

Second-Line Durvalumab plus Tremelimumab versus Lenvatinib after Atezolizumab plus Bevacizumab Failure in Hepatocellular Carcinoma: A Multi-Center Retrospective Study

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Abstract

Background

The optimal second-line treatment after atezolizumab plus bevacizumab (Atezo + Bev) failure in unresectable hepatocellular carcinoma (HCC) remains uncertain. We compared durvalumab plus tremelimumab (Dur + Tre) with lenvatinib in this setting.

Methods

We retrospectively analyzed 108 patients with unresectable HCC who experienced treatment failure during first-line Atezo + Bev and subsequently received Dur + Tre ($n = 22$) or lenvatinib ($n = 86$) as second-line therapy between January 2021 and March 2025 across eight Japanese institutions. Overall survival (OS), progression-free survival (PFS), tumor response, treatment-related adverse events (TRAEs), liver function at discontinuation, subsequent therapy, and post-treatment survival (PTS) were evaluated. Group comparisons were performed using the Mann–Whitney U test and Fisher’s exact test, and survival outcomes were analyzed using Kaplan–Meier methods, log-rank tests, and Cox proportional hazards models.

Results

Baseline characteristics were generally balanced, except for more prior Atezo + Bev courses in the Dur + Tre group. Median OS was 16.1 versus 10.4 months (hazard ratio [HR], 0.45; 95% confidence interval [CI], 0.19–1.04; $p = 0.063$), median PFS was 2.8 versus 4.0 months (HR, 1.00; 95% CI, 0.52–1.91; $p = 0.995$), and median PTS was 13.6 versus 5.8 months (HR, 0.50; 95% CI, 0.20–1.16; $p = 0.106$). Objective response rates were 13.6% versus 10.5%, and disease control rates were 31.8% versus 52.3%. Any-grade TRAEs were less frequent with Dur + Tre (54.5% vs. 89.5%; $p < 0.001$). Changes in Child–Pugh and albumin–bilirubin scores and subsequent systemic therapy rates did not differ significantly between the groups among evaluable patients.

Conclusions

Dur + Tre was associated with fewer any-grade TRAEs and nonsignificant trends toward longer OS, whereas lenvatinib achieved numerically higher disease control. Further studies are warranted to identify patients most likely to benefit from Dur + Tre therapy.

BACKGROUND

Hepatocellular carcinoma (HCC) remains a major cause of cancer-related mortality worldwide [1], and many patients present with unresectable or advanced disease [2]. Over the past decade, systemic

therapy for unresectable HCC has evolved substantially, with the introduction of molecular targeted agents and immune checkpoint inhibitor (ICI)-based combinations improving clinical outcomes. Sorafenib and lenvatinib were historically used as standard first-line tyrosine kinase inhibitors (TKIs) [3], whereas atezolizumab plus bevacizumab (Atezo + Bev), durvalumab plus tremelimumab (Dur + Tre), and ipilimumab plus nivolumab (Ipi+Nivo) have become preferred first-line options for eligible patients based on the results of phase 3 trials [4–6]. In current clinical practice, Atezo + Bev is the most commonly used first-line regimen for unresectable HCC [7], owing to its favorable efficacy and safety profile as well as accumulating real-world evidence.

Despite these advances, most patients eventually experience disease progression, making the selection of subsequent therapy increasingly important. In the era of sorafenib monotherapy, several agents, including regorafenib, ramucirumab, and cabozantinib, demonstrated survival benefits as second-line therapies in phase 3 trials [8–10]. However, these pivotal studies enrolled patients after sorafenib failure, and their findings cannot be directly extrapolated to patients previously treated with ICI-based combinations, such as Atezo + Bev. Therefore, the optimal second-line treatment after Atezo + Bev failure remains unclear. In real-world practice, systemic agents approved for first-line treatment, including Dur + Tre, Ipi+Nivo, and lenvatinib, are often used sequentially at the discretion of the treating physician, although robust comparative evidence to guide regimen selection remains limited.

Among the available options after Atezo + Bev failure, lenvatinib has been studied relatively extensively. In addition to several retrospective studies, a recent phase 2 trial reported promising efficacy, with a median progression-free survival (PFS) of 5.4 months and a disease control rate (DCR) of 82% [11]. In contrast, evidence on Dur + Tre after Atezo + Bev failure remains limited, particularly for second-line use [12, 13]. Because Dur + Tre is a mechanistically distinct ICI-based regimen that combines programmed death-ligand 1 (PD-L1) blockade with cytotoxic T lymphocyte antigen-4 (CTLA-4) inhibition, it may provide clinical benefit despite prior exposure to Atezo + Bev. However, its outcomes as second-line therapy after Atezo + Bev failure have not been fully established.

To address this evidence gap, we conducted a multicenter retrospective study comparing the efficacy and safety of Dur + Tre and lenvatinib as second-line therapy in patients with unresectable HCC who experienced disease progression during first-line Atezo + Bev treatment.

METHODS

Patients

We retrospectively reviewed 108 patients with unresectable HCC who received Dur + Tre or lenvatinib as second-line systemic therapy after failure of first-line Atezo + Bev across eight institutions in Japan. Patients were eligible if they had (1) histologically and/or radiologically confirmed HCC; (2) unresectable disease not amenable to curative treatment; (3) received Atezo + Bev as first-line systemic therapy; (4) evidence of treatment failure during Atezo + Bev therapy; (5) initiated Dur + Tre or lenvatinib as second-

line therapy between January 2021 and March 2025; and (6) were aged ≥ 18 years. Patients who discontinued Atezo + Bev because of treatment-related adverse events (TRAEs), deterioration in performance status, or worsening liver function without evidence of treatment failure were excluded.

Treatment failure during Atezo + Bev therapy was defined as radiologically confirmed progressive disease (PD) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or modified RECIST (mRECIST); unequivocal tumor marker elevation accompanied by radiological tumor enlargement that did not meet the (m)RECIST criteria for PD; or other clinical evidence of disease progression, as determined by the treating physician. Follow-up data were collected through September 2025.

The Kyoto University Graduate School and Faculty of Medicine, Ethics Committee approved the study protocol (approval no. R3950). The study was conducted with the permission from the head of each participating institution and adhered to the principles of the Declaration of Helsinki. The requirement for written informed consent was waived by the Kyoto University Graduate School and Faculty of Medicine, Ethics Committee because of the retrospective nature of the study. Information regarding the study was disclosed to patients, who were provided with the opportunity to opt out.

