Targeted Oncology (2024) 19:769–778
https://doi.org/10.1007/s11523-024-01092-7

ORIGINAL RESEARCH ARTICLE

Efficacy and Safety of Durvalumab/Tremelimumab in Unresectable Hepatocellular Carcinoma as Immune Checkpoint Inhibitor Rechallenge Following Atezolizumab/Bevacizumab Treatment

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Accepted: 14 August 2024 / Published online: 2 September 2024

Abstract

Background While guidelines recommend immune checkpoint inhibitor (ICI) rechallenge as second-line therapy for unresectable hepatocellular carcinoma (HCC), data supporting this remain limited, particularly regarding a standard regimen for first- and second-line treatments. Tremelimumab/durvalumab was recently approved but data on ICI rechallenge are lacking.

Objectives The purpose of this study was to evaluate the early efficacy and safety of tremelimumab/durvalumab for HCC as an ICI rechallenge following initial ICI therapy with atezolizumab/bevacizumab.

Patients and Methods This multicenter retrospective study included patients with HCC who underwent treatment with tremelimumab/durvalumab, with relevant available clinical information. We evaluated the safety and efficacy of tremelimumab/durvalumab as ICI rechallenge following initial treatment with atezolizumab/bevacizumab. We analyzed the outcomes in patients who underwent tremelimumab/durvalumab as an ICI rechallenge and those who received tremelimumab/durvalumab as their initial ICI therapy

Result A total of 45 patients treated with tremelimumab/durvalumab were included, with 55.6% (25/45) undergoing ICI rechallenge. The objective-response and disease-control rates in patients who underwent ICI rechallenge were 14.3% (3/21) and 47.6% (10/21), respectively, similar to those in patients initially treated with tremelimumab/durvalumab. All patients ($n = 3$) who experienced the best response to progressive disease (PD) with initial atezolizumab/bevacizumab experienced PD during ICI rechallenge. The incidence rates of adverse events were similar between patient groups treated with tremelimumab/durvalumab as ICI rechallenge and initial ICI. Among patients experiencing immune-related adverse events (irAEs) with atezolizumab/bevacizumab, 75% (3/4) encountered similar irAEs during ICI rechallenge.

Conclusion Early safety and efficacy profiles of durvalumab/tremelimumab as ICI rechallenge are satisfactory.

Takuya Sho and Goki Suda have contributed equally to this study.

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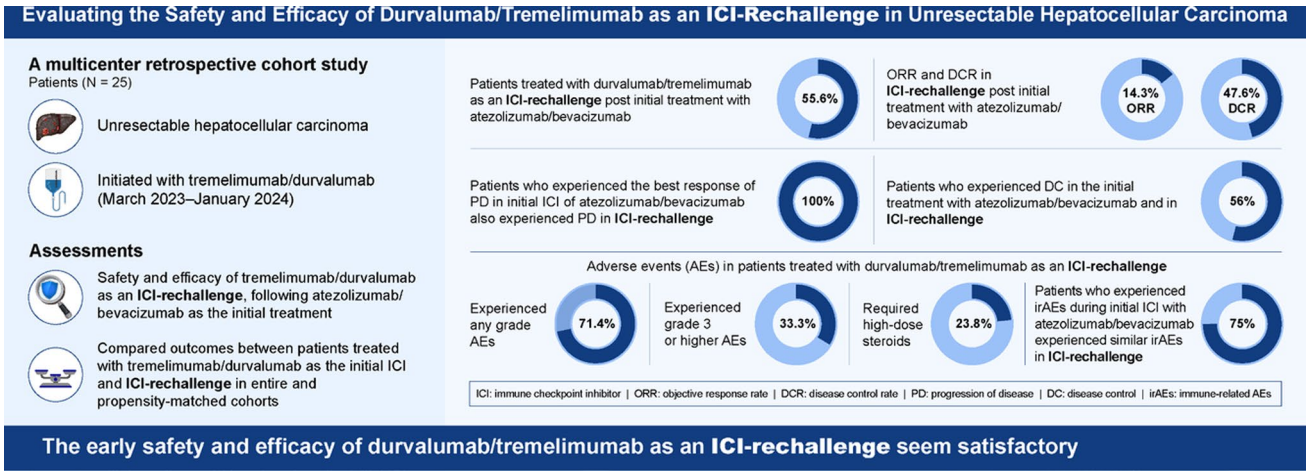
Graphical Abstract



Key Points

While guidelines recommend immune checkpoint inhibitor (ICI) rechallenge as second-line therapy for unresectable hepatocellular carcinoma (HCC), data supporting this recommendation are limited. There are no reports of a standard regimen for both first- and second-line treatments.

Our study demonstrates the promising safety and efficacy of durvalumab/tremelimumab as an ICI rechallenge after atezolizumab/bevacizumab failure in unresectable HCC ($n = 25$).

All patients who initially showed progressive disease (PD) as the best response with atezolizumab/bevacizumab also showed the best response of PD during the ICI rechallenge. Among patients experiencing immune-related adverse events (irAEs) with atezolizumab/bevacizumab, 75% (3/4) encountered similar irAEs during ICI rechallenge.

