrosine kinase inhibitors, such as sorafenib and lenvatinib, have been established, and early determination of first-line therapy is necessary to improve life expectancy. It has become apparent that immune checkpoint inhibitors (ICIs) will have a long-lasting effect in patients who show a therapeutic response early in treatment [7]. Therefore, even when using Dur/Tre, it is important to identify potential predictors of the response before or early in the course of treatment to predict the long-term response.

In the present study, we investigated which factors, including pretreatment factors and factors early in the course of treatment, are associated with the clinical response to Dur/Tre combination therapy for HCC in clinical practice.

2 | Methods

2.1 | Patients and Methods

The study comprised 70 patients (median age 74 years; 61 males) who received Dur/Tre combination therapy for HCC at Kobe University Hospital and 11 affiliated hospitals in Japan between March 2023 and September 2024 (Kobe City Medical Center Central City Hospital, Osaka Saiseikai Nakatsu Hospital, Hyogo Prefectural Hyogo Cancer Center, Yodogawa Christian Hospital, Konan Medical Center, Shiso General Hospital, Hyogo Prefectural Awaji Medical Center, Harima-Himeji General Medical Center, Kobe Asahi Hospital, Kakogawa Central City Hospital, and Hyogo Prefectural Kakogawa Medical Center).

HCC was diagnosed based on a tendency for elevated serum α-fetoprotein (AFP) and/or des-γ-carboxyprothrombin (DCP) levels, and typical imaging and/or pathological findings. In this study, we used 400 ng/mL and 400 mAU/mL as the cutoff values for baseline AFP and DCP, respectively [8, 9]. Patients who were positive for hepatitis B virus (HBV) surface antigen or anti-hepatitis C virus (HCV) were included. Patients with a history of alcohol intake of ≥ 60 g/day were defined as having alcoholic liver disease. Durvalumab was administered every 4 weeks and tremelimumab as a single dose, and treatment was continued at the physician's discretion depending on adverse events (AEs) and the patient's performance status. In principle, imaging evaluation with contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) was performed every 4–8 weeks, but the interval could be changed according to the patient's condition and the physician's judgment. The treatment response was evaluated according to the modified Response Evaluation Criteria in Solid Tumors (RECIST version 1.1.) based on contrast-enhanced CT or contrast-enhanced MRI. AEs were defined using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. This study was a retrospective analysis of medical records stored in an electronic database. This study was a retrospective analysis of medical records stored in an electronic database, and performed in accordance with the "Guidelines for Clinical Research" published by the Ministry of Health, Labour and Welfare. This study was approved by the Ethics Committee of Kobe University Graduate School of Medicine and each participating institution on September 4, 2024 (B230107).

2.2 | Statistical Analysis

Factors associated with the efficacy of Dur/Tre combination therapy were analyzed using *t* tests, and the Kaplan–Meier log-rank test was used to evaluate PFS and OS. Survival analyses were performed to identify factors that contributed significantly to PFS and OS. The area under the ROC curve (AUROC) was measured to estimate diagnostic performance, and the optimal cutoff values of ALC were determined using Youden's index. Statistical analysis was performed using SPSS version 28.

3 | Results

3.1 | Clinical Characteristics of the Patients

Seventy patients (aged 41–86 years, median 74 years; 61 men and 9 women) treated with Dur/Tre for advanced HCC between March 2023 and September 2024 were included in this study. Of the 70 patients, 59 patients (84%) were classified as Child–Pugh class A, 36 patients (51%) as modified albumin–bilirubin (mALBI) Grade 1/2a, 23 (33%) as Barcelona Clinic Liver Cancer (BCLC) Grade A/B, and 22 (31%) satisfied the Up-To-Seven criteria (Table 1). Esophageal varices were present in 15 patients (23%). The etiologies were hepatitis virus infection in 23 patients (13 with HBV, 8 with HCV, and 2 with HBV + HCV), alcoholic liver disease in 27 patients (39%), and nonalcoholic steatohepatitis in 16 patients (23%). Comorbidities included hypertension in 45 patients (64%) and diabetes in 25 patients (36%). Prior treatments consisted of transarterial chemoembolization (TACE) in 37 patients (53%), surgery in 35 patients (50%), and Atz/Bev

TABLE 1 | Clinical characteristics of the patients.