Treatment protocol

Dur + Tre was administered according to the single tremelimumab regular interval durvalumab (STRIDE) regimen, consisting of a single priming dose of tremelimumab 300 mg plus durvalumab 1500 mg, followed by durvalumab 1500 mg every 4 weeks [5]. The treating physicians determined treatment interruption or discontinuation according to each patient's clinical condition and adverse events.

Patients received oral lenvatinib once daily at an initial dose of 12 mg/day if they weighed ≥ 60 kg and 8 mg/day if they weighed < 60 kg [3]. The treating physicians determined dose modifications, including treatment interruption and dose reduction, according to each patient's clinical condition, liver function, and adverse events.

Treatment response was evaluated using contrast-enhanced computed tomography or magnetic resonance imaging at intervals of approximately 6–8 weeks, unless clinically contraindicated. Tumor markers, including alpha-fetoprotein and des-gamma-carboxy prothrombin, were measured according to routine clinical practice at each institution. Treatment continued until disease progression, death, unacceptable adverse events, or a physician's decision to discontinue treatment. Treatment beyond progression was permitted when the treating physician considered it clinically appropriate.

Study endpoints

The primary endpoint was overall survival (OS), defined as the interval from initiation of second-line treatment to death from any cause. Treatment initiation was defined as the date of the first Dur + Tre

infusion or the first lenvatinib dose.

Secondary endpoints were PFS, objective response rate (ORR), clinical benefit rate (CBR), DCR, and the frequency of TRAEs. PFS was defined as the interval from initiation of second-line treatment to disease progression or death from any cause. Patients who discontinued second-line treatment without documented progression or death were censored at the date of treatment discontinuation; patients who remained on second-line treatment without documented progression or death were censored at the date of the last follow-up. Radiological responses were assessed according to RECIST version 1.1 and mRECIST. ORR was the proportion of patients who achieved a complete response (CR) or partial response (PR), and DCR was defined as the proportion of patients who achieved CR, PR, or stable disease (SD). Consistent with our previous studies [14, 15], CBR was defined as the proportion of patients who achieved CR or PR, or SD lasting ≥ 180 days. TRAEs were graded according to the Common Terminology Criteria for Adverse Events, version 5.0.

Exploratory endpoints included liver function at treatment discontinuation, subsequent treatment, and post-treatment survival (PTS). Liver function was evaluated using Child–Pugh and albumin–bilirubin (ALBI) scores at the initiation and discontinuation of second-line treatment. Subsequent treatment was classified as any subsequent treatment and subsequent systemic therapy. PTS was evaluated among patients who discontinued second-line therapy during follow-up and was defined as the interval from second-line treatment discontinuation to death from any cause. These analyses were based on available-case data; no imputation was performed for missing values.

Statistical analysis

Baseline characteristics, treatment efficacy, and TRAE frequency were compared between the Dur + Tre and lenvatinib groups. Continuous and ordinal categorical variables were presented as medians with interquartile ranges or as numbers and percentages, as appropriate, and were compared using the Mann–Whitney U test. Nominal categorical variables were presented as numbers and percentages and were compared using Fisher’s exact test. Kaplan–Meier curves were generated for OS, PFS, and PTS and compared using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models, with lenvatinib as the reference group. Median follow-up was estimated using the reverse Kaplan–Meier method.

Because lenvatinib was already available when Atezo + Bev was approved, whereas Dur + Tre became available later, temporal bias related to treatment era was considered possible. To assess whether outcomes were consistent in a more contemporary cohort, we performed a sensitivity analysis restricted to patients who initiated second-line treatment on or after January 1, 2023, because Dur + Tre was approved in Japan on December 23, 2022.

We performed a post hoc exploratory comparison of PTS among patients receiving second-line lenvatinib according to whether they subsequently received Dur + Tre as third- or later-line treatment. Because subsequent Dur + Tre exposure was defined after the PTS time origin and the dates of Dur + Tre

initiation were not uniformly available, neither a landmark analysis nor a time-dependent Cox analysis could be performed. This comparison was therefore descriptive and inherently susceptible to immortal-time and treatment-selection bias. Another exploratory analysis was conducted to identify baseline characteristics or prior treatment-related factors associated with disease control in the Dur + Tre group, because disease control with Dur + Tre appeared to be associated with favorable long-term outcomes. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant. Statistical analyses were performed using R version 4.1.2 (R Foundation, Vienna, Austria).

RESULTS

Patient characteristics

The study included 108 patients with unresectable HCC; 22 received Dur + Tre and 86 received lenvatinib as second-line therapy after Atezo + Bev failure. Baseline characteristics at second-line treatment initiation are presented in Table 1. Overall, the groups were generally balanced. The median age was 76 years in the Dur + Tre group and 74 years in the lenvatinib group. Liver function, Barcelona Clinic Liver Cancer (BCLC) stage, macrovascular invasion, extrahepatic metastasis, and tumor marker levels did not differ significantly between groups. The number of prior Atezo + Bev treatment courses was higher in the Dur + Tre group than in the lenvatinib group (median, 12 vs. 8 courses; $p = 0.035$). The criteria for Atezo + Bev failure were also similar, with RECIST PD accounting for most cases.

Table 1
Baseline patient characteristics at second-line treatment initiation

Age, years	Dur + Tre (n = 22)	Lenvatinib (n = 86)	p-value
	76.0 [70.3–80.5]	74.0 [65.0–79.0]	0.364
Sex			0.170
Male	20 (90.9%)	64 (74.4%)	
Female	2 (9.1%)	22 (25.6%)	
Body mass index, kg/m ²	23.8 [20.9–25.4]	23.2 [20.4–25.8]	0.804
Performance status			0.424
0	15 (68.2%)	67 (77.9%)	
1	7 (31.8%)	15 (17.4%)	
2	0 (0.0%)	3 (3.5%)	
3	0 (0.0%)	1 (1.2%)	
Etiology			1.000
Viral	11 (50.0%)	43 (50.0%)	
Non-viral	11 (50.0%)	43 (50.0%)	
Child-Pugh score			0.610
5	11 (50.0%)	37 (43.0%)	
6	6 (27.3%)	30 (34.9%)	
7	4 (18.2%)	10 (11.6%)	
8	1 (4.5%)	6 (7.0%)	
9	0 (0.0%)	3 (3.5%)	
ALBI score	-2.19 [-2.32 to -1.83]	-2.30 [-2.60 to -1.99]	0.228
BCLC stage			0.436
A	1 (4.5%)	3 (3.5%)	
B	6 (27.3%)	33 (38.4%)	
Dur + Tre, durvalumab plus tremelimumab; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CRP, C-reactive protein; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin; Atezo + Bev, atezolizumab plus bevacizumab; RECIST, Response Evaluation Criteria in Solid Tumors; mRECIST, modified RECIST; PD, progressive disease.			
*p < 0.05			