1 Introduction

Hepatocellular carcinoma (HCC) is among the most lethal cancer types, with an increasing global incidence rate [1, 2]. Consequently, there is an urgent necessity for advancements in effective treatment options, especially for patients with unresectable HCC. Recent advancements in systemic chemotherapy for unresectable HCC have led to the development of a broader range of medications and improved prospects for extended overall survival (OS). Recently, immune checkpoint inhibitors (ICIs) have emerged as a treatment option for unresectable HCC. Currently, two ICI-based combination therapy regimens are approved for HCC: the combination of the anti-VEGF-A antibody bevacizumab with the programmed death ligand 1 (PD-L1) inhibitor atezolizumab, and the combination of the anti-cytotoxic T lymphocyte-associated antigen 4 inhibitor tremelimumab with the PD-L1 inhibitor durvalumab [3, 4]. In the IMbrave150 phase 3 clinical trial, the atezolizumab/bevacizumab combination demonstrated significantly longer OS compared with sorafenib, the previous standard of care for patients with unresectable HCC [4]. Similarly, in the HIMALAYA phase 3 clinical trial, tremelimumab/durvalumab significantly improved OS compared with sorafenib. Consequently, in the guidelines for systemic therapy of advanced HCC, ICI combination therapy with atezolizumab/bevacizumab and tremelimumab/durvalumab were recommended as first-line treatment [5]. However, owing to the lack of clear evidence from prospective studies on second-line therapies following first-line ICI-based therapy, all regimens not used in primary therapy are concurrently listed, including combination immunotherapies that are not utilized as first-line treatments. Data on ICI rechallenge therapy following initial ICI therapy for unresectable HCC are limited [6, 7], and the regimens used in the literature are diverse and non-standardized. Moreover, previous reports did not include the administration of tremelimumab/durvalumab, and

28.8% of patients who received ICI rechallenge experienced the same immune-related adverse events (irAEs) observed with the initial ICI treatment for various malignancies [8]. Therefore, there is a need to gather data on the early efficacy and safety of tremelimumab/durvalumab for unresectable HCC after the failure of atezolizumab and bevacizumab. In the HIMALAYA trial, the time to respond to tremelimumab/durvalumab for unresectable HCC was notably short, with a median of 2.17 months [5]. Thus, ICI rechallenge is an urgent clinical concern to elucidate the early efficacy and safety of tremelimumab/durvalumab for cases of unresectable HCC.

In this study, we aimed to evaluate the early efficacy and safety of tremelimumab/durvalumab for unresectable HCC as an ICI rechallenge following initial ICI therapy with atezolizumab/bevacizumab.

2 Materials and Methods

2.1 Patients

In this multicenter retrospective study conducted by the NORTE study group, we screened patients with unresectable HCC who commenced treatment with tremelimumab/durvalumab between March 2023 and January 2024. Patients aged ≥ 18 years who received tremelimumab/durvalumab within the specified time frame, whose clinical information was complete, and those who met the diagnostic criteria for HCC [9], as well as those who had unresectable HCC and underwent appropriate evaluation of treatment response, were included. Those with insufficient clinical data, deteriorated liver functional reserve, including Child–Pugh Grade C, and those receiving other anti-HCC treatments, such as transarterial chemoembolization, were excluded.

Clinical information collected included age, sex, laboratory data, tumor makers, history of ICI treatment, history of anti-HCC treatment, liver function (Child–Pugh grade and albumin-bilirubin score), etiology of liver disease and Barcelona Clinic Liver Cancer stage, and history of ICI treatment with atezolizumab/bevacizumab, as well as the occurrence and grading of irAEs and treatment response to atezolizumab/bevacizumab. Attending physicians evaluated patients every 4 weeks for laboratory tests, physical assessments, and adverse event (AE) monitoring, while treatment response was assessed using dynamic computed tomography (CT) or magnetic resonance imaging (MRI) scans every 8–12 weeks. Subsequently, the safety and efficacy of tremelimumab/durvalumab as ICI rechallenge therapy for unresectable HCC were evaluated following treatment with atezolizumab and bevacizumab.

This study protocol was approved by the ethics committee of Hokkaido University Hospital (approval no. 023-0141) and the ethical committees of the participating institutions within the NORTE study group. The study design adhered to the ethical principles outlined in the Declaration of Helsinki, and informed consent was obtained from all participants.

2.2 Treatment Protocol and Assessment of AEs

Tremelimumab (300 mg) and durvalumab (1500 mg) were administered on day 1, followed by subsequent administration of 1500 mg durvalumab every 4 weeks. Treatment discontinuation occurred either due to unacceptable AEs or disease progression (PD). In cases where patients experienced AEs of grade 3 or higher or AEs considered intolerable, therapy was temporarily discontinued. Resumption of treatment depended on the resolution of symptoms and adherence to the prescription information for durvalumab/tremelimumab.