Clinical factors	Value	Blood tests	Value
Age (years)	74 (68–77)	WBC count (/mm^3)	5050 (3982–6500)
Sex (male)	61 (87%)	Neutrocyte count (/mm^3)	3156 (2573–4362)
BMI (kg/m^2)	23.3 (21.6–25.6)	Lymphocyte count (/mm^3)	1018 (832–1398)
Viral hepatitis	23 (33%)	NLR	3.12 (2.21–5.31)
Esophageal varices	15 (23%)	Hemoglobin (g/dL)	12.1 (11.0–14.0)
Prior TACE	37 (53%)	Platelet count (×10^3/μL)	16.5 (12.0–20.2)
Prior surgery	35 (50%)	AST (IU/L)	38 (25–59)
Chemotherapy line	2 (1–5)	ALT (IU/L)	26.5 (17–40)
Prior Atz/Bev	44 (63%)	γGTP (IU/L)	105 (35–218)
Child–Pugh score A	59 (84%)	Total bilirubin (mg/dL)	0.7 (0.5–0.9)
mALBI Grade 1/2a	36 (51%)	Albumin (g/dL)	3.55 (3.1–3.9)
BCLC Grade A/B	23 (33%)	AFP (ng/mL)	52.8 (5–641)
Within Up-to-Seven criteria	22 (31%)	AFP > 400 ng/mL	18 (26%)
Vessel invasion	17 (25%)	DCP (mAU/L)	606 (84–6612)
Extrahepatic metastasis	28 (40%)	DCP > 400 mAU/L	38 (56%)

Note: Values are *n*, *n* (%), or median (IQR).
Abbreviations: AFP, α-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Atz, atezolizumab; Bev, bevacizumab; BMI, body mass index; DCP, des-γ-carboxy prothrombin; mALBI, modified albumin–bilirubin; NLR, neutrophil-to-lymphocyte ratio; TACE, transcatheter arterial chemoembolization; WBC, white blood cell.

combination therapy in 44 patients (63%). Twenty-four patients (34.3%) received Dur/Tre as initial treatment, and the subsequent treatment lines were: second-line treatment in 16 patients (22.9%), third-line treatment in 17 patients (24.3%), fourth-line treatment in 9 patients (12.9%), and fifth-line treatment in 4 patients (5.7%).

Of the 70 patients, we excluded 8 because the treatment efficacy was not determined; therefore, the subsequent analyses were performed using 62 patients. The median duration of treatment was 77.5 days (interquartile range [IQR] 28–187 days). The best responses, according to RECIST, were complete response (CR) in 2 patients, partial response (PR) in 14 patients, stable disease (SD) in 20 patients, and progressive disease (PD) in 26 patients. Thus, the ORR (sum of CR + PR) was 25.8%, and the disease control rate (DCR; sum of CR + PR + SD) was 58.1% (Figure 1). The median (IQR) PFS and OS were 82 (61–133) and 415 (337–NA) days, respectively.

3.2 | Examination of Factors Associated With the Response to Treatment and Survival

We first examined the factors associated with ORR. In the univariate analyses, the pretreatment platelet count ($p = 0.038$) and the absolute lymphocyte count (ALC) at 4 weeks after treatment ($p = 0.050$) were higher, and the DCP level at 4 weeks after treatment ($p = 0.010$) was lower in patients with CR/PR (Table 2).

When we examined factors associated with achieving disease control (i.e., CR/PR/SD), the significant factors in univariate analysis were pretreatment DCP ≤ 400 mAU/L ($p = 0.016$), low Child–Pugh score ($p < 0.001$), mALBI Grade 1/2a ($p = 0.007$), and high ALC at 4 weeks after starting treatment (Table 3).

In the multivariable analysis of factors associated with PFS, high ALC after 4 weeks of treatment (hazard ratio [HR] 0.998, 95% confidence interval [CI] 0.997–1.000, $p = 0.019$) and low DCP after 4 weeks of treatment (HR 0.283, 95% CI 0.091–0.877, $p = 0.029$) were significant factors (Table 4). For OS, no significant factors were identified in the multivariable analysis (data not shown).

