

Pretreatment Positron Emission Tomography with ^{18}F -Fluorodeoxyglucose May Be a Useful New Predictor of Early Progressive Disease following Atezolizumab plus Bevacizumab in Patients with Unresectable Hepatocellular Carcinoma

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Keywords

Hepatocellular carcinoma · Atezolizumab plus bevacizumab · Malignant potential · Poorly differentiated · Rapid progressive disease · ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography

Abstract

Background and Aims: The aim of this study was to identify the utility of ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG-PET/CT) as a predictor of early progressive disease (e-PD) in patients with hepatocellular carcinoma (HCC) treated with atezolizumab plus bevacizumab (Atezo/Bev). **Methods:** Twenty consecutive patients with measurable intrahepatic target nodules who received Atezo/Bev treatment were reviewed. The oncological aggressiveness of tumors estimated by ^{18}F -FDG-PET/CT was analyzed using the rate of e-PD within 12 weeks and early progression-free survival (e-PFS) and overall survival (OS). Multivariate analysis was used to identify poten-

tial confounders for PD during Atezo/Bev therapy. **Results:** Using the Response Evaluation Criteria in Solid Tumors version 1.1, a tumor-to-normal liver ratio (TLR) ≥ 2 , indicating higher oncological aggressiveness in HCCs, was associated with lower objective response rates compared with TLR values < 2 (18% vs. 33%, respectively). Moreover, TLR values ≥ 2 were significantly associated with higher e-PD rates compared with TLR values < 2 (64% vs. 11%, respectively) and worse e-PFS ($p = 0.021$). In multivariate analysis, TLR ≥ 2 showed marginal significance as a predictor of e-PD ($p = 0.053$), and utility as a predictor for worse e-PFS (hazard ratio, 7.153; 95% confidence interval, 1.258–40.689; $p = 0.027$). In contrast, no significant differences in OS with/without e-PD were observed during the treatment course. In this study, 8 patients experienced e-PD and almost 40% of patients experienced acceptable disease control following subsequent lenvatinib treatment. **Conclusion:** Pretreatment ^{18}F -FDG-PET/CT may be a useful new predictor of e-PD and may enable early decision-making based on early treatment changes following Atezo/Bev treatment of HCC.

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Introduction

Recently, atezolizumab plus bevacizumab (Atezo/Bev) has become available in Japan as a newly recommended first-line combination of an immune checkpoint inhibitor and a molecularly targeted agent for the treatment of unresectable advanced hepatocellular carcinoma (HCC). This regimen is recommended in other countries and is expected to provide better therapeutic efficacy than previously introduced first-line molecularly targeted agents (sorafenib and lenvatinib) to improve the prognosis of this patient population [1–4]. Approximately one-third of HCC patients achieve an objective response with Atezo/Bev [3]; this response rate is almost twice as high as that observed with anti-programmed death receptor-1 monotherapy [5, 6]. However, hyperprogressive disease (HPD), defined as accelerated tumor growth during the administration of systemic chemotherapy, has been reported in patients receiving immune checkpoint inhibitors. HPD affects survival in patients with certain malignancies, including lung cancer, melanoma, and head and neck cancers [7–12]. In HCC, HPD has been observed in patients treated with nivolumab or pembrolizumab, both of which failed to meet phase 3 trial primary endpoints [13, 14]. Recently, in patients with HCC receiving Atezo/Bev, a higher neutrophil-to-lymphocyte ratio (NLR) at baseline has been reported to increase the risk of HPD [15]. However, the characteristics and predictors of HPD in patients with HCC treated with Atezo/Bev remain unclear. Similarly, predictors of early progressive disease (e-PD) during Atezo/Bev therapy are not known. With respect to tumor characteristics, the efficacy of lenvatinib to treat HCCs with high malignant potential (e.g., poorly differentiated type and non-simple nodular type) was recently established based on several clinical reports [16, 17].

Regarding ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG-PET/CT) imaging features, ^{18}F -FDG-PET/CT positivity has been reported to be associated strongly with poorly differentiated HCC [18]. Therefore, ^{18}F -FDG-PET/CT-positive HCC is usually a negative predictor of response to various treatments (i.e., surgical resection, transarterial chemoembolization [TACE], and sorafenib) [19–22]. Recently, we reported a high treatment response rate to lenvatinib in patients who had ^{18}F -FDG-PET/CT-positive HCC [23]. However, the utility of ^{18}F -FDG-PET/CT for predicting the prognosis of patients treated with Atezo/Bev has not been sufficiently evaluated. Therefore, the aim of

this study was to evaluate the utility of ^{18}F -FDG-PET/CT for predicting e-PD in patients with unresectable HCC following administration of Atezo/Bev.

Patients and Methods

Study Population

From November 2020 to October 2021, 43 patients received systemic anticancer treatment using Atezo/Bev for unresectable HCC at the Department of Hepatology, Toranomon Hospital, Tokyo, Japan. The inclusion criteria for the study were: (1) dynamic CT or magnetic resonance imaging (MRI) performed prior to initiation of Atezo/Bev, (2) tumors showing hyperenhancement in the arterial phase of dynamic CT or MRI, (3) ^{18}F -FDG-PET/CT performed prior to initiation of Atezo/Bev, (4) Child-Pugh class A liver function at the time of lenvatinib initiation, (5) Barcelona Clinic Liver Cancer (BCLC) stage A-C tumor(s), (6) unresectable HCC in patients not wanting to undergo local ablation or chemoembolization therapy for various reasons (i.e., tumor size, number, and location; extrahepatic metastasis; TACE failure/refractoriness [24]; and various complications), (7) no history of treatment with Atezo/Bev, and (8) an observation period of ≥ 6 weeks. A total of 20 patients met these inclusion criteria. The study was approved by the institutional review board of our hospital (protocol no. 1438-H/B).