AEs and their severity were assessed following the definitions outlined by the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE; version 5.0) and the clinical practice guidelines of the American Society of Clinical Oncology [10].

2.3 Assessment of Treatment Efficacy

In this retrospective analysis, patients underwent dynamic CT or MRI examinations at the pretreatment point and subsequently every 8–12 weeks following the initiation of durvalumab/tremelimumab therapy. The categorization of treatment responses was according to the Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1) and was determined by two experienced hepatologists and an experienced radiologist. Similarly, in patients who underwent ICI rechallenge, treatment responses to initial ICI therapy with atezolizumab/bevacizumab were evaluated using RECIST 1.1 criteria.

2.4 Statistical Analysis

Depending on the data distribution, continuous variables were analyzed using either the paired *t*-test or the Mann–Whitney *U* test, and categorical variables were analyzed using the chi-squared test and Fisher's exact test, as appropriate. Survival curves were generated using the Kaplan–Meier method.

A total of 25 patients who received durvalumab/tremelimumab as an ICI rechallenge and 20 patients treated with durvalumab/tremelimumab as initial ICI therapy were included. All statistical analyses were conducted using the Prism 9.41 application (GraphPad Software, La Jolla, CA,

USA) and EZR software (Saitama Medical Centre at Jichi Medical University, Saitama, Japan). A p-value < 0.05 was considered statistically significant.

3 Results

3.1 Patient characteristics

A total of 45 patients diagnosed with unresectable HCC and started on durvalumab/tremelimumab between March 2023 and January 2024 at the participating institutes of the NORTE study group were included in this study. The average age of the patients was 71 (range 52–87) years, with 55.6% (25/45) undergoing durvalumab/tremelimumab treatment as an ICI rechallenge. Among these 25 patients, all had previously received atezolizumab/bevacizumab as initial ICI therapy. A comparison of patients with and without prior ICI treatment with atezolizumab or bevacizumab is presented in Table 1. Tumor marker (AFP and des-gamma-carboxy prothrombin) levels were significantly elevated, and body mass index (BMI) was notably lower in patients who underwent ICI rechallenge than in those treated with durvalumab/tremelimumab as initial ICI therapy.

3.2 Efficacy of Durvalumab/Tremelimumab as ICI Rechallenge and Comparison of the Efficacy of Durvalumab/Tremelimumab Between Patients With or Without a History of ICI Treatment with Atezolizumab/Bevacizumab

We assessed the efficacy of durvalumab/tremelimumab as an ICI rechallenge in patients who were followed up for > 2 months after treatment initiation. For six cases, a treatment period of more than 2 months was not achieved at the time of this analysis, and thus the treatment efficacy was not evaluated. In this period, all six patients were under treatment, and no patient died. Therefore, at the time of analysis, 21 patients who underwent ICI rechallenge and 18 without a history of ICI were included in the evaluation of treatment response. The objective response rate (ORR) and disease control rate (DCR) in patients treated with durvalumab/tremelimumab as an ICI rechallenge were 14.3% (3/21) and 47.6% (10/21), respectively (Table 2). Detailed information is provided in Online Resource S1.

Subsequently, progression-free survival (PFS) was analyzed. The median PFS in patients who underwent ICI rechallenge was 4.0 (range 2.3–7.2) months, as shown in Fig. 1. The PFS between patients treated with durvalumab/tremelimumab as an ICI rechallenge or initial ICI therapy were similar (Fig. 1A, B). The data on OS and time to progression are provided in the Online Resource S2.

3.3 Treatment Response in Patients Treated with Durvalumab/Tremelimumab as an ICI Rechallenge According to the Initial ICI of Atezolizumab/Bevacizumab (ICI-1) Response

The proportions of patients who achieved disease control upon ICI rechallenge, among those who had an objective response (OR), stable disease (SD), and PD during ICI-1, were 33% (1/3), 60% (9/15), and 0% (0/3), respectively. However, all patients who experienced PD during ICI-1 exhibited PD during the ICI rechallenge, with a rate of 100% (3/3) (Table 3).

3.4 Safety of Durvalumab/Tremelimumab as ICI Rechallenge and Comparison of the Safety of Durvalumab/Tremelimumab Between Patients With or Without a History of ICI Treatment

Finally, we analyzed the safety profile of durvalumab/tremelimumab in 39 patients assessed for treatment response. Table 4A and Online Resource 3 summarize the safety profiles of patients treated with durvalumab/tremelimumab as an ICI rechallenge. As presented in Table 4, 71.4% (15/21) of patients experienced AEs of any grade, with 33.3% (7/21) experiencing AEs of grade 3 or higher. The most common were rash (33.3%, 7/21) and diarrhea/colitis (28.6%, 6/21) among AEs of any grade, with diarrhea/colitis (9.5%, 2/21) being predominant among grade 3 or higher AEs. Additionally, 23.8% (5/21) of patients required high-dose steroids. These incidence rates were comparable between patients treated with durvalumab/tremelimumab as initial ICI therapy and those undergoing ICI rechallenge (p = 0.464 for any grade AEs, p = 1.00 in grade 3 or higher grade AEs, and p = 1.0 for the rate of administration of high-dose steroids).