To examine the role of ALC at 4 weeks after the start of treatment, we performed receiver operating characteristic (ROC) curve analysis to determine the optimal cutoff value. The AUROC was 0.69, and the optimal cutoff value was 1125/mm^3 (Figure 2a). When the patients were divided into two groups according to this cutoff value, OS was significantly longer in patients with an ALC of ≥ 1125/mm^3 at 4 weeks after the start of treatment according to the log-rank test. Similarly, when the log-rank test was applied according to whether their DCP level increased or decreased at 4 weeks after the start of treatment, OS was significantly longer in patients whose DCP decreased after starting treatment than in patients whose DCP increased (Figure 2b,c).

Although PFS did not differ between patients whose AFP decreased at 4 weeks after the start of treatment and patients whose AFP increased ($p = 0.316$), PFS was significantly prolonged in patients whose DCP decreased at this time ($p = 0.024$). A significantly shorter PFS ($p = 0.029$) was observed in patients

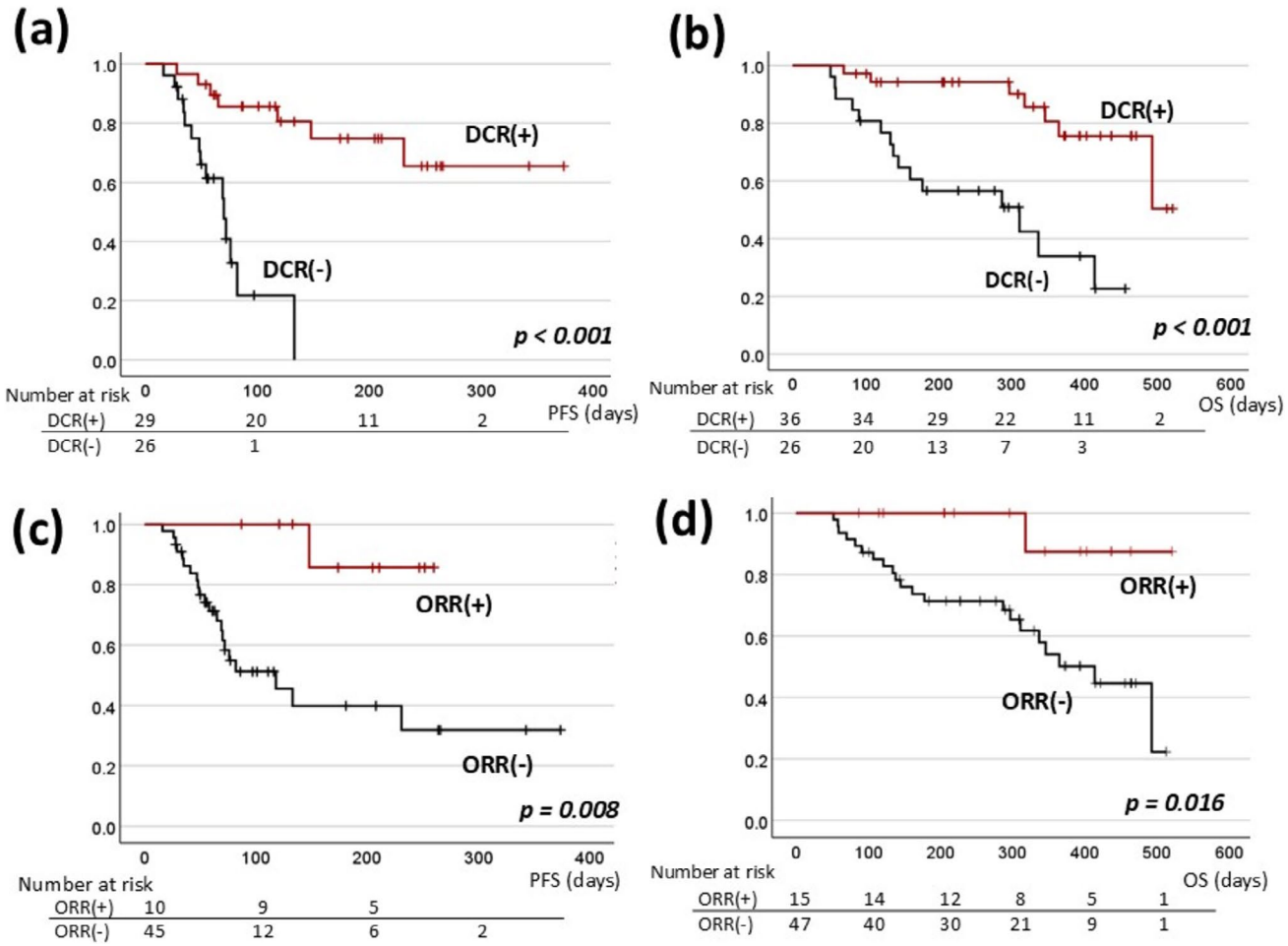

FIGURE 1 | Kaplan–Meier analysis of PFS and OS. Kaplan–Meier curves of PFS (a) and OS (b) according to disease control. The red lines indicate patients with CR/PR/SD and the black lines indicate patients with PD. Kaplan–Meier curves for PFS (c) and OS (d) according to the overall response. The red lines indicate patients with CR/PR and the black lines indicate patients with SD/PD. CR, complete response; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

with high AFP (>400 ng/mL) before treatment, indicative of a worse prognosis (data not shown).

3.3 | Examination of Grade ≥3 AEs

Grade ≥3 AEs occurred in 20 patients (28.6%). The most frequent AE was diarrhea in seven patients (35%), followed by adrenal insufficiency and fatigue in two patients (10%) each. The Kaplan–Meier log-rank test showed no association between the occurrence of Grade ≥3 AEs and PFS ($p = 0.05$). Among eight patients who were unable to continue treatment due to AEs, one patient had a Grade 2 AE, five patients had a Grade 3 AE, and two patients had a Grade 4 AE.