Diagnosis of HCC

The diagnosis of HCC was based predominantly on analysis of dynamic CT or MRI images that was governed by a protocol reported elsewhere [16, 25]. Briefly, when a liver nodule showed hyperattenuation in the arterial phase and washout in the portal or delayed phases in dynamic studies, the nodule was diagnosed as an HCC.

Imaging Analysis of HCC Using ^{18}F -FDG-PET/CT

Within 1 month before initiation of lenvatinib, ^{18}F -FDG-PET/CT was performed using a dedicated whole-body PET scanner (Biograph mCT Flow40; Siemens Healthcare, Erlangen, Germany). Synapse Vincent software ver. 4 (Fujifilm Medical Systems, Tokyo, Japan) was used for semiquantitative analysis, with the volume of interest drawn along the outline of the tumor, and the maximum SUV and mean SUV in each intra- and extrahepatic target tumor then calculated. Of the lesions measured, the one with the highest ^{18}F -FDG uptake was selected and used to calculate the tumor-to-normal liver ratio (TLR). We next measured normal liver activity by drawing 3 nonoverlapping spherical 1-cm³ volume of interests on axial PET images of the liver (2 in the right lobe and 1 in the left lobe), avoiding the HCC areas seen on dynamic CT. The TLR was calculated using the following equation: $\text{TLR} = \text{maximum SUV of the tumor} / \text{mean SUV of normal liver tissue}$. Based on previous reports [19, 20, 26], we selected a $\text{TLR} \geq 2$ to indicate a high malignant potential.

Atezo/Bev Treatment and Adverse Event Assessment

Patients received intravenous Atezo (1200 mg) plus Bev (15 mg/kg) every 3 weeks. Treatment was discontinued following observation of any unacceptable or serious adverse event (AE) or clinical tumor progression. For assessment of AEs, the National

Cancer Institute Common Terminology Criteria for AEs, ver. 4.0 [27] was used. Manufacturer guidelines for Atezo/Bev treatment were used.

Treatment Response Evaluation

Treatment response was evaluated according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) [28]. After initiation of Atezo/Bev, we assessed the best tumor response during the 6–24-week period. Treatment responses were assessed independently by an expert hepatologist (Y. Kawamura) and an expert hepatobiliary surgeon (J. Shindoh) who were blinded to the clinical data. Discrepancies between these two examiners were resolved by consensus review that included an additional reviewer (K. Ikeda).

Definition of e-PD

In this study, e-PD was defined as a target tumor showing PD by RECIST 1.1 criteria within 12 weeks of initiation of Atezo/Bev.

Definition of Early Progression-Free Survival

In this study, early progression-free survival (e-PFS) was defined as the time from initiation of Atezo/Bev to e-PD or death from any cause.

Definition of HPD

Tumor growth dynamics were assessed as the ratio of posttreatment tumor growth to pretreatment tumor growth using tumor growth kinetics (TGK) in the same target lesions. TGK_{PRE} was defined as the difference of the sum of the largest diameters of the target lesions (according to RECIST 1.1) per unit of time between pre-baseline and baseline imaging. Similarly, TGK_{POST} was defined as the difference in the sum of the largest diameters of the target lesions per unit of time between baseline and time of PD diagnosis within 12 weeks of initiation of Atezo/Bev treatment.

The TGK ratio (TGK_R) was defined as the ratio of TGK_{POST} to TGK_{PRE} . A $TGK_R > 1$ indicated tumor growth acceleration, while $0 < TGK_R < 1$ and $TGK_R < 0$ indicated tumor deceleration and tumor shrinkage, respectively. HPD was defined as $TGK_R \geq 2$ [8].

Assessments of Hepatic Reserve Function

The Child-Pugh classification [29] and albumin-bilirubin (ALBI) grade were used to assess hepatic reserve function. ALBI grade was calculated based on serum albumin and total bilirubin values using the following formula: $ALBI\ score = (0.66 \times \log_{10}\text{bilirubin} [\mu\text{mol/L}]) + (-0.085 \times \text{albumin} [\text{g/L}])$, with the result defined by the following scores: $\leq -2.60 = \text{Grade 1}$, > -2.60 to $\leq -1.39 = \text{Grade 2}$, and $> -1.39 = \text{Grade 3}$ [30]. For more detailed evaluations of patients with Grade 2 ALBI function, we used modified ALBI grading consisting of 4 levels, which included subgrading for grade (2a and 2b) based on an ALBI score of -2.27 as the cutoff, which was previously reported as an indocyanine green retention after 15 min value of 30% [31].

Follow-Up Protocol

Physicians examined patients every 1–3 weeks after initiation of Atezo/Bev, and laboratory biochemical and urine tests were also performed. After initiation of Atezo/Bev, patients underwent dynamic CT or MRI every 6–12 weeks to evaluate responses during the treatment period.

Statistical Analysis

Statistical analysis was performed using IBM SPSS software (ver. 27.0 SPSS Inc., Chicago, IL, USA). Data were expressed as the median and range. Differences in background features between each parameter were analyzed using Fisher's exact test. p values < 0.05 were considered statistically significant. e-PFS and overall survival (OS) after introduction of Atezo/Bev were estimated by the Kaplan-Meier method, with values compared using the log-rank test.