3.5 Incidence of irAEs in Patients Undergoing ICI Rechallenge With Durvalumab/Tremelimumab Based on the Status of irAEs During ICI-1

Of the 21 patients who underwent ICI rechallenge, 19.0% (4/21) experienced irAEs in the ICI-1 group (n = 3; grade 1 and 2 irAEs, n = 1; ≥ grade 3 irAEs). A total of 52.4% (11/21) of the patients experienced irAEs during ICI rechallenge. Among the 17 patients without irAEs in ICI-1, 47.1% (8/17) experienced irAEs in ICI rechallenge [29.4% (5/17) had grade 1 and 2 irAEs, and 17.6% (3/17) had ≥ grade 3 irAEs]. Of the three patients with irAEs of grades 1 and 2 in

Table 1 Baseline patient characteristics

Clinical characteristics	Overall cohort ($n = 45$)	Initial ICI ($n = 20$)	ICI re-challenge ($n = 25$)	p-Value
Age, years (range)	71 (52–87)	73 (52–87)	70 (54–84)	0.354
Sex				
Male/female	31 (68.9%)/14 (31.1%)	16 (80.0%)/4 (20.0%)	15 (60.0%)/10 (40.0%)	0.202
Etiology				
HBV	12 (26.7%)	3 (15.0%)	9 (36.0%)	0.177
HCV	8 (17.8%)	5 (25.0%)	3 (12.0%)	0.435
Others	25 (55.5%)	12 (60.0%)	13 (52.0%)	0.764
ECOG PS				
0/1–2	33 (73.3%)/12 (26.7%)	14 (70.0%)/6 (30.0%)	19 (76.0%)/6 (24.0%)	0.741
BMI, kg/m^2	23.1 (15.7–33.1)	24.1 (17.5–33.1)	21.6 (15.7–31.3)	0.004
Proteinuria (0–1+/2+)	38/2	18/0	20/2	0.492
Urine TP/Cr	0.24 (0.02–5.73)	0.14 (0.02–1.29)	0.28 (0.02–5.73)	0.126
White blood cell, mm^3	4900 (2300–12,300)	5120 (2300–12,330)	4740 (3000–9600)	0.927
Neutrophil count, mm^3	3267 (1178–10,012)	3670 (1178–10,012)	3070 (1548–5424)	0.670
Lymphocyte count, mm^3	1093 (228–5795)	1056 (228–5795)	1158 (380–2760)	0.201
Neutrophil/Lymphocyte ratio	2.70 (0.81–43.9)	3.15 (1.02–43.91)	2.44 (0.81–9.84)	0.222
Platelet, $\times 10^9$/L	139 (56–359)	159 (56–284)	136 (56–359)	0.882
Prothrombin time, %	99.4 (39.6–143.0)	98.0 (39.7–131.0)	99.4 (75.9–143.0)	0.213
NH3, μg/dl	50 (11–181)	55 (11–181)	49 (16–137)	0.470
Albumin, g/dl	3.6 (2.5–4.4)	3.8 (2.5–4.1)	3.6 (2.6–4.4)	0.559
Total bilirubin, mg/dl	0.7 (0.1–2.2)	0.7 (0.3–2.2)	0.7 (0.1–1.8)	0.765
ALBI score	−2.36 (−2.96 to 1.13)	−2.36 (−2.82 to 1.13)	−2.36 (−2.96 to 1.48)	0.937
mALBI grade				
1–2a/2b–3	32 (71.1%)/13 (28.9%)	15 (75.0%)/5 (25.0%)	17 (68.0%)/8 (32.0%)	0.745
AST, IU/l	35 (9–176)	28 (9–176)	39 (16–135)	0.107
ALT, IU/l	28 (7–80)	27 (7–57)	28 (10–80)	0.552
Child–Pugh grade				
A/B	42 (93.3%)/3 (6.7%)	17 (85.0%) /3 (15.0%)	25 (100.0%) /0 (0.0%)	0.080
Child–Pugh score				
5	19 (42.2%)	7 (35.0%)	12 (48.0%)	0.545
6	23 (51.1%)	10 (50.0%)	13 (52.0%)	1.000
7−	3 (6.7%)	3 (15.0%)	0 (0.0%)	0.080
AFP, ng/ml	46.7 (1.6–200,000.0)	14.6 (1.6–33,324.0)	180.6 (3.5–200,000.0)	0.042
AFP≧400 ng/ml	13 (28.9%)	3 (15.0%)	10 (40.0%)	0.100
DCP, mAU/ml	426 (17–111,252)	91 (17–111,252)	708 (17–46,276)	0.046
Maximum intrahepatic tumor size, mm	38 (0–180)	41 (0–179)	37 (0–180)	0.696
More than 50% liver involvement	5 (11.1%)	2 (10.0%)	3 (12.0%)	1.000
Diffuse type	4 (8.9%)	2 (10.0%)	2 (8.0%)	1.000
Number of intrahepatic tumors				
Multiple	39 (86.7%)	16 (80.0%)	23 (92.0%)	0.383
BCLC stage				
B/C	24 (53.3%)/21 (46.7%)	10 (50.0%)/10 (50.0%)	14 (56.0%)/11 (44.0%)	0.769
Up to 7 in/out	9 (20.0%)/36 (80.0%)	6 (70.0%)/14 (70.0%)	3 (12.0%)/22 (88.0%)	0.157
Positive for Vp	8 (17.8%)	4 (20.0%)	4 (16.0%)	1.000
Positive for Vv	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
Positive for bile duct invasion	2 (4.4%)	1 (5.0%)	1 (5.0%)	1.000
Positive for LN metastasis	8 (17.8%)	3 (15.0%)	5 (20.0%)	0.716
Positive for EHM	12 (26.7%)	5 (25.0%)	7 (28.0%)	1.000
History of DM	21 (46.7%)	10 (50.0%)	11 (44.0%)	0.769