4 | Discussion

Drug therapy for advanced HCC is undergoing major transformation with the introduction of combined immunotherapy. First-line drug therapies for advanced HCC include the combination of atezolizumab, a fully humanized anti-programmed death ligand 1 (anti-PD-L1) antibody, with bevacizumab, a vascular endothelial growth factor (VEGF) targeting antibody (Atz/Bev), or tremelimumab, a cytotoxic T lymphocyte-associated antigen 4 (anti-CTLA-4) antibody, with durvalumab, an anti-PD-L1 antibody (Dur/Tre). OS with either therapy was significantly longer than with sorafenib, the prior standard of therapy. Dur/Tre was shown to be highly effective, especially for immunologically hot tumors, because this combination includes an ICI [10]. Dur/Tre is also preferred for patients at risk of bleeding and proteinuria, especially if bevacizumab is not available. However, there are still few reports investigating the predictors of the clinical efficacy of Dur/Tre combination therapy.

The ORR, DCR, and PFS in this study were 25.8%, 58.1%, and 2.7 months, respectively, which were comparable to the results in the HIMALAYA study (ORR 20.1%, DCR 60.1%, PFS 3.78 months) [5]. In addition, patients in our study who achieved an overall response or disease control with Dur/Tre combination therapy had significantly longer OS and PFS. It has been reported that the long-term survival conferred by combining a PD-L1/programmed death 1 (PD-1) inhibitor with an anti-CTLA-4 antibody may be due to the expansion of $CD4^+Ki67^+$ and $CD8^+Ki67^+$ T cells induced by anti-CTLA-4 therapy, priming the immune response achieved by PD-L1/PD-1 inhibitors [11]. In the present study, the pretreatment ALC was greater in patients with an overall response or disease control, although

TABLE 2 | Comparison of clinical characteristics between patients with or without an overall response (CR/PR vs. SD/PD).