Age, years	Dur + Tre (n = 22)	Lenvatinib (n = 86)	p-value
	76.0 [70.3–80.5]	74.0 [65.0–79.0]	0.364
C	15 (68.2%)	50 (58.1%)	
Macrovascular invasion	5 (22.7%)	20 (23.3%)	1.000
Extrahepatic metastasis	13 (59.1%)	40 (46.5%)	0.416
Tumor diameter, cm	3.3 [1.9–5.4]	3.4 [2.1–5.8]	0.926
CRP, mg/dL	0.36 [0.16–1.75]	0.33 [0.17–1.46]	0.962
AFP, ng/mL	24 [5–1177]	104 [7–2538]	0.207
DCP, mAU/mL	1474 [173–18722]	1161 [221–9686]	0.526
Prior Atezo + Bev courses	12 [6.3–17.5]	8 [5–13]	0.035*
Best response to Atezo + Bev			0.344
Complete response	0 (0.0%)	1 (1.2%)	
Partial response	7 (31.8%)	16 (18.6%)	
Stable disease	11 (50.0%)	39 (45.3%)	
Progressive disease	4 (18.2%)	30 (34.9%)	
Criteria for Atezo + Bev failure			0.894
RECIST PD	20 (90.9%)	74 (86.0%)	
mRECIST PD	1 (4.5%)	4 (4.7%)	
Tumor marker elevation	1 (4.5%)	7 (8.1%)	
Other	0 (0.0%)	1 (1.2%)	
Dur + Tre, durvalumab plus tremelimumab; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CRP, C-reactive protein; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin; Atezo + Bev, atezolizumab plus bevacizumab; RECIST, Response Evaluation Criteria in Solid Tumors; mRECIST, modified RECIST; PD, progressive disease.			
*p < 0.05			

Overall survival and progression-free survival

During a median follow-up of 17.6 months (10.3 months in the Dur + Tre group and 18.5 months in the lenvatinib group), six patients (27.3%) in the Dur + Tre group and 56 (65.1%) in the lenvatinib group died. The median OS was 16.1 months with Dur + Tre and 10.4 months with lenvatinib (HR, 0.45; 95% CI, 0.19–1.04; $p = 0.063$). OS was numerically longer with Dur + Tre, although the difference was not statistically

significant (Fig. 1A). In contrast, PFS did not differ between groups: median PFS was 2.8 months in the Dur + Tre group and 4.0 months in the lenvatinib group (HR, 1.00; 95% CI, 0.52–1.91; $p = 0.995$) (Fig. 1B).

The sensitivity analysis restricted to patients who initiated second-line therapy in 2023 or later yielded consistent results. In this contemporary cohort, the median OS was 16.1 months with Dur + Tre and 10.4 months with lenvatinib (HR, 0.47; 95% CI, 0.19–1.14; $p = 0.096$), whereas median PFS was 2.8 and 3.7 months, respectively (HR, 1.30; 95% CI, 0.61–2.76; $p = 0.495$; Figure S1 in Additional file 1).

Tumor response and clinical benefit

Table 2 summarizes tumor response according to RECIST version 1.1. The ORR was 13.6% in the Dur + Tre group and 10.5% in the lenvatinib group ($p = 0.707$), and the CBR was 18.2% and 24.4%, respectively ($p = 0.777$). The DCR was numerically lower with Dur + Tre than with lenvatinib, although the difference was not statistically significant (31.8% vs. 52.3%; $p = 0.099$). Assessment using mRECIST likewise showed no significant between-group differences in ORR, CBR, or DCR, although DCR was numerically lower with Dur + Tre (Table S1 in Additional file 1).

Table 2
Tumor response according to RECIST version 1.1

Best overall response	Dur + Tre (n = 22)	Lenvatinib (n = 86)	p-value
Complete response	1 (4.5%)	0 (0.0%)	
Partial response	2 (9.1%)	9 (10.5%)	
Stable disease	4 (18.2%)	36 (41.9%)	
Progressive disease	12 (54.5%)	20 (23.3%)	
Not evaluable	3 (13.6%)	21 (24.4%)	
Objective response rate	3 (13.6%)	9 (10.5%)	0.707
Clinical benefit rate	4 (18.2%)	21 (24.4%)	0.777
Disease control rate	7 (31.8%)	45 (52.3%)	0.099
Dur + Tre, durvalumab plus tremelimumab; RECIST, Response Evaluation Criteria in Solid Tumors			

One patient in the Dur + Tre group achieved a CR according to RECIST. This 67-year-old man had hepatitis C virus- and alcohol-related liver disease and multifocal intrahepatic HCC classified as BCLC stage B. His performance status was 0, and his Child–Pugh score was 5. After five courses of first-line Atezo + Bev, the initial radiological assessment showed PD according to RECIST version 1.1. He subsequently received Dur + Tre as second-line therapy. Tumor marker levels decreased promptly, and computed

tomography confirmed CR after six courses of Dur + Tre. At the last follow-up, he remained on Dur + Tre and continued to maintain CR (Fig. 2).

Safety

TRAEs are summarized in Table 3. Any-grade TRAEs were significantly less frequent with Dur + Tre than with lenvatinib (54.5% vs. 89.5%; $p < 0.001$). Grade 3/4 TRAEs occurred in 31.8% and 48.8% of patients, respectively, with no statistically significant between-group difference ($p = 0.230$). Hypertension, proteinuria, and fatigue, as well as Grade ≥ 3 fatigue were significantly less frequent in the Dur + Tre group. TRAEs led to treatment discontinuation in three patients (13.6%) in the Dur + Tre group and 28 patients (32.6%) in the lenvatinib group ($p = 0.113$). The TRAEs leading to Dur + Tre discontinuation were colitis ($n = 1$), hepatitis ($n = 1$), and ascites ($n = 1$; baseline Child–Pugh score, 7).