To identify factors associated with e-PD and e-PFS after initiation of Atezo/Bev, a multivariate analysis was performed using logistic regression with backward elimination. Among potential independent variables, factors with a marginal association ($p < 0.1$) in univariate analysis were included in the initial model. Then, after stepwise selection, only factors that showed a statistically significant association with e-PD at $p < 0.1$ were included in the final model.

Results

Overview

Table 1 summarizes the baseline characteristics of the study population. The median age was 72.5 years and 16 (80%) patients were male. The median size of the largest tumor was 27.5 mm (range, 11.0–74.5 mm) and the median tumor number was 6 (range, 1–50). Of the 20 patients, 2 (10%) with BCLC stage A disease received Atezo/Bev due to tumor location, TACE failure/refractoriness, and patient preference; 10 (50%) patients presented with BCLC stage C disease (macrovascular invasion [$n = 4$]) (Vp2, $n = 2$; Vp4 = 1; and Vb2, $n = 1$); while 6 had extrahepatic metastasis. Seven patients (35%) had a history of treatment with lenvatinib and 11 patients (55%) had a TACE failure/refractoriness status. About the treatment line of Atezo/Bev, 13 of 20 (65%) patients received as first-line treatment, and the remaining patients received Atezo/Bev treatment as second to fourth-line treatment. Seven patients had died at the time of database lock (December 14, 2021), with the median duration of Atezo/Bev administration being 3.2 months and a median observation period of 7.4 months.

Best Treatment Response and e-PD Rate after Initiation of Atezo/Bev according to TLR Value on ^{18}F -FDG-PET/CT

At first, a cut-off TLR of 2 was used to define HCCs with high malignant potential. Based on TLR values calculated by RECIST 1.1, the objective response rate for tumors with TLR values or ≥ 2 and < 2 was 18% and 33%, respectively; this difference was not statistically significant ($p = 0.617$) (Table 2). Based on TLR values calculated

Table 1. Clinical profiles and laboratory data of patients with HCC treated with Atezo/Bev

Patient characteristics and laboratory data	
Patients, <i>n</i>	20
Males:females, <i>n</i>	16:4
Age, years (range) [†]	72.5 (52–88)
HCV:HBV:NonB, NonC	9:1:10
Performance status 0:1, <i>n</i> (%)	16 (80):4 (20)
Platelet count, ×10 ³ /μL (range) [†]	121 (78–248)
Albumin, g/dL (range) [†]	3.8 (3.4–4.5)
Total bilirubin, mg/dL (range) [†]	0.9 (0.5–2.9)
Prothrombin activity, % (range) [†]	86.4 (71.3–107.9)
AST, IU/L (range) [†]	33 (18–214)
AFP, μg/L (range) [†]	46.6 (2.1–30,353.0)
DCP, AU/L (range) [†]	90.0 (14.0–27,045.0)
Child-Pugh score 5:6, <i>n</i> (%)	12 (60):8 (40)
mALBI score (1:2a:2b:3), <i>n</i> (%)	3 (15):9 (45):8 (40):0 (0)
History of lenvatinib treatment, <i>n</i> (%)	7 (35)
Treatment line of Atezo/Bev 1st:2nd:3rd, 4th, <i>n</i> (%)	13 (65):3 (15):3 (15):1 (5)
Tumor characteristics	
Largest tumor diameter, mm (range) [†]	27.5 (11.0–74.5)
Tumors, <i>n</i> , <i>n</i> (range)	6 (1–50)
Macrovascular invasion, <i>n</i> (%)	4 (20)
Extrahepatic metastasis, <i>n</i> (%)	6 (30)
BCLC stage A:B:C, <i>n</i> (%)	2 (10):8 (40):10 (50)
TACE failure/refractoriness, <i>n</i> (%)	11 (55)
¹⁸ F-FDG-PET/CT findings	
TLR ≥ 2.0, <i>n</i> (%)	11 (55)

AFP, alpha-fetoprotein; Atezo/Bev, atezolizumab plus bevacizumab; BCLC, Barcelona Clinic Liver Cancer; AST, aspartate aminotransferase; DCP, des-γ-carboxy prothrombin; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IU, international units; mALBI, modified albumin-bilirubin; NonB, NonC, neither HBV nor HCV infection present; TACE, transarterial chemoembolization; TLR, tumor-to-normal liver standardized uptake value ratio. [†] Data expressed as median (range).

Table 2. Evaluation of best treatment response after initiation of Atezo/Bev, grouped according to ¹⁸F-FDG-PET/CT findings and analysis of imaging features using RECIST 1.1

¹⁸ F-FDG-PET/CT TLR	Response evaluation using RECIST 1.1, <i>n</i> (%)			
	CR	PR	SD	PD
TLR ≥ 2.0 (<i>n</i> = 11)	0 (0)	2 (18)	6 (55)	3 (27)
TLR < 2.0 (<i>n</i> = 9)	0 (0)	3 (33)	6 (67)	0 (0)
ORR, %				
TLR ≥ 2.0 (<i>n</i> = 11)	18			
TLR < 2.0 (<i>n</i> = 9)	33			

¹⁸F-FDG-PET/CT, ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography; Atezo/Bev, atezolizumab plus bevacizumab; CR, complete response; CT, computed tomography; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TLR, tumor-to-normal liver ratio.

