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RESEARCH

Treatment response to durvalumab plus tremelimumab after progression with previous immune checkpoint inhibitor in unresectable hepatocellular carcinoma

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Summary
Although immune checkpoint inhibitors (ICI) are used for unresectable hepatocellular carcinoma (HCC), it is unclear whether sequential ICI treatment—durvalumab plus tremelimumab (DT) after progression on atezolizumab plus bevacizumab (AB)—is effective for HCC. In this nationwide multicenter study, we aimed to investigate the effect of DT treatment based on the timing of treatment. A total of 85 patients receiving DT treatment were enrolled. The *primary endpoint* is treatment response at week 8 among patients receiving first-line DT treatment, those receiving second-line or later treatment without prior AB therapy, and those receiving second-line or later treatment with prior AB therapy. Objective response rates (ORRs) in patients with first-line treatment, second-line treatment without AB, and second-line treatment with prior AB were 44%, 54%, and 5%, respectively ($p < 0.001$). Similarly, disease control rates (DCRs) were 69%, 91%, and 26%, respectively ($p < 0.001$). ORR and DCR were significantly lower in patients with prior AB treatment. Progression free survival (PFS) was significantly shortened in patients receiving second-line therapy following prior AB treatment and an adjusted hazard ratio (95% confidence interval) in those patients for PFS, using first-line therapy as a reference, was 2.35 (1.1–5.1, $p = 0.03$). In conclusion, the impact of DT sequencing following AB treatment was limited. However, even after second-line treatment, the treatment effect can be equivalent to that of first-line treatment in cases with no history of AB treatment. Thus, prior treatment history should be taken into account when initiating DT treatment.

Keywords Hepatocellular carcinoma (HCC) · Durvalumab plus tremelimumab · Atezolizumab plus bevacizumab · Immune checkpoint inhibitor (ICI)

Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer death [1]. HCC cases stemming from viral hepatitis are decreasing due to therapeutic advancements, whereas those arising from steatotic liver disease are increasing [2–6]. Early detection and treatment of HCC remain critical clinical concerns. In recent years, several drug treatments have become available for advanced HCC [7–10]. Atezolizumab, an immune checkpoint inhibitor (ICI) targeting Programmed Death-Ligand 1 (PD-L1), combined with bevacizumab (AB), is used for unresectable HCC [11]. Recently, the combined ICI treatment durvalumab plus tremelimumab (DT), targeting Cytotoxic T-lymphocyte antigen 4 (CTLA-4) with tremelimumab and PD-L1 with durvalumab, has been approved for HCC [12]. Guidelines recommend systemic chemotherapy for unresectable HCC with either AB treatment or DT treatment as the first-line treatment [13–15].

Phase 3 clinical trial of DT treatment demonstrated superior overall survival compared to sorafenib [12]. Patients without prior systemic chemotherapy were enrolled in this clinical trial, and all received DT treatment as first-line therapy. Conversely, in clinical practice, there are instances where patients previously treated with systemic therapy subsequently receive DT treatment as a second-line or later

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intervention. In particular, some cases are introduced to DT treatment following treatment with prior ICI of AB treatment. However, the effectiveness of DT treatment remains unclear in cases where it is used as a second-line treatment or later, especially after progression with prior ICI of AB treatment. To address the existing knowledge gap, this nationwide, multicenter, prospective study was conducted to evaluate the efficacy of DT treatment in patients administered DT as a second-line or later therapy, and in those who underwent DT treatment following prior ICI therapy (AB treatment).

Methods

Study protocol

This nationwide, multicenter, prospective study includes 17 hospitals from the Japanese Red Cross Liver Study Group. A total of 104 patients who received DT treatment from March 2023 to January 2024 were prospectively registered. The exclusion criteria were as follows: (1) observation period within 4 weeks ($n=7$), (2) absence of imaging examination ($n=9$), (3) lack of blood test data ($n=2$), and (4) Child–Pugh class C ($n=1$). Finally, 85 patients with unresectable HCC who received DT treatment were enrolled in the study. All patients underwent imaging at week 8 to assess treatment response. Followup was also conducted to assess progression-free survival (PFS).

Written informed consent was obtained from all patients before entering the study. The study protocol was approved by the ethics review committees of Musashino Red Cross Hospital (approval number: 4054), and conformed to the ethical guidelines of the Declaration of Helsinki.

Treatment response assessment

All patients underwent enhanced computed tomography or magnetic resonance imaging at week 8 to assess treatment response. Modified Response Evaluation Criteria in Solid Tumors, version 1.1 (mRECIST) was used for the assessment, and all patients were stratified into four groups: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) [16]. The rates of CR and PR are defined as the objective response rate (ORR), and the rates of CR, PR, and SD are defined as the disease control rate (DCR). Treatment response was assessed in each hospital.