Variable	CR/PR ($n=17$)	SD/PD ($n=46$)	p
Age (years)	73.0 (68.0–76.0)	74.0 (68.0–78.0)	0.978
Sex (male)	14 (93%)	39 (83%)	0.240
Prior Atz/Bev	7 (47%)	33 (70%)	0.130
Prior surgery	6 (40%)	25 (53%)	0.389
Prior TACE	8 (53%)	26 (55%)	0.897
Viral hepatitis	5 (33%)	18 (38%)	0.735
WBC count (/mm^3)	6400 (5000–6610)	4800 (4000–6500)	0.156
Lymphocyte count (/mm^3)	1271 (936–1618)	1002 (835–1350)	0.201
Platelet count ($\times10^3/\mu$L)	21.0 (17.0–24.0)	16.0 (12.0–18.0)	0.038*
NLR	3.14 (1.32–4.72)	3.25 (2.22–3.94)	0.979
AFP > 400 ng/mL	4 (27%)	13 (28%)	0.942
DCP > 400 mAU/L	7 (50%)	29 (61%)	0.495
Child–Pugh A	14 (93%)	39 (83%)	0.240
mALBI Grade 1/2a	9 (60%)	25 (53%)	0.654
BCLC Grade B	3 (20%)	17 (36%)	0.218
Within Up-to-Seven criteria	5 (33%)	13 (28%)	0.694
Vessel invasion	6 (40%)	9 (20%)	0.170
Extrahepatic metastasis	5 (33%)	18 (38%)	0.735
Lymphocyte count at 4 weeks	1408 (1096–1843)	1024 (832–1361)	0.050*
NLR at 4 weeks	2.32 (1.46–4.37)	3.72 (2.27–5.60)	0.162
NLR decreased at 4 weeks	10 (67%)	18 (40%)	0.080
AFP decreased at 4 weeks	8 (62%)	16 (37%)	0.142
DCP decreased at 4 weeks	10 (77%)	15 (37%)	0.010*

Note: Values are *n*, *n* (%), or median (IQR).
Abbreviations: AFP, α-fetoprotein; Atz, atezolizumab; Bev, bevacizumab; CR, complete response; DCP, des-γ-carboxyprothrombin; mALBI, modified albumin–bilirubin; NLR, neutrophil-to-lymphocyte ratio; PD, progressive disease; PR, partial response; SD, stable disease; TACE, transcatheter arterial chemoembolization; WBC, white blood cell.
*$p < 0.05$.

the difference was not significant. Furthermore, at 4 weeks after the start of treatment, the ALC was significantly greater in patients with an overall response or disease control. Studies of blood samples from patients treated with anti-CTLA4 antibodies indicated that an increase in ALC (especially above the cutoff value of 1000 cells/μL) after treatment was associated with improved prognosis [12, 13]. The results of this study may also support the notion that T cells are induced by anti-CTLA4 antibody preparations in patients who respond to treatment.

Both AFP and DCP are useful in the diagnosis of HCC and in the evaluation of tumor progression and prognosis. Regarding the prognosis of patients in the present study, the survival rate was significantly lower in patients with high AFP (> 400 ng/mL) than that of patients with low AFP (< 400 ng/mL). The univariate and multivariable analyses suggested that a decrease in DCP at 4 weeks after the start of treatment may be predictive of prolonged PFS. Although there are reports showing that a transient increase in DCP after treatment initiation is associated with the efficacy of sorafenib [14, 15], we found that a decrease in the DCP level early in treatment was a more relevant factor for the efficacy of treatment than AFP. It was reported that the DCP levels were associated with OS and PFS in patients with HCC who underwent TACE [16]. Saeki et al. also reported that DCP can predict the overall response in patients with HCC who received Dur/Tre combination therapy [17], supporting the validity of our findings. In general, anti-VEGF therapies create a hypoxic environment in tumors, making it difficult to predict the therapeutic relevance of DCP for regimens using anti-VEGF agents [18]. However, Dur/Tre is a regimen combining two ICIs that do not include anti-VEGF agents, suggesting that this is a direct reflection of the anti-tumor effect. However, Saeki et al. and Uchikawa et al. reported that AFP could also be a predictor of the therapeutic efficacy of these therapies [17, 19, 20], which is different from our results. Further studies with larger numbers of patients are needed. In this study, by including factors early

TABLE 3 | Comparison of clinical characteristics between patients with or without disease control (CR/PR/SD vs. PD).