Table 3
Frequencies of any-grade and grade 3/4 TRAEs

	Any-grade			Grade 3/4		
	Dur + Tre (<i>n</i> = 22)	Lenvatinib (<i>n</i> = 86)	<i>p</i> - value	Dur + Tre (<i>n</i> = 22)	Lenvatinib (<i>n</i> = 86)	<i>p</i> - value
Hypertension	0 (0.0%)	33 (38.4%)	< 0.001*	0 (0.0%)	5 (5.8%)	0.581
Proteinuria	2 (9.1%)	46 (53.5%)	< 0.001*	1 (4.5%)	12 (14.0%)	0.461
Hand-foot syndrome	0 (0.0%)	11 (12.8%)	0.115	0 (0.0%)	1 (1.2%)	1.000
Liver injury	3 (13.6%)	15 (17.4%)	1.000	1 (4.5%)	7 (8.1%)	1.000
Kidney injury	2 (9.1%)	4 (4.7%)	0.600	0 (0.0%)	0 (0.0%)	1.000
Diarrhea/colitis	2 (9.1%)	2 (2.3%)	0.184	2 (9.1%)	1 (1.2%)	0.105
Pneumonitis	1 (4.5%)	0 (0.0%)	0.204	0 (0.0%)	0 (0.0%)	1.000
Thyroid dysfunction	0 (0.0%)	12 (14.0%)	0.121	0 (0.0%)	0 (0.0%)	1.000
Fatigue	0 (0.0%)	51 (59.3%)	< 0.001*	0 (0.0%)	18 (20.9%)	0.021*
Other TRAEs	8 (36.4%)	27 (31.4%)	0.799	4 (18.2%)	11 (12.8%)	0.502
Any TRAEs	12 (54.5%)	77 (89.5%)	< 0.001*	7 (31.8%)	42 (48.8%)	0.230
Dur + Tre, durvalumab plus tremelimumab; TRAE, treatment-related adverse events						

Liver function changes and post-treatment survival

Among the 96 patients who discontinued second-line treatment, liver function at discontinuation and subsequent treatment data were available for 80 patients, including 16 of 17 patients (94.1%) in the Dur + Tre group and 64 of 79 patients (81.0%) in the lenvatinib group. Median Child–Pugh scores at treatment discontinuation were 7.5 [interquartile range, 6.5–8.0] in the Dur + Tre group and 7.0 [6.0–8.0] in the lenvatinib group ($p = 0.705$), and median changes from baseline were + 1.0 [0.0–3.0] and + 1.0 [0.0–2.0], respectively ($p = 0.636$). Median ALBI scores at treatment discontinuation were – 1.52 [– 2.09 to – 1.24] and – 1.82 [– 2.26 to – 1.35], respectively ($p = 0.434$), and median changes were + 0.49 [– 0.05 to 0.80] and + 0.38 [0.13–0.63], respectively ($p = 0.947$). Thus, neither liver function at discontinuation nor its change from baseline differed significantly between groups (Table S2 in Additional file 1). After second-line treatment discontinuation, eight (50.0%) and 35 (54.7%) patients in the Dur + Tre and lenvatinib groups, respectively, received any subsequent treatment ($p = 1.000$), and six patients (37.5%) and 28 patients (43.8%), respectively, received subsequent systemic therapy ($p = 0.784$; Table S2 in Additional file 1).

PTS was evaluable in 94 patients, including 17 patients in the Dur + Tre group and 77 in the lenvatinib group. Six and 56 patients died after discontinuation of second-line treatment, respectively. Median PTS was 13.6 months with Dur + Tre and 5.8 months with lenvatinib (HR, 0.50; 95% CI, 0.20–1.16; $p = 0.106$; Figure S2A in Additional file 1). Among the 63 patients in the lenvatinib group with available subsequent-treatment information, median PTS was 21.6 months among those who received Dur + Tre as later-line treatment and 3.7 months among those who did not (HR, 0.17; 95% CI, 0.07–0.38; $p < 0.001$; Figure S2B in Additional file 1). Because Dur + Tre exposure was defined after the PTS time origin, this association is subject to immortal-time and treatment-selection bias and should not be interpreted causally.

Exploratory analysis of disease control in the Dur + Tre group

We evaluated survival outcomes according to best overall response among patients treated with Dur + Tre. Patients who achieved disease control had favorable PFS and OS compared with those who had progressive disease or were not evaluable for response (Figure S3 in Additional file 1). We therefore explored clinical factors associated with disease control in the Dur + Tre group. Baseline characteristics and prior Atezo + Bev treatment-related factors did not differ significantly between patients with and without disease control, and no clear clinical predictor of disease control with Dur + Tre was identified (Table 4).

Table 4
Comparison of patients with and without disease control in the Dur + Tre group

Age, years	Disease control (n = 7)	No disease control (n = 15)	p-value
	76 [70–82]	76 [70.5–78]	0.621
Sex			1.000
Male	6 (85.7%)	14 (93.3%)	
Female	1 (14.3%)	1 (6.7%)	
Performance status			0.827
0	5 (71.4%)	10 (66.7%)	
1	2 (28.6%)	5 (33.3%)	
Etiology			0.360
Viral	2 (28.6%)	9 (60.0%)	
Non-viral	5 (71.4%)	6 (40.0%)	
Child-Pugh score			0.541
5	3 (42.9%)	8 (53.3%)	
6	2 (28.6%)	4 (26.7%)	
7	1 (14.3%)	3 (20.0%)	
8	1 (14.3%)	0 (0.0%)	
ALBI score	-2.02 [-2.31 to -1.95]	-2.19 [-2.44 to -1.79]	0.778
BCLC stage			0.091
A	0 (0.0%)	1 (6.7%)	
B	4 (57.1%)	2 (13.3%)	
C	3 (42.9%)	12 (80.0%)	
Macrovascular invasion	1 (14.3%)	4 (26.7%)	0.921
Extrahepatic metastasis	2 (28.6%)	11 (73.3%)	0.128
CRP, mg/dL	0.33 [0.16–0.41]	1.10 [0.15–2.39]	0.314
AFP, ng/mL	39 [15–6131]	6 [5–330]	0.502
Dur + Tre, durvalumab plus tremelimumab; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CRP, C-reactive protein; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin; Atezo + Bev, atezolizumab plus bevacizumab; RECIST, Response Evaluation Criteria in Solid Tumors; mRECIST, modified RECIST; PD, progressive disease.			