Table 3. Evaluation of e-PD after initiation of Atezo/Bev according to ¹⁸F-FDG-PET/CT findings using RECIST 1.1

¹⁸ F-FDG-PET/CT TLR	Rate of e-PD, <i>n</i> (%)	
	e-PD positive	e-PD negative
TLR ≥ 2.0 (<i>n</i> = 11)	7 (64)	4 (36)
TLR < 2.0 (<i>n</i> = 9)	1 (11)	8 (89)

¹⁸F-FDG-PET/CT, ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography; Atezo/Bev, atezolizumab plus bevacizumab; e-PD, early progressive disease; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors; TLR, tumor-to-normal liver ratio.

Fig. 1. e-PFS according to TLR value on ^{18}F -FDG-PET/CT prior to introduction of Atezo/Bev.

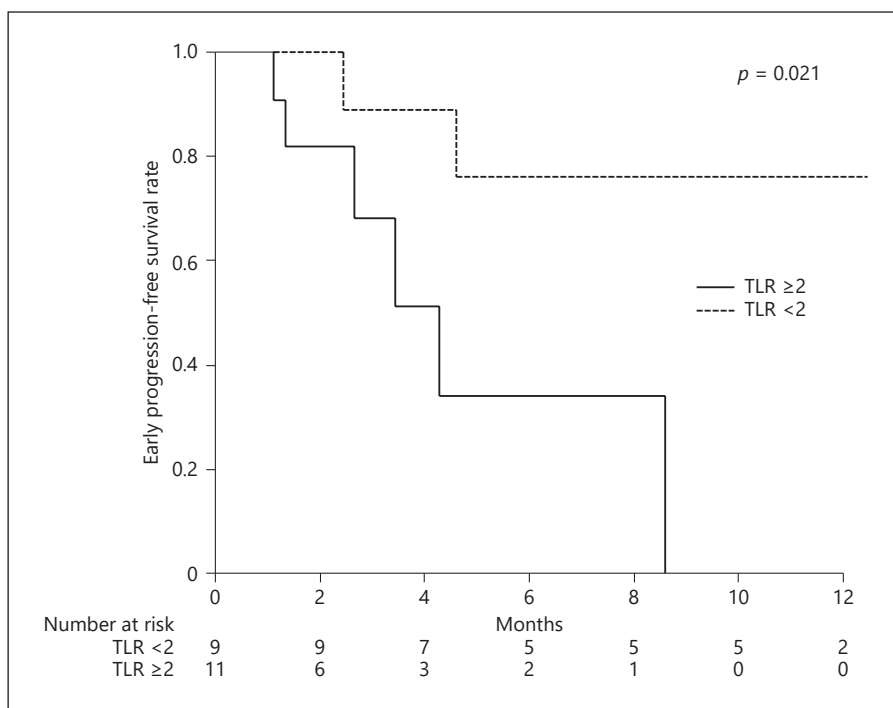
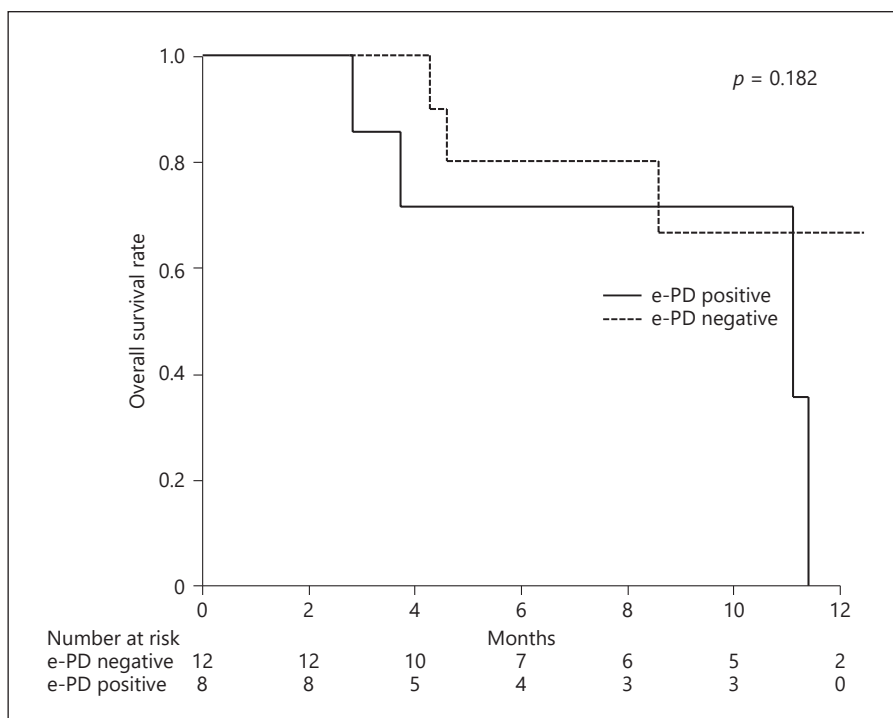


Fig. 2. PFS according to TLR value on ^{18}F -FDG-PET/CT prior to introduction of Atezo/Bev.



by RECIST 1.1, the e-PD rate for TLR values of ≥ 2 and < 2 was 64% and 11%, respectively; this difference was statistically significant ($p = 0.028$) (Table 3). About, overall best treatment response calculated by RECIST 1.1, objective

response rate was 25% (online suppl. Table 1; see www.karger.com/doi/10.1159/000523850 for all online suppl. material).