Variable	CR/PR/SD ($n=36$)	PD ($n=26$)	p
Age	74.0 (68.0–77.0)	73.5 (67.3–78.3)	0.672
Sex (male)	31 (86%)	22 (85%)	0.873
Prior Atz/Bev	21 (58%)	19 (73%)	0.231
Viral hepatitis	12 (33%)	11 (42%)	0.483
WBC count (/mm^3)	5500 (4025–6500)	4950 (3975–6625)	0.447
Lymphocyte count (/mm^3)	1195 (857–1539)	935 (791–1208)	0.064
Platelet count ($\times10^3/\mu L$)	17.5 (12.9–23.8)	15.5 (12.0–18.0)	0.052
NLR	3.04 (1.78–4.27)	3.27 (2.32–3.93)	0.369
AFP > 400 ng/mL	8 (22%)	9 (35%)	0.300
DCP > 400 mAU/L	17 (46%)	20 (76%)	0.016*
Child–Pugh A	35 (97%)	18 (69%)	0.007*
mALBI Grade 1/2a	25 (69%)	9 (35%)	0.007*
BCLC Grade B	13 (36%)	7 (27%)	0.448
Within Up-to-Seven criteria	12 (33%)	6 (23%)	0.380
Vessel invasion	10 (29%)	5 (19%)	0.411
Extrahepatic metastasis	13 (36%)	10 (38%)	0.853
Lymphocyte count at 4 weeks	1352 (1010–1701)	960 (790–1203)	0.029*
NLR at 4 weeks	2.86 (2.06–4.68)	3.85 (2.22–5.77)	0.214
NLR decreased at 4 weeks	16 (47%)	12 (46%)	0.946
AFP decreased at 4 weeks	16 (52%)	8 (32%)	0.143
DCP decreased at 4 weeks	17 (57%)	8 (33%)	0.089

Note: Values are *n*, *n* (%), or median (IQR).
Abbreviations: AFP, α-fetoprotein; Atz, atezolizumab; Bev, bevacizumab; CR, complete response; DCP, des-γ-carboxyprothrombin; mALBI, modified albumin–bilirubin; NLR, neutrophil-to-lymphocyte ratio; PD, progressive disease; PR, partial response; SD, stable disease; WBC, white blood cell.
*$p<0.05$.

TABLE 4 | Variables associated with progression-free survival.

Variables	HR	95% CI	p
Age	0.996	0.937–1.060	0.91
Sex	0.513	0.120–2.184	0.366
Platelet	0.998	0.911–1.093	0.971
mALBI Grade 1/2a	0.574	0.201–1.644	0.301
Lymphocyte count at 4 weeks	0.998	0.997–1.000	0.019*
DCP decreased at 4 weeks	0.283	0.090–0.877	0.029*

Abbreviations: CI, confidence interval; DCP, des-γ-carboxyprothrombin; HR, hazard ratio; mALBI, modified albumin–bilirubin.
*$p<0.05$.

after treatment initiation, such as ALC and lower DCP, we managed to identify them as statistically predictive of treatment response. Clinically, it would be most useful if the effect could be predicted by pretreatment factors. It is hoped that pretreatment markers that predict treatment efficacy will become available in the future.

There are several limitations to this study. First, although this was a multicenter study, the number of patients was relatively small, and the results of PFS and OS did not always match due to the potential effects of prior and subsequent therapies. Secondly, in this study, we did not measure $CD4^+$ and $CD8^+$ T cells. From the pharmacological effects of ICI, it can be inferred that the measurement of CD4 and CD8 positive T cells is a predictor of therapeutic response. Further investigation of these factors is warranted in the near future. Recently, there have been reports that Dur/Tre combination therapy is less effective after Atz/Bev combination therapy [21–23], and we found that the ORR tended to be lower in patients with a history of Atz/Bev combination therapy. The Clinical Practice Guidelines of the National Comprehensive Cancer Network and the American Association for the Study of Liver Diseases recommend a tyrosine kinase inhibitor as second-line therapy, and the efficacy of Dur/Tre combination therapy following Atz/Bev therapy is limited [4, 24]. Tomonari et al. reported that the use of Dur/Tre combination therapy as first-line treatment resulted in an excellent DCR and a high transition rate to second-line therapy, suggesting that Dur/Tre therapy may be beneficial as a first-line option in the pharmacological treatment of HCC [24]. In the present study, the patients without prior Atz/Bev therapy had