Age, years	Disease control (n = 7)	No disease control (n = 15)	p-value
	76 [70–82]	76 [70.5–78]	0.621
DCP, mAU/mL	1287 [279–11734]	1474 [519–24843]	0.533
Prior Atezo + Bev courses	16 [8.5–25.5]	12 [6.5–13.5]	0.322
Best response to Atezo + Bev			0.378
Partial response	3 (42.9%)	4 (26.7%)	
Stable disease	2 (28.6%)	9 (60.0%)	
Progressive disease	2 (28.6%)	2 (13.3%)	
Criteria for Atezo + Bev failure			0.598
RECIST PD	7 (100.0%)	13 (86.7%)	
mRECIST PD	0 (0.0%)	1 (6.7%)	
Tumor marker elevation	0 (0.0%)	1 (6.7%)	
Dur + Tre, durvalumab plus tremelimumab; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CRP, C-reactive protein; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin; Atezo + Bev, atezolizumab plus bevacizumab; RECIST, Response Evaluation Criteria in Solid Tumors; mRECIST, modified RECIST; PD, progressive disease.			

DISCUSSION

In this multicenter retrospective study, we compared Dur + Tre and lenvatinib as second-line therapy after Atezo + Bev failure in patients with unresectable HCC. The main findings were as follows. First, Dur + Tre was associated with numerically longer OS, although the difference was not statistically significant; PFS was similar, and DCR was numerically lower than that with lenvatinib. Second, available-case analyses, liver function at treatment discontinuation, changes from baseline, and the proportions receiving subsequent treatment did not differ significantly between the two groups while PTS was numerically longer in the Dur + Tre group. Third, any-grade TRAEs were significantly less frequent with Dur + Tre. Finally, disease control with Dur + Tre was associated with favorable long-term outcomes, although no clear clinical predictor of disease control was identified.

When selecting second-line therapy after Atezo + Bev, the reason for discontinuation of first-line Atezo + Bev should be considered. If Atezo + Bev is discontinued because of adverse events, the optimal subsequent regimen may depend on the type of toxicity. For example, when Atezo + Bev is discontinued due to immune-related adverse events, further ICI-based therapy may be difficult to administer, and lenvatinib may be a reasonable option. Conversely, after vascular endothelial growth factor (VEGF) inhibition-related toxicities, such as hypertension or proteinuria, lenvatinib may be less suitable and an

ICI-based regimen may be preferable. Therefore, the present study focused specifically on patients who discontinued Atezo + Bev because of tumor progression.

To the best of our knowledge, nine retrospective studies have evaluated lenvatinib as second-line therapy after progression during Atezo + Bev treatment. Across cohorts of 14–125 patients, median OS ranged from 8.3 to 18.9 months, median PFS from 3.5 to 6.1 months, ORR from 7.5% to 33.3%, and DCR from 57.1% to 76.8% [16–24]. In addition, Kim et al. recently reported a single-arm prospective trial of lenvatinib in 50 patients in this setting, with a median OS of 9.8 months, median PFS of 5.4 months, ORR of 14%, and DCR of 82% [11]. In our study, lenvatinib likewise achieved numerically higher disease control than Dur + Tre, with a DCR of 52.3%, whereas the median OS in the lenvatinib group was less than 1 year. This pattern of relatively favorable disease control but modest OS has been observed consistently and may characterize lenvatinib after Atezo + Bev failure. Lenvatinib therefore remains an important option when early tumor stabilization is needed, although disease control does not necessarily translate into prolonged survival in every patient.

By contrast, evidence on Dur + Tre in this setting remains limited, particularly for second-line use. Miura et al. reported no objective responses among 16 patients treated with Dur + Tre after Atezo + Bev [13]. Ishihara et al. reported a median PFS of 0.94 months in seven patients [12], and Nishioka et al. reported a median PFS of 1.7 months in 14 patients [24]. However, these studies were small, and cohort characteristics and study designs differed. For example, in Nishioka et al., only 8 of 14 patients (57.1%) had received Atezo + Bev for at least 3 months, whereas the median prior exposure in our Dur + Tre group was 12 courses. Their first imaging assessment was scheduled at 4 weeks, compared with 6–8 weeks in our study. In our cohort, Dur + Tre achieved an ORR of 13.6%, a median PFS of 2.8 months, and a median OS of 16.1 months, outcomes that appear more favorable than those in previous second-line reports. Studies that included patients receiving Dur + Tre as third- or later-line therapy also reported ORRs exceeding 10%, suggesting that Dur + Tre can induce meaningful responses in a subset of patients despite prior Atezo + Bev exposure [25, 26]. Kawamura et al. similarly reported two cases that responded well to Dur + Tre after Atezo + Bev [27]. Collectively, these findings suggest that Dur + Tre may retain activity after Atezo + Bev failure in a subset of patients.

A notable finding of this study was the numerically longer OS with Dur + Tre despite similar PFS and a numerically lower DCR than with lenvatinib. This apparent discrepancy may reflect the distinct pattern of benefit associated with ICI-based therapy. Although only a small proportion of patients achieved disease control with Dur + Tre, those who did experienced durable clinical benefit. Previous comparisons of treatment classes after Atezo + Bev failure support this interpretation. Wu et al. and Marell et al. suggested that ICI-based therapy may produce a long-tail survival pattern relative to TKI- or anti-VEGF-based therapy [28, 29]. This pattern is biologically plausible because immunotherapy may not control disease in every patient but may confer prolonged survival once an effective antitumor immune response is established [30].

Identifying patients likely to benefit from Dur + Tre after Atezo + Bev failure remains a key challenge. In our study, baseline characteristics, liver function, tumor burden, extrahepatic metastasis, macrovascular invasion, tumor markers, and prior Atezo + Bev treatment-related factors, including the number of Atezo + Bev courses, did not differ significantly between patients with and without disease control. Conventional clinical variables alone may therefore be insufficient for selecting patients for Dur + Tre in this setting. Translational studies are needed to clarify the mechanisms of response to CTLA-4–containing immunotherapy after prior Atezo + Bev exposure. Meanwhile, the post-Atezo + Bev therapeutic landscape continues to evolve. Prospective studies have reported promising activity of regorafenib and cabozantinib after first-line Atezo + Bev therapy [31, 32], and combinations of ICIs with tyrosine kinase inhibitors are also under investigation [33]. These developments highlight the need not only to identify biomarkers for Dur + Tre benefit but also to establish a broader treatment-selection framework that can appropriately position second-line Dur + Tre after Atezo + Bev failure.