Table 1 (continued)

Clinical characteristics	Overall cohort ($n = 45$)	Initial ICI ($n = 20$)	ICI re-challenge ($n = 25$)	p-Value
History of operation	21 (46.7%)	8 (40.0%)	13 (52.0%)	0.550
History of RFA	21 (46.7%)	7 (35.0%)	14 (56.0%)	0.231
History of TACE	28 (62.2%)	9 (45.0%)	19 (76.0%)	0.062
History of systemic chemotherapy	26 (57.8%)	1 (5.0%)	25 (100.0%)	< 0.001
Atezolizumab+bevacizumab	25 (55.6%)	0 (0.0%)	25 (100.0%)	< 0.001
Lenvatinib	19 (42.2%)	1 (5.0%)	18 (72.0%)	< 0.001
Sorafenib	3 (6.7%)	0 (0.0%)	3 (12.0%)	0.242
Observation period, days	126 (15–302)	133 (15–302)	121 (35–280)	0.431

*Data are presented as median (range) or *n*

Abbreviations: *HCV* hepatitis C virus, *HBV* hepatitis B virus, *ECOG PS* Eastern Cooperative Oncology Group performance status, *BMI* body mass index, *AST* aspartate transaminase, *ALT* alanine aminotransferase, *mALBI grade* modified albumin–bilirubin grade, *AFP* alpha-fetoprotein, *EHM* extrahepatic metastasis, *DM* diabetes mellitus, *TKI* tyrosine kinase inhibitor, *DCP* des-gamma-carboxy prothrombin, *BCLC* Barcelona Clinic Liver Cancer, *Vp* portal vein invasion, *Vv* hepatic vein invasion, *LN* lymph node, *RFA* radiofrequency ablation, *TACE* transcatheter arterial chemoembolization

Table 2 Treatment response in patients receiving durvalumab plus tremelimumab as initial ICI therapy and ICI rechallenge

Treatment response	Overall cohort ($n = 39$)	Initial ICI ($n = 18$)	ICI rechallenge ($n = 21$)
Complete response, *n* (%)	1 (2.6)	1 (100.0)	0 (0.0)
Partial response, *n* (%)	6 (15.4)	3 (16.7)	3 (14.3)
Stable disease, *n* (%)	15 (38.5)	8 (44.4)	7 (33.3)
Progressive disease, *n* (%)	16 (41.0)	5 (27.8)	5 (52.4)
Not evaluated, *n* (%)	1 (2.6)	1 (5.6)	0 (0.0)
Objective response rate, *n* (%)	7 (17.9)	4 (22.2)	3 (14.3)
Disease control rate, *n* (%)	22 (56.4)	12 (66.7)	10 (47.6)

*Six cases were excluded at the time of this analysis because they had not been treated for more than 2 months since the initiation of treatment.

Abbreviations: *ICI* immune checkpoint inhibitor

ICI-1, 66.7% (2/3) experienced irAEs during ICI rechallenge [66.6% (2/3) had grade 1 and 2 irAEs, and 0% (0/3) had ≥ grade 3 irAEs]. The only patient with ≥ grade 3 irAEs in ICI-1 experienced irAEs during the ICI rechallenge, specifically, grade 1 and 2 irAEs during the rechallenge, but no grade 3 or higher irAEs. Furthermore, 75% (3/4) of the patients with irAEs in ICI-1 experienced similar irAEs during the ICI rechallenge (Table 5B).

4 Discussion

The emergence of novel drugs for unresectable HCC has revolutionized the landscape of systemic therapy for this condition. Various therapeutic options, including ICI combination therapy, are now available for patients with unresectable HCC. While guidelines recommend ICI rechallenge as a second-line therapy for unresectable HCC, available supporting data are limited. Although previous studies have assessed several ICI rechallenges and initial ICI regimens, a uniform standardized treatment approach is urgently required.