Primary outcome

The *primary outcome* of the study is the response to DT treatment. ORR and DCR were compared among three groups: patients receiving first-line DT treatment, patients receiving second-line or later treatment without prior AB treatment, and patients receiving second-line or late treatment with prior AB treatment. Followup was conducted, and PFS was compared among three groups.

Statistical analyses

ORR and DCR were compared using Fisher's exact test. Logistic regression analysis was conducted to examine the odds ratio (OR) with a 95% confidence interval (CI) for ORR and DCR. PFS and overall survival were analyzed using the Kaplan–Meier method and the log-rank test. The multivariable analysis was conducted using the Cox proportional hazards model to examine the hazard ratio (HR) with a 95% CI for PFS. Statistical significance was set at $p<0.05$. All statistical analyses were conducted using EZR (Saitama Medical Center, Jichi Medical University, Shimotsuke, Japan), a graphical user interface for R version 3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria) [17].

Results

Patient characteristics

A total of 85 patients with unresectable HCC who underwent DT treatment were included in the study (Table 1). The mean age (interquartile range [IQR]) was 75 (70–79) years, and 74 (87%) of the participants were male. Child–Pugh class A was observed in 59 patients (69%), and class B in 26 patients (31%). Barcelona Clinic Liver Cancer stages A, B, and C were observed in 1 (1%), 39 (46%), and 45 (53%) patients, respectively. DT treatment was introduced as the first-line treatment in 16 (19%) cases and as the second-line or later treatment in 69 (81%) cases. Among patients undergoing second-line or subsequent treatments, 58 received AB therapy prior to DT therapy. Patients who received DT treatment as the second-line or later treatment without AB treatment ($n=11$) received tyrosine kinase inhibitors as prior treatment and did not receive ICI treatment.

Comparison of treatment response

The treatment response in all 85 patients was 2 (2.4%), 14 (16.5%), 18 (21.2%) and 51 (60%) for CR, PR, SD and PD, respectively, and ORR and DCR were 16 (19%) and 34 (40%), respectively. First, the treatment response was compared between patients receiving first-line treatment and those receiving second-line or later treatments. ORRs in patients receiving first-line treatment and those receiving

Table 1 Patient characteristics

	First line ($n=16$)	Second or later line without AB treatment ($n=11$)	Second or later line with AB treatment ($n=58$)	p value
Age, years	75 (70–80)	79 (75–81)	74 (70–76)	0.08
Males, *n* (%)	15 (93.8%)	9 (81.8%)	50 (86.2%)	0.6
PS, *n* (%)				0.03
0	15 (93.8%)	6 (54.5%)	48 (82.8%)	
1	1 (6.2%)	5 (45.5%)	10 (17.2%)	
Etiology of liver disease, *n* (%)				0.1
SLD	13 (81.3%)	5 (45.4%)	23 (39.7%)	
HBV	1 (6.2%)	1 (9.1%)	12 (20.7%)	
HCV	2 (12.5%)	4 (36.4%)	18 (31.0%)	
Others	0 (0%)	1 (9.1%)	5 (8.6%)	
Child–Pugh Grade, *n* (%)				0.2
A	8 (50.0%)	8 (72.7%)	43 (74.1%)	
B	8 (50.0%)	3 (27.3%)	15 (25.9%)	
BCLC stage, *n* (%)				0.8
A	0 (0.0%)	0 (0.0%)	1 (1.7%)	
B	9 (56.2%)	4 (36.4%)	26 (44.8%)	
C	7 (43.8%)	7 (63.6%)	31 (53.5%)	
Extrahepatic spread, *n* (%)	4 (25.0%)	6 (54.5%)	22 (37.9%)	0.3
Macrovascular invasion, *n* (%)	5 (31.2%)	3 (27.3%)	8 (13.8%)	0.2

Continuous data are shown in median (interquartile range)

P value indicated the comparison between first-line, second or later line without AB treatment and second or later line with AB treatment

BCLC Barcelona clinic liver cancer; *SLD* Steatotic liver disease; *HCV* Hepatitis C virus; *HBV* Hepatitis B virus; *PS* Performance status; *AB* Atezolizumab plus bevacizumab

second-line or later treatments were 44% and 13%, respectively ($p=0.009$). Similarly, DCRs in patients receiving first-line treatment were 69%, compared to 33% in those receiving second-line or later treatments ($p=0.01$). ORR and DCR were significantly higher in patients receiving first-line treatment compared to those undergoing second-line or later treatments Next, patients receiving second-line or later treatments were stratified based on prior exposure to AB treatment (second-line with prior AB treatment and second-line without prior AB treatment). ORRs in patients receiving first-line treatment, second-line treatment without AB therapy, and second-line treatment following AB therapy were 44%, 54%, and 5%, respectively ($p<0.001$, Fig. 1A). Similarly, DCRs were 69%, 91%, and 26%, respectively ($p<0.001$, Fig. 1B). ORR and DCR were significantly lower in patients receiving second-line or later therapy following prior AB treatment.