This study has several limitations. First, its retrospective design and physician-directed treatment selection introduce the possibility of selection bias and unmeasured confounding. Although the sensitivity analysis restricted to patients treated in 2023 or later reduced differences in treatment era, it could not eliminate temporal bias. Second, the size of the Dur + Tre cohort and the number of OS events were limited, resulting in wide confidence intervals and low statistical power. Third, tumor response was assessed in routine clinical practice without central radiological review. Fourth, liver-function and subsequent-treatment data were unavailable for 28 of the 96 patients who discontinued therapy, and data availability was lower in the Dur + Tre group, making the available-case analyses vulnerable to informative missingness.

CONCLUSIONS

In conclusion, second-line Dur + Tre after Atezo + Bev failure was associated with fewer any-grade TRAEs and numerically longer OS and PTS, although the survival differences were not statistically significant. Lenvatinib achieved numerically higher DCR. These distinct profiles suggest that Dur + Tre and lenvatinib may have complementary roles as second-line options after Atezo + Bev failure. Treatment selection should therefore be individualized through shared decision-making. Further studies are warranted to identify biomarkers that can predict durable benefit from Dur + Tre therapy in this setting.

Abbreviations

- HCC
Hepatocellular carcinoma
- Atezo + Bev
Atezolizumab plus bevacizumab
- Dur + Tre
Durvalumab plus tremelimumab
- OS

Overall survival

- PFS

Progression-free survival

- TRAE

Treatment-related adverse event

- PTS

Post-treatment survival

- HR

Hazard ratio

- CI

Confidence interval

- ICI

Immune checkpoint inhibitors

- TKI

Tyrosine kinase inhibitor

- Ipi+Nivo

Ipilimumab plus nivolumab

- DCR

Disease control rate

- PD-L1

Programmed death-ligand 1

- CTLA-4

Cytotoxic T lymphocyte antigen-4

- PD

Progressive disease

- RECIST

Response Evaluation Criteria in Solid Tumors

- mRECIST

Modified Response Evaluation Criteria in Solid Tumors

- ORR

Objective response rate

- CBR

Clinical benefit rate

- CR

Complete response

- PR

Partial response

- SD

Stable disease

- ALBI

Albumin–bilirubin

- BCLC

Barcelona Clinic Liver Cancer

- VEGF

Vascular endothelial growth factor

- CRP

C-reactive protein

- AFP

Alpha-fetoprotein

- DCP

Des-gamma-carboxy prothrombin

Declarations

Ethics approval and consent to participate:

The study protocol was approved by Kyoto University Graduate School and Faculty of Medicine, Ethics Committee (approval number: R3950). Informed consent was obtained from all patients included in the study in an opt-out protocol.

Consent for publication:

Written informed consent was obtained from the patient for publication of the clinical details and accompanying images presented in Fig. 2. A copy of the written consent is available for review by the Editor upon request.

Competing interests:

All authors declare no conflicts of interest.

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Author Contribution

MUe: Study design, data collection, analysis, data interpretation, manuscript writing, and manuscript approval. HT and AT: Study design, data analysis, data interpretation, manuscript writing, and manuscript approval. HMo, TM, SN, NN, SI, MUm, AI, KN, MM, TI, KT, MN, and TU: Data collection and manuscript approval. HMa, YO, EH, and HS: Supervision and manuscript approval.

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Availability of data and materials:

The datasets generated and/or analysed during the current study are not publicly available due to ethical and privacy considerations but are available from the corresponding author on reasonable request.

References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74:229–63.
2. Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. *Nat Rev Dis Primers*. 2021;7:6.
3. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet*. 2018;391:1163–73.
4. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382:1894–905.
5. Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. *NEJM Evid*. 2022;1:EVIDoa2100070.
6. Yau T, Galle PR, Decaens T, et al. Nivolumab plus ipilimumab versus lenvatinib or sorafenib as first-line treatment for unresectable hepatocellular carcinoma (CheckMate 9DW): an open-label, randomised, phase 3 trial. *Lancet*. 2025;405:1851–64.
7. Asaoka Y, Tateishi R, Yamada Y, et al. A newly launched nationwide database revealed real-world evidence on systemic therapy for unresectable hepatocellular carcinoma in Japan: hepatoma registry of integrating and aggregating electronic health record (Heritage). *Liver Cancer*. 2025;15:77–89.
8. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2017;389:56–66.
9. Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α -fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019;20:282–96.

10. Abou-Alfa GK, Meyer T, Cheng A-L, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med*. 2018;379:54–63.
11. Kim HD, Sym SJ, Chon HJ, et al. Multicenter single-arm phase II trial of lenvatinib in patients with advanced hepatocellular carcinoma after progression on first-line atezolizumab plus bevacizumab. *J Hepatol*. 2026;84:308–15.
12. Ishihara N, Komatsu S, Yano Y, et al. Treatment outcomes of tyrosine kinase inhibitors and durvalumab plus tremelimumab after atezolizumab plus bevacizumab for hepatocellular carcinoma. *Anticancer Res*. 2025;45:251–60.
13. Miura R, Ono A, Yano S, et al. Real-world efficacy and safety of durvalumab-tremelimumab as second-line systemic therapy after atezolizumab-bevacizumab in unresectable hepatocellular carcinoma. *Med (Baltim)*. 2024;103:e39289.
14. Ueno M, Takeda H, Takai A, et al. CRAFITY score as a predictive marker for refractoriness to atezolizumab plus bevacizumab therapy in hepatocellular carcinoma: a multicenter retrospective study. *J Gastroenterol*. 2024;59:1107–18.
15. Ueno M, Takeda H, Takai A, et al. Lenvatinib versus Atezolizumab Plus bevacizumab as first-line treatment for advanced hepatocellular carcinoma with a CRAFITY score of 2: A multi-center retrospective study. *Hepatol Res*. 2026;56:100–10.
16. Yoo C, Kim JH, Ryu MH, et al. Clinical outcomes with multikinase inhibitors after progression on first-line atezolizumab plus bevacizumab in patients with advanced hepatocellular carcinoma: a multinational multicenter retrospective study. *Liver Cancer*. 2021;10:107–14.
17. Lombardi P, Kim JS, Manfredi GF, et al. Lenvatinib vs. sorafenib as second-line treatment post atezolizumab plus bevacizumab for hepatocellular carcinoma: the Leviathan study. *JHEP Rep*. 2025;7:101595.
18. Chen YH, Chen YY, Wang JH, Hung CH. Efficacy and safety of lenvatinib after progression on first-line atezolizumab plus bevacizumab treatment in advanced hepatocellular carcinoma patients. *Anticancer Res*. 2023;43:1377–84.
19. Cheon J, Shimose S, Kim HD, et al. Lenvatinib versus sorafenib as second-line therapy following progression on atezolizumab–bevacizumab in patients with unresectable hepatocellular carcinoma: a multicenter retrospective study from Korea and Japan. *J Cancer Res Clin Oncol*. 2025;151:52.
20. Yano S, Kawaoka T, Yamasaki S, et al. Therapeutic efficacy and safety of lenvatinib after atezolizumab plus bevacizumab for unresectable hepatocellular carcinoma. *Cancers (Basel)*. 2023;15:5406.
21. Kato D, Suzuki T, Matsuura K, et al. Poor Tolerability of lenvatinib in Elderly Patients with Advanced Hepatocellular Carcinoma after Disease Progression following First-Line Atezolizumab Plus bevacizumab: a Multicenter Study. *Oncology*. 2025;103:311–9.
22. Persano M, Casadei-Gardini A, Tada T, et al. Lenvatinib versus sorafenib Second-Line Therapy in Patients with Hepatocellular Carcinoma Progressed to Atezolizumab plus bevacizumab: a Retrospective Real-World Study. *Oncology*. 2025;103:456–68.