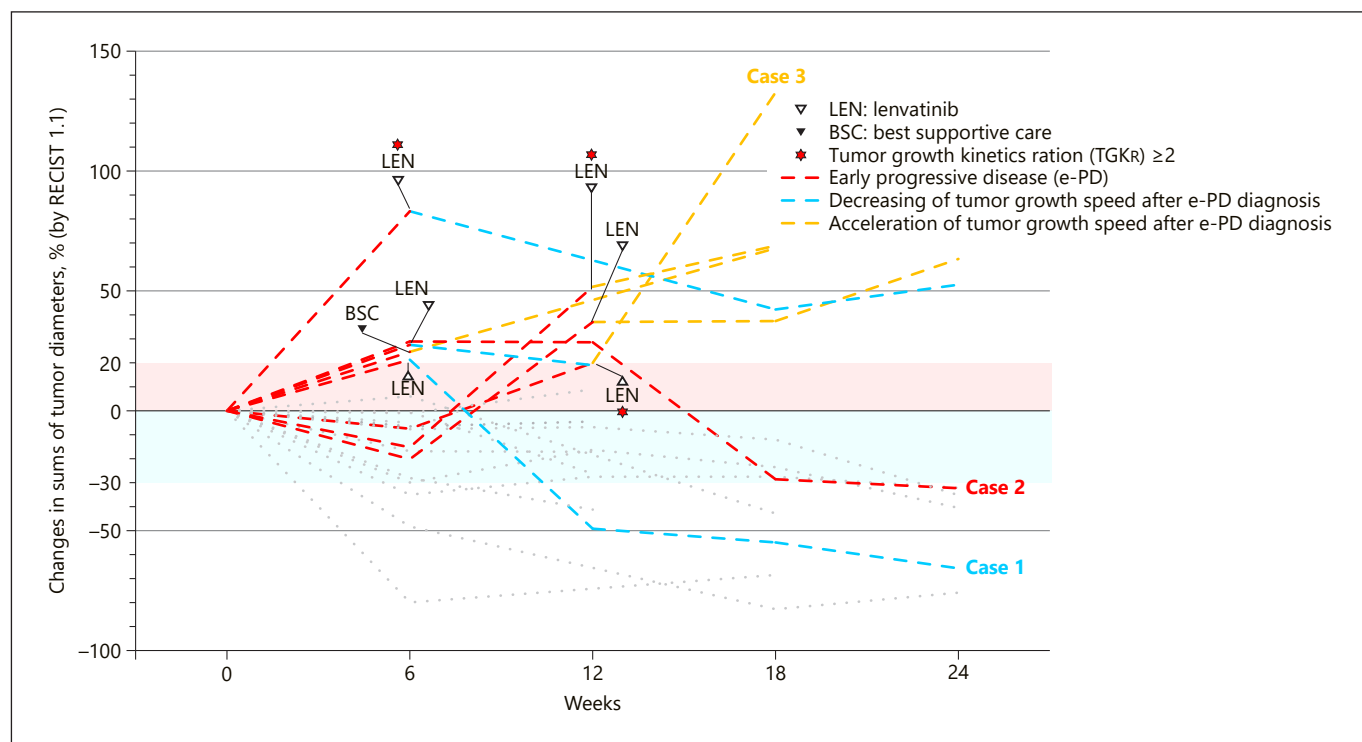


Fig. 3. Changes in sums of tumor diameters were evaluated by RECIST 1.1 during Atezo/Bev treatment.

e-PFS after Initiation of Atezo/Bev according to TLR Value on ^{18}F -FDG-PET/CT

Figure 1 shows e-PFS according to TLR value; a significant difference was observed between groups ($p = 0.021$). On the other hand, overall e-PFS was 57% for 6 months and 47% for 12 months (online suppl. Fig. 1).

OS after Initiation of Atezo/Bev according to Presence of e-PD

Figure 2 shows OS according to the presence of e-PD. The difference between groups was not statistically significant ($p = 0.182$). On the other hand, overall OS was 76% for 6 months and 38% for 12 months (online suppl. Fig. 2).

Treatment Course after Diagnosis of e-PD

Figure 3 shows changes in tumor diameter during the treatment period using RECIST 1.1. Among patients who experienced e-PD, 6 patients received subsequent lenvatinib therapy; 3 of these patients experienced tumor shrinkage and 3 experienced further disease progression from the time of e-PD diagnosis. In addition, 1 patient showed marked tumor shrinkage, decreasing ^{18}F -FDG

accumulation, and tumor thrombus disappearance (Fig. 3, Case 1; Fig. 4).

One patient experienced tumor shrinkage while receiving Atezo/Bev treatment. Therefore, this patient potentially had pseudoprogression during immunotherapy (Fig. 3, Case 2; Fig. 5). Among patients who experienced e-PD, only 1 patient showed ^{18}F -FDG-PET/CT-negative result (TLR < 2) at the time of Atezo/Bev initiation (Fig. 3, Case 3).

Predictors of e-PD and Unfavorable e-PFS after Introduction of Atezo/Bev

Table 4 summarizes the results of multivariate analysis for predictive factors for e-PD. Of the 14 variables tested, ^{18}F -FDG-PET/CT positivity (TLR ≥ 2) (odds ratio, 14.485; 95% confidence interval [CI], 0.961–218.314; $p = 0.053$) and lenvatinib treatment history (odds ratio, 8.673; 95% CI, 0.686–109.734; $p = 0.095$) showed marginal significance as predictors of e-PD during Atezo/Bev treatment. Moreover, in multivariate analysis for predictive factors for unfavorable e-PFS, ^{18}F -FDG-PET/CT positivity (TLR ≥ 2) (hazard ratio, 7.153; 95% CI, 1.258–40.689; $p = 0.027$), and des- γ -carboxy prothrombin level (hazard ratio,