In this study, we analyzed the early safety and efficacy of durvalumab/tremelimumab as an ICI rechallenge following atezolizumab and bevacizumab treatment in patients with unresectable HCC. Among the 45 patients for whom treatment with durvalumab/tremelimumab was initiated, 55.6% (25/45) underwent treatment with durvalumab/tremelimumab as an ICI rechallenge following prior atezolizumab/bevacizumab therapy. The ORR and DCR in patients treated with durvalumab/tremelimumab as an ICI rechallenge were 14.3% (3/21) and 47.6% (10/21), respectively. Notably, all patients ($n = 3$) who exhibited the best response to PD during ICI-1 showed the best response to PD in the ICI rechallenge group, with a 100% consistency rate (Table 3).

Regarding safety, 71.4% (15/21) of patients experienced AEs of any grade, with 33.3% (7/21) encountering grade 3 or

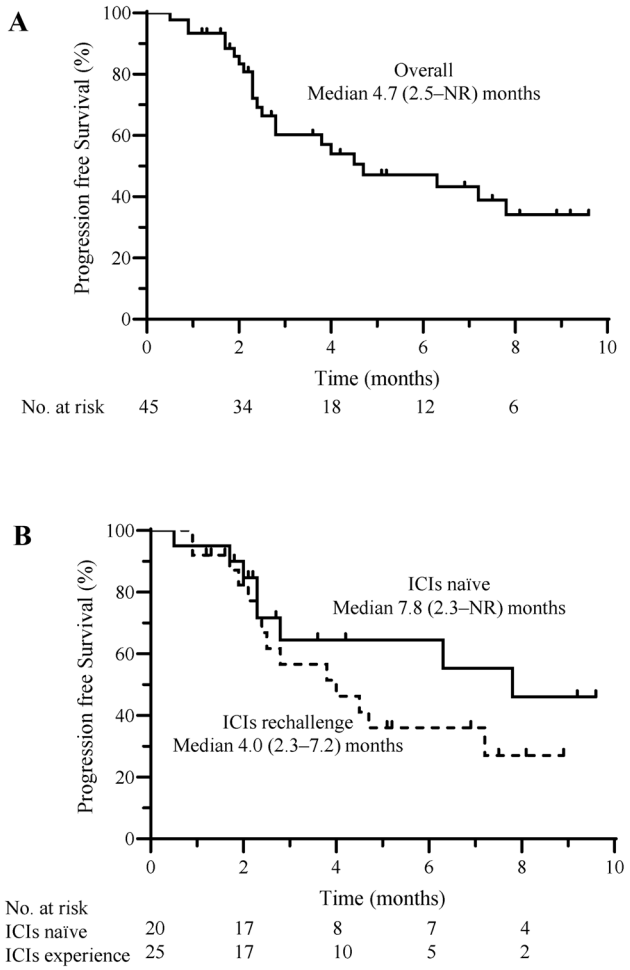


Fig. 1 **A** Kaplan–Meier estimates of progression-free survival (PFS) in patients treated with durvalumab/tremelimuma, **B** Kaplan–Meier estimates of PFS in treatment with durvalumab/tremelimumab as the initial immune checkpoint inhibitor (ICI) therapy and ICI rechallenge groups; NR, not reached

Table 3 Treatment response of durvalumab/tremelimumab as ICI rechallenge according initial ICI of atezolizumab/bevacizumab treatment (ICI-1) response

	ICI re-challenge response ($n = 21$)		
	CR/PR ($n = 3$) in ICI-1 response	SD ($n = 15$) in ICI-1 response	PD ($n = 3$) in ICI-1 response
CR *n*, (%)	0 (0.0)	0 (0.0)	0 (0.0)
PR *n*, (%)	0 (0.0)	3 (20.0)	0 (0.0)
SD *n*, (%)	1 (33.3)	6 (40.0)	0 (0.0)
PD *n*, (%)	2 (66.7)	6 (40.0)	3 (100.0)
ORR (%)	0.0	20.0	0.0
DCR (%)	33.3	60.0	0.0

Abbreviations: *ICI* immune checkpoint inhibitor, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *ORR* objective response rate, *DCR* disease control rate

higher AEs. Additionally, 23.8% (5/21) of patients required high-dose steroids to manage these AEs. The occurrence rates of AEs were similar between patients treated with durvalumab/tremelimumab as an ICI rechallenge and those receiving it as an initial ICI therapy.

Among the 21 patients who underwent ICI rechallenge, 19.0% (4/21) experienced irAEs during ICI-1 (three had grade 1–2 irAEs, and one had ≥ grade 3 irAEs). Among the four patients with irAEs in ICI-1, 75% (3/4) experienced similar irAEs during the ICI rechallenge (Table 5, Online Resource 3).