23. Chon YE, Kim DY, Kim MN, et al. Sorafenib vs. lenvatinib in advanced hepatocellular carcinoma after atezolizumab/bevacizumab failure: a real-world study. *Clin Mol Hepatol*. 2024;30:345–59.
24. Nishioka C, Tahata Y, Maesaka K, et al. Comparison of outcomes of second-line durvalumab plus tremelimumab versus lenvatinib following first-line atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *PLoS ONE*. 2026;21:e0341395.
25. Hiraoka A, Tada T, Hirooka M, et al. Efficacy of durvalumab plus tremelimumab treatment for unresectable hepatocellular carcinoma in immunotherapy era clinical practice. *Hepatol Res*. 2025;55:444–53.
26. Sho T, Suda G, Ohara M, et al. Efficacy and safety of Durvalumab/Tremelimumab in unresectable hepatocellular carcinoma as immune checkpoint inhibitor rechallenge following Atezolizumab/Bevacizumab treatment. *Target Oncol*. 2024;19:769–78.
27. Kawamura Y, Akuta N, Fujiyama S, Suzuki F, Kumada H. Two cases of advanced hepatocellular carcinoma who responded well to the combination of durvalumab plus tremelimumab after disease progression during atezolizumab plus bevacizumab therapy under bevacizumab withdrawal. *Cureus*. 2023;15:e45385.
28. Wu M, Fulgenzi CAM, D'Alessio A, et al. Second-line treatment patterns and outcomes in advanced HCC after progression on atezolizumab/bevacizumab. *JHEP Rep*. 2025;7:101232.
29. Marell P, Kournoutas I, Gile J, et al. Second-line therapies in advanced hepatocellular carcinoma following first-line atezolizumab and bevacizumab: multicenter single institution cohort experience. *Oncologist*. 2025;30:oyae342.
30. Sangro B, Chan SL, Kelley RK, et al. Four-year overall survival update from the phase III Himalaya study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. *Ann Oncol*. 2024;35:448–57.
31. Cheon J, Ryoo BY, Chon HJ, et al. Multicenter Phase 2 trial of second-line regorafenib in patients with unresectable hepatocellular carcinoma after progression on atezolizumab plus bevacizumab. *Liver Cancer*. 2025;14:446–55.
32. Chan SL, Ryoo BY, Mo F, et al. Multicentre phase II trial of cabozantinib in patients with hepatocellular carcinoma after immune checkpoint inhibitor treatment. *J Hepatol*. 2024;81:258–64.
33. Ascari S, Chen R, De Sinno A, et al. Post-immunotherapy second-line strategies for hepatocellular carcinoma: state of the art and ongoing trials. *World J Gastroenterol*. 2026;32:111528.