Changes in tumor viability and thrombi during treatment course

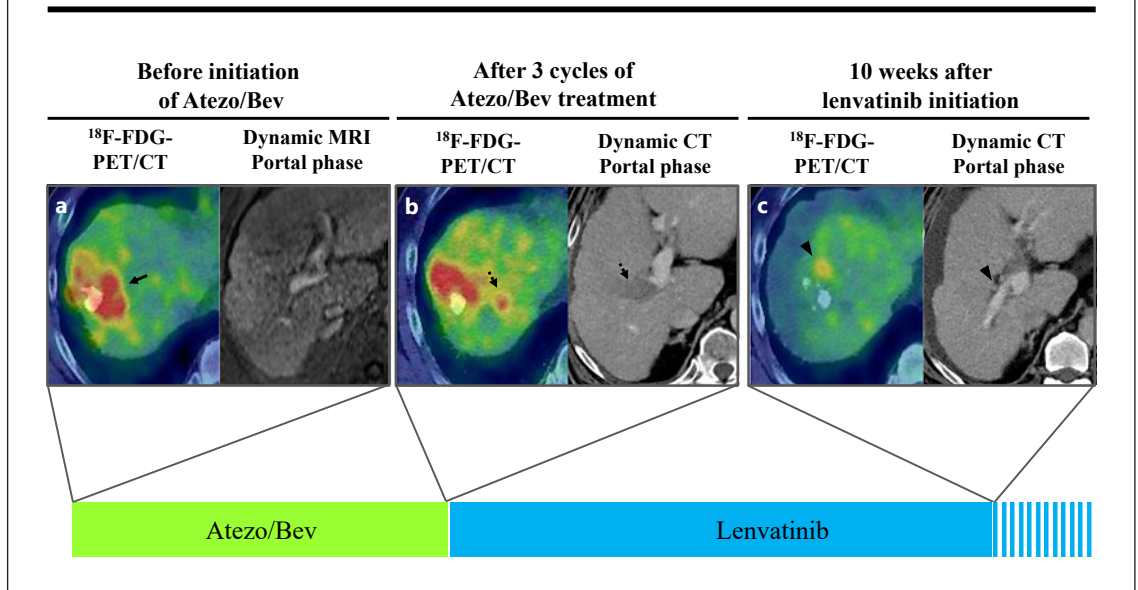


Fig. 4. Changes in tumor viability and thrombi during the Atezo/Bev treatment course. **a** Before initiation of Atezo/Bev, the tumor was ¹⁸F-FDG-PET/CT–positive (arrow). **b** After three cycles of Atezo/Bev, the tumor showed rapid progression and massive portal vein invasion (dotted arrow). **c** Ten weeks after lenvatinib initiation, the tumor showed marked shrinkage and decreasing FDG accumulation (arrowhead).

Changes in tumor size during treatment course

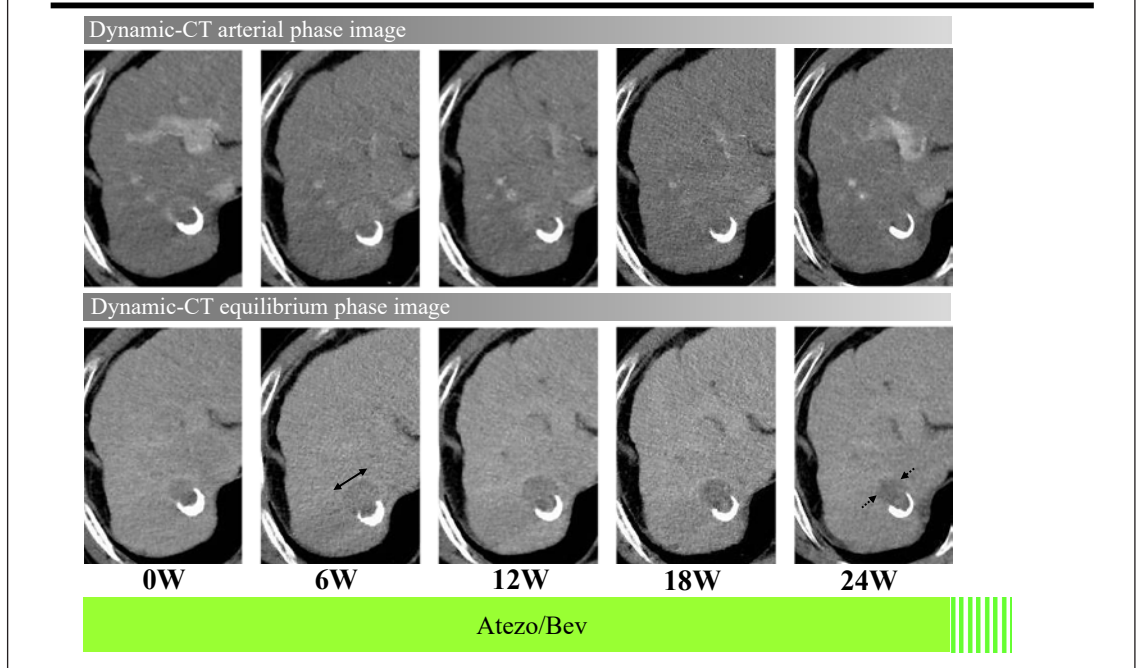


Fig. 5. Pseudoprogession of HCC during Atezo/Bev treatment. The tumor showed rapid progression at 6 weeks after Atezo/Bev initiation. However, the tumor size gradually decreased until 24 weeks after Atezo/Bev initiation.