Previous studies have assessed the safety and efficacy of ICI therapy as an ICI rechallenge for unresectable HCC cases [6, 7, 11, 12]. For instance, Schelner et al. reported that among 994 patients treated with ICIs, 58 (6%) were rechallenged with ICIs after initial ICI therapy for advanced HCC [6]. This finding suggests that the standardization of ICI rechallenge for HCC is challenging in real-world practice. In their study, the effectiveness of ICI rechallenge, assessed on the basis of ORR, DCR, and time to progression (TTP) based on RECIST v1.1 criteria, yielded values of 26%, 55%, and 5.2 months, respectively, showing no significant difference from the initial ICI therapy. These findings align with our results. However, initial ICI treatments varied, with either a single ICI, ICI+ICI, or ICI+anti-VEGF inhibitor chosen in 45%, 2%, and 53% of cases, respectively. For the second ICI treatment, choices included a single ICI, ICI+ICI, or ICI+ anti-VEGF inhibitor in 7%, 21%, and 72% of cases, respectively, some of which have not been approved for unresectable HCC cases in Japan. Thus, given the diverse and non-uniform nature of treatment regimens, data on ICI rechallenge and treatment outcomes in cases where both the initial and ICI rechallenge therapies are standardized are urgently needed.

In this study, the initial ICI treatment and ICI rechallenge regimen were consistently atezolizumab/bevacizumab and durvalumab/tremelimumab, respectively. This eliminated bias due to variability in the treatment regimen and focused solely on currently approved medications. These results offer relevant insights and serve as a valuable reference for therapeutic strategies in clinical practice.

Furthermore, our study revealed that all patients who exhibited the best response to PD with ICI-1 also experienced the best response to PD during ICI rechallenge, suggesting that alternative treatment options beyond ICI rechallenge may warrant consideration in patients demonstrating the best response to PD with an initial ICI regimen. However, this finding contrasts with those of a previous study [6], wherein some cases with PD as the best response to initial ICI-1 exhibited responses to ICI rechallenge. This discrepancy may be attributed to variations in treatment regimens or the sequence of therapeutic interventions, necessitating further analysis.

Table 4 Adverse events between patients treated with durvalumab/tremelimumab as initial ICI or ICI rechallenge

Event	Overall cohort ($n = 39$)	Initial ICI ($n = 18$)	ICI rechallenge ($n = 21$)	p-Value
Any grade, n (%)	30 (76.9)	15 (83.3)	15 (71.4)	0.464
Grade 3 or 4, n (%)	13 (33.3)	6 (33.3)	7 (33.3)	1.000
Leading to discontinuation, n (%)	10 (25.6)	4 (22.2)	6 (28.6)	0.726
Leading to death, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Immune-mediated requiring high-dose steroids, n (%)	10 (25.6)	5 (27.8)	5 (23.8)	1.000

Table 5 Incidence of immune-related adverse events (irAEs) in patients undergoing ICI rechallenge with durvalumab/tremelimumab based on the status of irAEs during initial ICI of atezolizumab/bevacizumab (ICI-1)

All irAEs A	ICI rechallenge irAE (−)	ICI rechallenge irAE grade 1–2	ICI rechallenge irAE ≧ grade 3
ICI-1 irAE (−) ($n = 17$)	9 (52.9)	5 (29.4)	3 (17.7)
ICI-1 irAE grade 1–2 ($n = 3$)	1 (33.3)	2 (66.7)	0 (0.0)
ICI-1 irAE≧ grade 3 ($n = 1$)	0 (0.0)	1 (100.0)	0 (0.0)
Rash B	ICI rechallenge AE (−)	ICI rechallenge irAE grade 1–2	ICI rechallenge irAE ≧ grade 3
ICI-1 irAE (−) ($n = 19$)	14 (73.7)	4 (21.0)	1 (5.3)
ICI-1 irAE grade 1–2 ($n = 2$)	0 (0.0)	2 (100.0)	0 (0.0)
ICI-1 irAE ≧ grade 3 ($n = 0$)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea/colitis	ICI rechallenge irAE (−)	ICI rechallenge irAE grade 1–2	ICI rechallenge irAE ≧ grade 3
ICI-1 AE (−) ($n = 19$)	14 (73.7)	3 (15.8)	2 (10.5)
ICI-1 irAE grade 1–2 ($n = 1$)	1 (100.0)	0 (0.0)	0 (0.0)
ICI-1 irAE ≧ grade 3 ($n = 1$)	0 (0.0)	1 (100.0)	0 (0.0)

Abbreviations: *ICI* immune checkpoint inhibitor, *irAEs* immune-related adverse events

Among the 18 patients who achieved disease control with the initial ICI treatment, 56% (10/18) maintained disease control upon ICI rechallenge, suggesting that the outcomes of initial ICI treatment may influence the response to a rechallenge with durvalumab/tremelimumab.

While the effectiveness of ICI re-challenge remains controversial in other malignancies [13, 14], the Contact-03 trial [13], a randomized phase III study investigating the additive effect of atezolizumab to cabozantinib compared with that of cabozantinib alone in cases that showed radiological PD after initial ICI treatment, demonstrated similar PFS and OS rates between the atezolizumab plus cabozantinib and cabozantinib alone groups. Consequently, in cases of advanced HCC, a prospective randomized controlled study may be necessary to elucidate the issues surrounding ICI rechallenge in the near future.