Figures

Figure 1

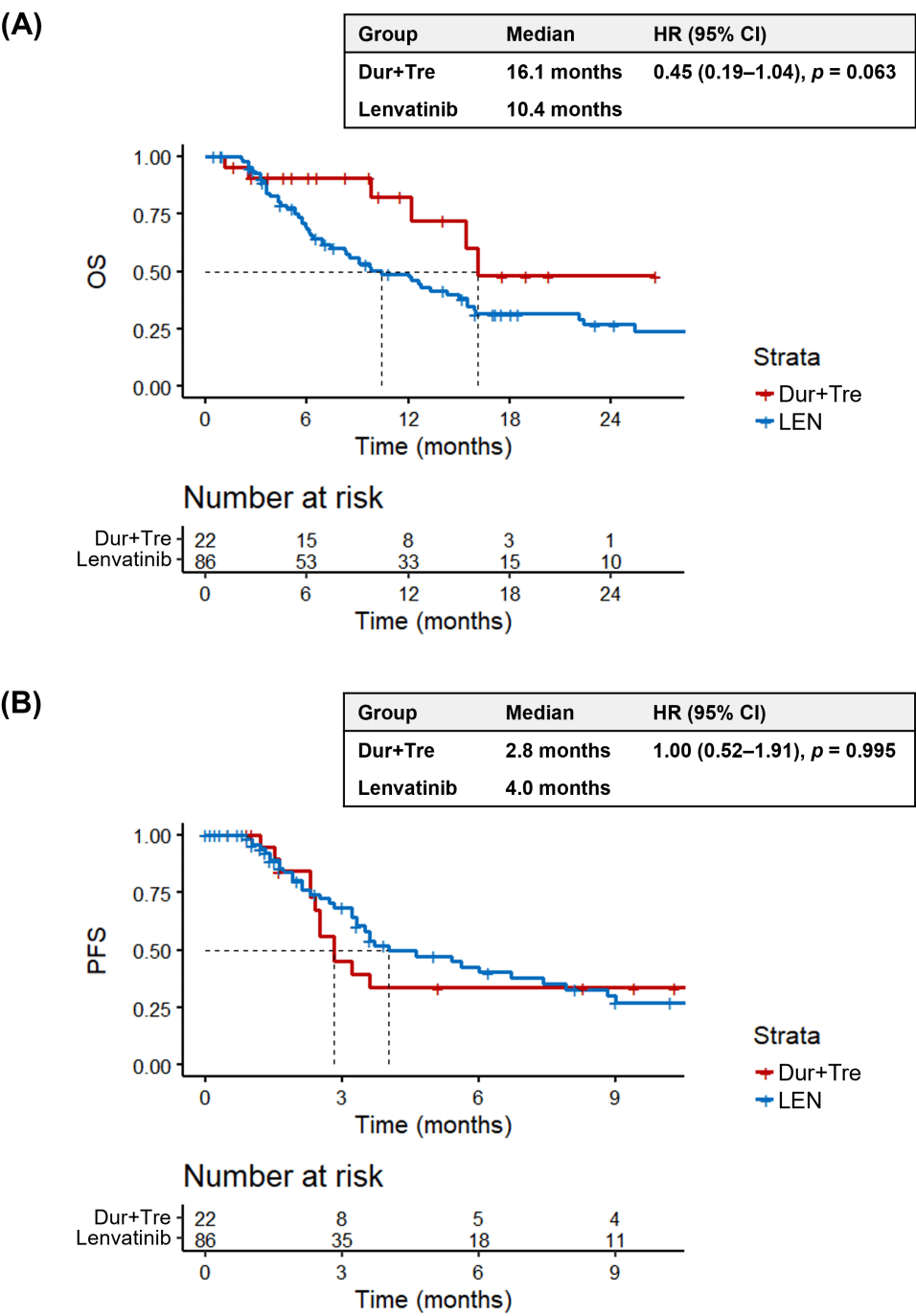


Figure 1

Comparison of OS and PFS between the Dur+Tre and lenvatinib groups

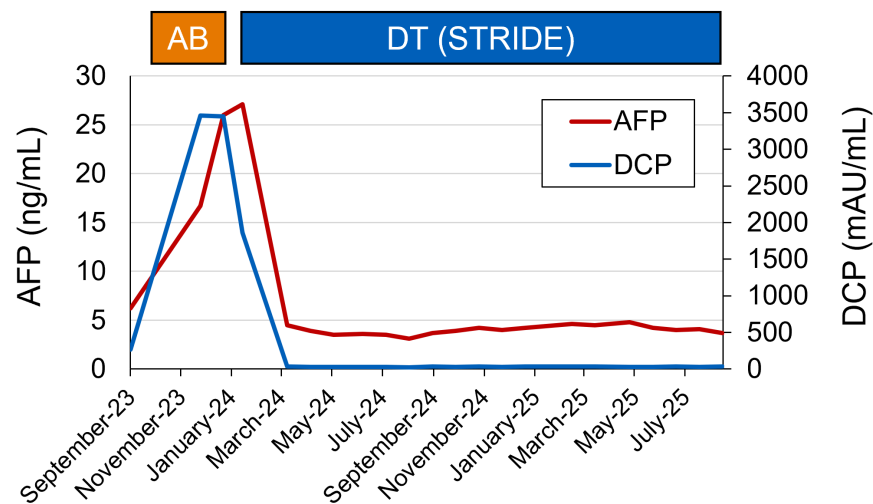
(A) OS in patients treated with Dur+Tre or lenvatinib as second-line therapy after Atezo+Bev failure. The median OS was 16.1 months in the Dur+Tre group and 10.4 months in the lenvatinib group (HR, 0.45; 95% CI, 0.19–1.04; $p = 0.063$).

(B) PFS in patients treated with Dur+Tre or lenvatinib. The median PFS was 2.8 months in the Dur+Tre group and 4.0 months in the lenvatinib group (HR, 1.00; 95% CI, 0.52–1.91; $p = 0.995$).

Atezo+Bev, atezolizumab plus bevacizumab; CI, confidence interval; Dur+Tre, durvalumab plus tremelimumab; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Figure 2

(A)



(B)

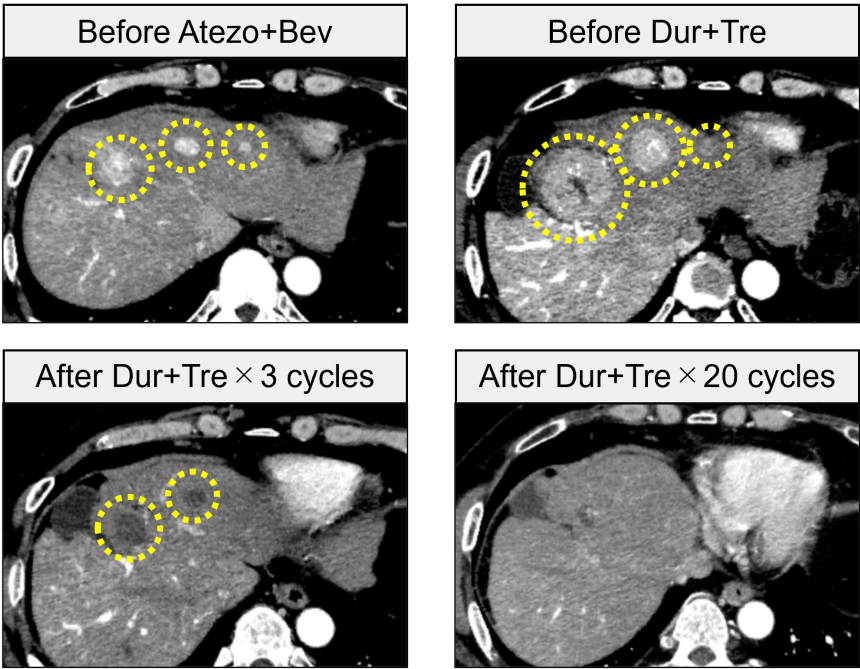


Figure 2

Representative case of complete response to second-line Dur+Tre after Atezo+Bev failure

(A) Changes in serum AFP and DCP levels during treatment with Atezo+Bev and Dur+Tre. Tumor marker levels decreased promptly after initiation of Dur+Tre.

(B) Contrast-enhanced computed tomography images (arterial phase) before Atezo+Bev, before Dur+Tre, after three cycles of Dur+Tre, and at the last follow-up. After three cycles of Dur+Tre, arterial phase hyperenhancement disappeared and the tumor decreased in size. Complete response was maintained at the last follow-up.

AFP, alpha-fetoprotein; Atezo+Bev (AB), atezolizumab plus bevacizumab; DCP, des-gamma-carboxyprothrombin; Dur+Tre (DT), durvalumab plus tremelimumab; STRIDE, single tremelimumab regular interval durvalumab.

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