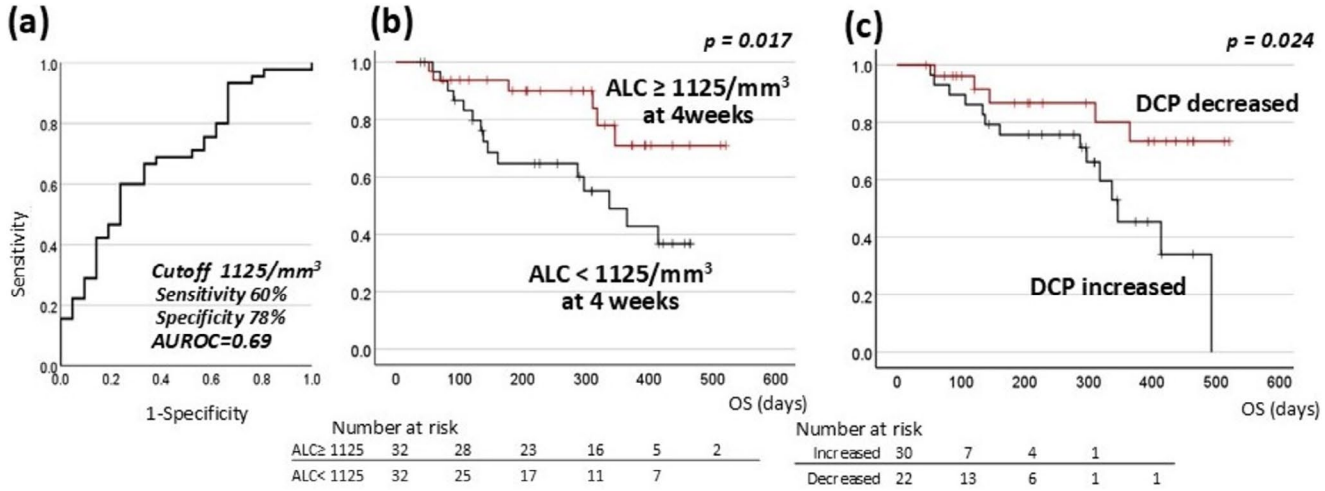

FIGURE 2 | (a) Receiver operating characteristic curve analysis of the ALC at 4 weeks after the start of treatment for clinical efficacy. (b) Kaplan–Meier curves for OS according to the ALC at 4 weeks after the start of treatment. The red line indicates patients with an ALC above the cutoff (i.e., $\geq 1125/mm^3$) and the black line indicates patients with an ALC below the cutoff (i.e., $< 1125/mm^3$). (c) Kaplan–Meier curves of OS according to the change in DCP at 4 weeks. The red line indicates patients whose DCP level increased at 4 weeks and the black line indicates patients whose DCP level decreased at 4 weeks. ALC, absolute lymphocyte count; AUROC, area under the ROC curve; DCP, des-γ-carboxy prothrombin; OS, overall survival; ROC, receiver operating characteristic.

a higher rate of reduction in AFP and DCP in the first 4 weeks of treatment, but there was no significant survival benefit (data not shown). Although the number of cases analyzed was small, and the observation period was short, further accumulation of cases is desirable. In a randomized phase III trial, nivolumab exhibited superior efficacy over chemotherapy in patients with advanced melanoma previously treated with an anti-CTLA-4 inhibitor [25]. Therefore, further validation of the efficacy of Atz/Bev therapy after Dur/Tre therapy is needed. In the future, it will be important to increase the number of cases so that the background treatment sequence can be matched and compared.

5 | Conclusion

Higher ALC and lower DCP after treatment initiation were associated with the clinical efficacy of Dur/Tre combination therapy in patients with advanced HCC.

Conflicts of Interest

The authors declare no conflicts of interest.

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