Notably, 33.3% (7/21) of patients who underwent ICI rechallenge experienced grade 3 or higher AEs, and 23.8% required high-dose steroids (5/21). These results were similar to the safety profile of patients treated with durvalumab/tremelimumab as initial ICI therapy and were consistent with the results of previous studies [6, 7, 11, 12]. However, it is plausible that patients who experienced severe adverse effects during ICI-1 treatment did not undergo ICI rechallenge, and this potential selection bias among patients must be considered when interpreting the results.

Furthermore, in this study, among the 21 patients who underwent ICI rechallenge, 19.0% (4/21) experienced irAEs during the initial ICI-1 treatment, and 52.4% (11/21) of patients had irAEs during the ICI rechallenge phase. Notably, 75% (3/4) of patients who experienced irAEs during ICI-1 also experienced irAEs during ICI rechallenge

(Table 5B). This underscores the importance of careful monitoring for irAEs during ICI rechallenge, particularly in patients with a history of irAEs during the initial ICI treatment (Table 5B, Online Resource 3). A previous study reported a high rate of irAE recurrence after ICI rechallenge [8], whereby 452 irAEs were recorded in ICI rechallenge cases, and 130 (28.8%) were recurrences of irAEs observed during initial ICI therapy. Thus, careful attention to irAEs experienced during the initial ICI treatment is crucial when considering ICI rechallenge in sequential therapy.

Despite its strengths, this study has some limitations. First, the sample size was relatively small. Therefore, caution is advised when interpreting the results due to the possibility of selection bias, as patients with severe AEs during initial ICI therapy might have been excluded from ICI rechallenge by the attending physician. Second, the observation period was limited. Therefore, it was insufficient to analyze and discuss OS. In the ICI rechallenge group, OS may be shorter due to treatment being administered at later lines. However, in this study, the observation period may not have been sufficient to fully evaluate this outcome. Further analysis is needed to draw more definitive conclusions. Therefore, a prospective study involving a larger cohort of patients and an extended follow-up period is necessary to validate the findings of this study.

In conclusion, our findings indicate that the safety and efficacy of using durvalumab and tremelimumab for unresectable HCC as an ICI rechallenge appear promising and comparable to those observed with ICI initial therapy. Notably, all patients ($n = 3$) who exhibited the best response to PD during the initial ICI treatment with atezolizumab/bevacizumab also experienced PD during the ICI rechallenge with durvalumab/tremelimumab. However, extensive and long-term studies are necessary to validate these results.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11523-024-01092-7.

Acknowledgments The authors would like to thank all participating patients and their families.

Declarations

Funding This study was partly supported by grants from the Japan Agency for Medical Research and Development (AMED; grant nos. JP24fk0210126, JP24fk0310501, JP24fk0210121, JP24fk0210112, JP24fk0210142, JP24fk0210111, JP24fk0310524, JP24fk0210123, JP24fk0210157, JP24fk0310518, JP24fk0210103, JP24fk0210104, JP24fk0210113, and JP24fk0210143).

Conflict of interest Professor Naoya Sakamoto received lecture fees from Chugai Pharmaceutical Co., Ltd. and research grants from Gilead Sciences, Inc. and AbbVie, Inc. Dr. Goki Suda received research grants from Gilead Sciences. Takuya Sho, Masatsugu Ohara, Risako Kohya, Takashi Sasaki, Sonoe Yoshida, Shunichi Hosoda, Koji Ogawa, Takashi Kitagataya, Osamu Maehara, Shunsuke Ohnishi, Naoki Kawagishi, Mitsuteru Natsuizaka, Masato Nakai, Masaru Baba, Yoshiya Yamamoto, Yoko Tsukuda, Takashi Meguro, Ren Yamada, Tomoe Kobayashi, and Tomofumi Takagi declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

Ethics approval The ethics committee of Hokkaido University Hospital verified that the study protocol (institutional review board no.: 023-0141) adhered to the ethical guidelines of the Declaration of Helsinki.

Consent to participate Patients who provided written informed consent or did not express their refusal to participate were included in this study. Additionally, the ethics committee of Hokkaido University Hospital granted specific approval for the inclusion of patients who did not actively refuse to participate as an alternative to obtaining written informed consent.

Consent for publication Not applicable.

Availability of data and material This article includes all data generated or analyzed during this study, as well as the supplementary data. Further inquiries can be directed to the corresponding author.

Author contributions G.S. designed the study. T.Sho, G.S., and M.O. performed examinations and statistical analyses. T.S. and G.S. revised the manuscript. T.Sho, R.K., G.S., M.O., S.H., T.Sasaki, S.Y., K.O., T.K., O.M., Y.T., S.O., N.K., M.Natsuizaka, M.Nakai, M.B., Y.Y., T.M., R.Y., T.T., and T.K. collected samples and clinical data. M.Natsuizaka, K.O., and N.S. provided hepatological advice. N.S. revised the manuscript for the intellectual content.

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