Table 4. Predictive factors for e-PD

	<i>p</i> value*	Coefficients [†]	SE	Wald χ^2	OR	95% CI
¹⁸ F-FDG-PET/CT-positive (TLR \geq 2)	0.053	2.673	1.384	3.730	14.485	0.961–218.314
History of lenvatinib treatment	0.095	2.160	1.295	2.784	8.673	0.686–109.734

¹⁸F-FDG-PET/CT, ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography; Atezo/Bev, atezolizumab plus bevacizumab; CI, confidence interval; SE, standard error; TLR, tumor-to-normal liver ratio; OR, odds ratio. Multivariate logistic regression was applied using stepwise backward selection. Of the potential predictors, factors showing a marginal association ($p < 0.1$) with e-PD after introduction of Atezo/Bev in univariate analysis were included in the initial model. The factors that showed no or limited statistically significant association ($p > 0.1$) adjusted for the remaining factors in the model were then deleted from the model in a stepwise fashion. The following 14 variables were tested (p values in univariate analysis): age (0.063), sex (0.501), etiology (HCV vs. other) (0.153), mALBI grade (0.255), prothrombin activity (0.212), serum alpha-fetoprotein (0.562), plasma des- γ -carboxy prothrombin (0.554), tumor diameter (0.979), tumor number (0.949), macrovascular invasion (0.650), extrahepatic metastasis (0.552), ¹⁸F-FDG-PET/CT positivity (TLR \geq 2) (0.032), TACE failure/refractoriness (0.714), and lenvatinib treatment history (0.046). * Based on the likelihood test adjusted for other factors in the final model. [†] Estimated coefficient for the variable and associated SE.

Table 5. Predictive factors for e-PFS

	<i>p</i> value*	Coefficients [†]	SE	Wald χ^2	HR	95% CI
¹⁸ F-FDG-PET/CT positivity (TLR \geq 2)	0.027	1.968	0.887	4.921	7.153	1.258–40.689
DCP + 100 AU/L	0.021	0.012	0.005	5.322	1.012	1.002–1.022

¹⁸F-FDG-PET/CT, ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography; Atezo/Bev, atezolizumab plus bevacizumab; CI, confidence interval; DCP, des- γ -carboxy prothrombin; HR, hazard ratio; SE, standard error; TLR, tumor-to-normal liver ratio; mALBI, modified albumin-bilirubin. Multivariate Cox regression was applied using stepwise backward selection. Of the potential predictors, factors showing a marginal association ($p < 0.1$) with e-PFS after introduction of Atezo/Bev in univariate analysis were included in the initial model. The factors that showed no or limited statistically significant association ($p > 0.1$) adjusted for the remaining factors in the model were then deleted from the model in a stepwise fashion. The following 14 variables were tested (p values in univariate analysis): age (0.580), sex (0.768), etiology (HCV vs. other) (0.102), mALBI grade (0.546), prothrombin activity (0.142), serum alpha-fetoprotein (0.030), plasma des- γ -carboxy prothrombin (0.026), tumor diameter (0.203), tumor number (0.618), macrovascular invasion (0.414), extrahepatic metastasis (0.508), ¹⁸F-FDG-PET/CT positivity (TLR \geq 2) (0.037), TACE failure/refractoriness (0.827), and lenvatinib treatment history (0.052). * Based on the likelihood test adjusted for other factors in the final model. [†] Estimated coefficient for the variable and associated SE.

1.012; 95% CI, 1.002–1.0022; $p = 0.021$) were significantly associated with poor e-PFS (Table 5).

Frequency of Grade \geq 3 AEs following Initiation of Atezo/Bev

With respect to Grade 3 AEs, 3 of 20 patients (15%) experienced proteinuria, 1 of 20 (5%) experienced hypertension, 1 of 20 (5%) experienced fatigue, 1 of 20 (5%) experienced dizziness, 1 of 20 (5%) experienced bone infection, and 1 of 20 (5%) experienced ascites, respectively. With respect to Grade 4 or greater AEs, 1 of 20 (5%) experienced myocardial infarction, 1 of 20 (5%) experi-

enced interstitial pneumonia, and 1 of 20 (5%) experienced sepsis. Finally, 2 patients died during the treatment course of AE (interstitial pneumonia and sepsis).

Discussion

¹⁸F-FDG-PET/CT is considered useful for predicting the degree of histological differentiation. ¹⁸F-FDG-PET/CT positivity has been reported to be strongly associated with poorly differentiated HCCs [18] and is therefore often a negative predictor of response to various treatments