Using patients receiving first-line treatment as a reference and adjusting for age, gender, etiology, BCLC stage and Child–Pugh Grade, ORs (95% CI) for ORR and DCR in patients with second-line with prior AB treatment were 0.07 (0.01–0.4, $p=0.005$) and 0.07 (0.01–0.40, $p=0.003$), respectively. Similarly, the ORs (95% CI) for ORR and DCR in patients without second-line with prior AB treatment were 1.8 (0.2–14, $p=0.6$) and 5.1 (0.3–79, $p=0.2$), respectively. There was no significant difference in ORR and DCR between patients with first-line and patients with second-line without AB treatment. Conversely, ORR and DCR were worse in patients with second-line with AB treatment. Other factors (age, gender, etiology, BCLC stage and Child–Pugh Grade) were not associated with ORR and DCR.

Progression-free survival and overall survival

PFS was compared among three groups. The median PFS in patients receiving first-line treatment, second-line treatment without AB therapy, and second-line treatment following AB therapy were 5.2 months, not reached, and 2.9 months, respectively ($p=0.001$, Fig. 2). Multivariable analysis showed that after adjusting for age, gender, and Child–Pugh class, with first-line treatment as a reference, the HRs for PFS were 0.28 (95% CI, 0.06–1.4; $p=0.1$) for patients receiving second-line treatment without AB therapy and 2.35 (95% CI, 1.1–5.1; $p=0.03$) for those receiving second-line treatment following AB therapy. PFS was significantly shortened in patients receiving second-line therapy following prior AB treatment.