[19–22]. Moreover, the utility of ^{18}F -FDG-PET/CT for predicting patient outcomes, including HPD during immunotherapy, has been reported in other cancers [32–38]. However, as we reported previously [23, 39], ^{18}F -FDG-PET/CT positivity (TLR ≥ 2) was correlated with a better response to lenvatinib, and PFS was similar in patients with ^{18}F -FDG-PET/CT-negative disease (TLR < 2). In contrast, in the present study, ^{18}F -FDG-PET/CT positivity (TLR ≥ 2) was significantly associated with a high e-PD rate and poor e-PFS compared with a ^{18}F -FDG-PET/CT-negative result (TLR < 2) to Atezo/Bev treatment. In multivariate analysis, ^{18}F -FDG-PET/CT positivity (TLR ≥ 2) and previous history of lenvatinib treatment showed marginal significance as factors predictive of e-PD. This study cohort had a high rate of previous lenvatinib treatment (35%). Overall, 8 of 20 (40%) patients experienced e-PD during the treatment period, and 5 of these 8 (63%) patients received lenvatinib immediately before Atezo/Bev treatment initiation. As we reported previously, in some patients with FDG accumulation changes, ^{18}F -FDG-PET/CT-negative disease becomes positive during lenvatinib treatment [40]. Therefore, clinical history may have affected the present results. In addition, in this study, 3 of 20 (15%) patients showed HPD (TGK_R ≥ 2) (Fig. 3); all 3 of these patients had previously received lenvatinib, and in 2 of 3 (67%) patients, readministration of lenvatinib controlled the rate of disease progression. As in the previous reports [41, 42], readministration of lenvatinib after diagnosed disease progression during immunotherapies has the potential of disease control effect in some patients. Recently, other researchers reported the utility of NLRs for predicting patient outcomes following Atezo/Bev treatment of HCC [15, 43–45]. Furthermore, Maesaka et al. [15] reported an NLR cut-off value of ≥ 3 as a useful predictor for HPD. However, in the present cohort, no significant differences in NLR were observed between the e-PD and non-e-PD populations (median NLR, 3.29 vs. 2.91, $p = 0.624$). This difference may have been due to the small number of cases in the current study. In addition, it should be noted that previously reported NLR cut-off values for predicting patient outcomes differ between studies [15, 43–45], and NLRs change due to various patient conditions (e.g., infections and certain medications, particularly steroid-based immunosuppressive regimens). Therefore, more robust NLR cut-off values are desirable for use in daily clinical practice. In contrast, TLR values acquired on ^{18}F -FDG-PET/CT are useful predictive factors of patient outcomes, with a well-established cut-off value of ≥ 2 [18–20, 26]. In general, this value is not affected by patient condi-

tions that do not alter blood glucose levels. Hence, TLR value on ^{18}F -FDG-PET/CT appears to be a useful predictor of e-PD and e-PFS during Atezo/Bev treatment of HCC, and it has the potential to be widely used globally. A large-scale, multicenter study is required to evaluate the significance of TLRs prior to Atezo/Bev treatment.

This study had some limitations. First, it was a retrospective, single-center study that enrolled a relatively small series of patients. Second, the diagnosis of HCC was based exclusively on imaging analysis. Third, the follow-up period was relatively short compared with that of the global Phase III IMbrave150 study [4] (median follow-up period, 7.4 vs. 15.6 months, respectively). It was therefore not possible to conduct a high-quality prognostic analysis. Fourth, although ^{18}F -FDG-PET/CT analysis is an optional imaging tool, it cannot be performed as easily compared as other types of imaging studies, such as CT or MRI, for various reasons, including the relatively high cost and the small number and uneven distribution of instruments required for the scans. Therefore, a large-scale, multicenter study is required to evaluate the utility of ^{18}F -FDG-PET/CT for predicting overall prognosis and e-PD in patients with HCC receiving Atezo/Bev.

In conclusion, pretreatment ^{18}F -FDG-PET/CT positivity may be a useful new predictor of e-PD and e-PFS and may enable early decision-making based on early treatment changes following Atezo/Bev treatment of HCC. For patients with a high TLR (≥ 2) prior to initiation of Atezo/Bev treatment, careful imaging follow-up should be conducted to identify e-PD.

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Statement of Ethics

This retrospective, noninterventional study was approved by the Institutional Review Board, Toranomon Hospital (protocol No. 1438-H/B). The study was performed in accordance with the Declaration of Helsinki. Because the data were anonymized and the opt out option was disclosed on our institution's homepage (https://toranomon.kkr.or.jp/crc/files/uploads/2020/06/rinken_1438HB-3.pdf), the requirement for additional informed consent to participate in this study was deemed unnecessary according to the Japanese national regulations “Ethical Guidelines for Medical and Health Research Involving Human Subjects” (<https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf>).

Conflict of Interest Statement

Yusuke Kawamura, MD, PhD reports honoraria from Eisai Co., Ltd., and Chugai Pharmaceutical Co., Ltd. Masahiro Kobayashi, MD reports honoraria from Eisai Co., Ltd. Junichi Shindoh, MD, PhD reports honoraria from Eisai Co., Ltd., and Chugai Pharmaceutical Co., Ltd. Hiromitsu Kumada, MD, PhD reports honoraria from Eisai Co., Ltd. The other authors declare no conflicts of interest.

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Author Contributions

Yusuke Kawamura, MD, PhD: study concept and design, acquisition of data, statistical analysis, and drafting of the manuscript. Masahiro Kobayashi, MD: acquisition of data and statistical

analysis. Junichi Shindoh, MD, PhD: acquisition of data and critical revision. Masaru Matsumura, MD, PhD: acquisition of data. Satoshi Okubo, MD, PhD: acquisition of data. Nozomu Muraishi, MD: acquisition of data. Shunichiro Fujiyama, MD: acquisition of data. Tetsuya Hosaka, MD: acquisition of data. Satoshi Saitoh, MD: acquisition of data. Hitomi Sezaki, MD: acquisition of data. Norio Akuta, MD, PhD: acquisition of data. Fumitaka Suzuki, MD, PhD: acquisition of data. Yoshiyuki Suzuki, MD, PhD: acquisition of data. Kenji Ikeda, MD, PhD: acquisition of data, statistical analysis, and study supervision. Yasuji Arase, MD, PhD: acquisition of data. Masaji Hashimoto, MD, PhD: acquisition of data. Hiromitsu Kumada, MD, PhD: acquisition of data.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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