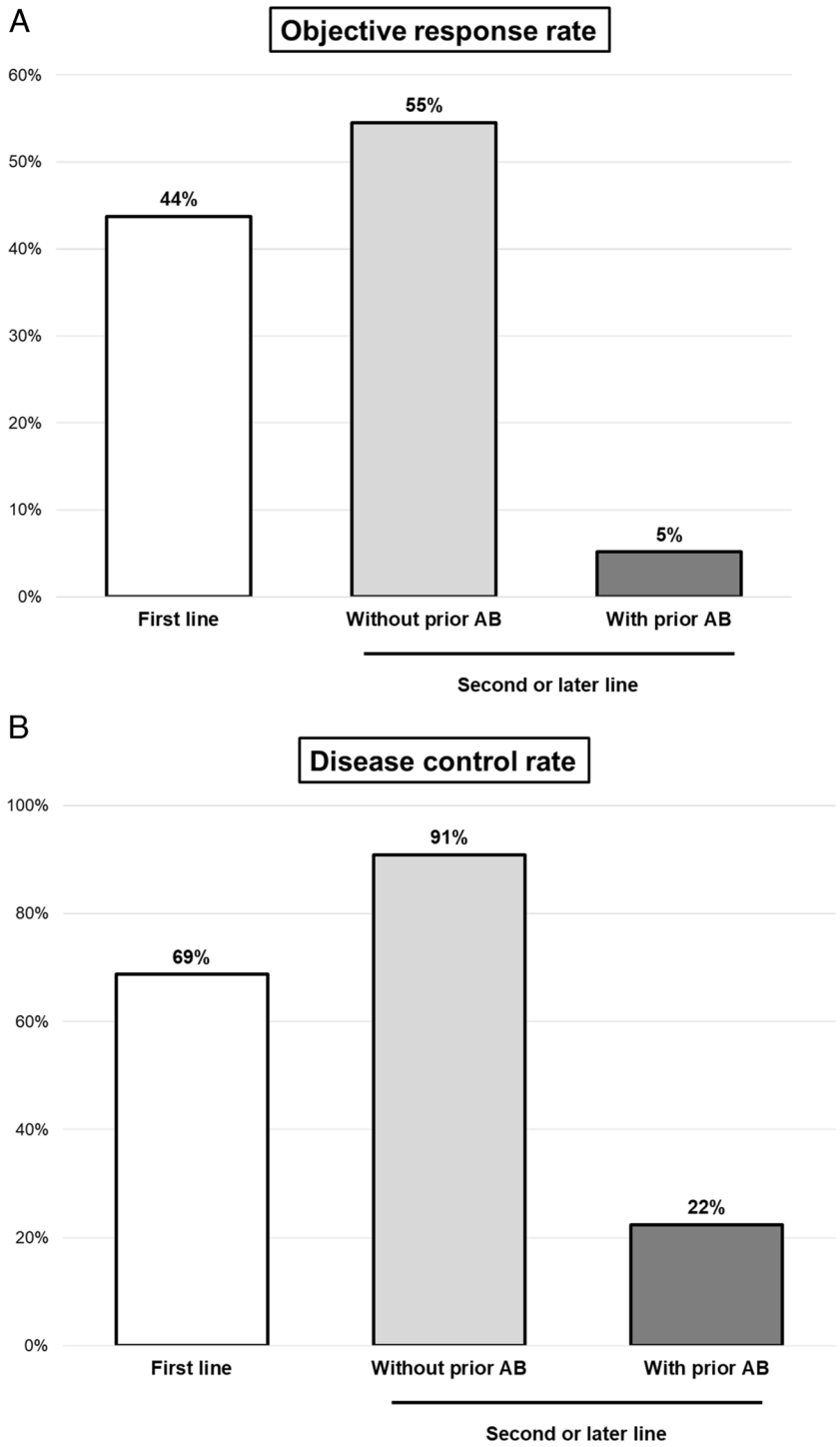

Fig. 1 Treatment response in patients with first-line treatment, second-line or later treatment without AB, and second-line treatment with prior AB. **A** Objective response rate, and **B** disease control rate. AB, atezolizumab plus bevacizumab

Overall survival was also compared among three groups. The 6-month survival rates for patients receiving first-line treatment, second-line treatment without AB therapy, and second-line treatment with AB therapy were 79%, 67% and 80%, respectively, and there was no significant difference ($p = 0.8$).

Discussion

Main findings

In this nationwide multicenter study, we observed that the efficacy of DT treatment diminished in patients previously

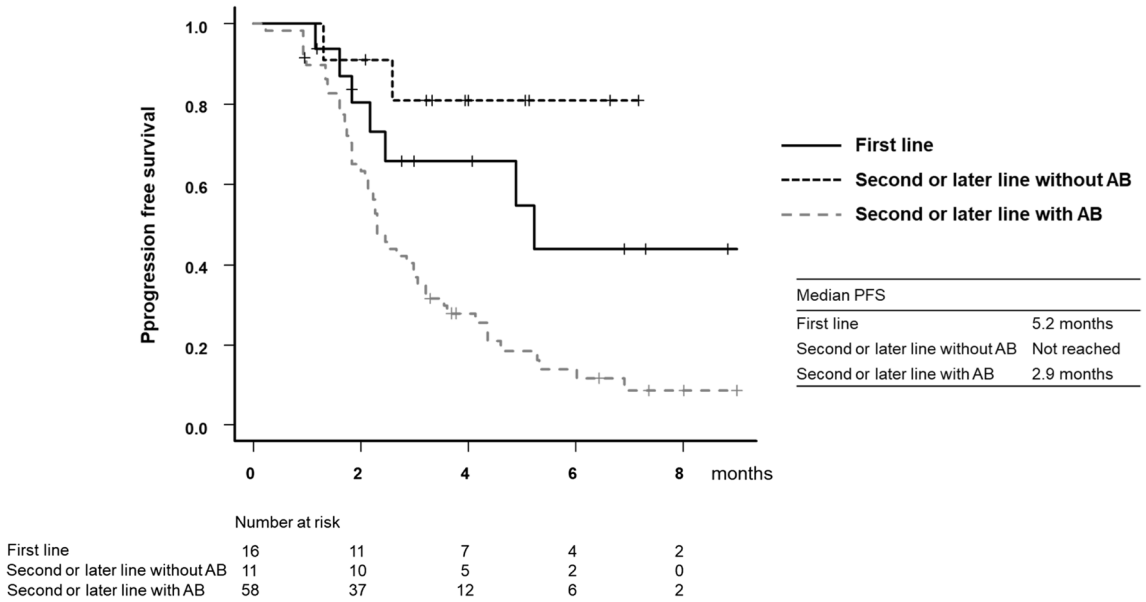

Fig. 2 Progression free survival in patients with first-line treatment, second-line or later treatment without AB, and second-line treatment with prior AB. AB, atezolizumab plus bevacizumab; PFS, progression free survival

treated with AB treatment. Conversely, introducing DT in patients treated with second or later lines without prior AB therapy can achieve similar treatment outcomes as in the first line. Therefore, the indication for DT treatment should be based on a history of treatment with ICI.

In context with published literature

For the treatment of unresectable HCC, the recommended first-line treatments are AB or DT [13–15]. Both AB and DT treatments, which include ICI, can be used sequentially in Japan for HCC. As AB treatment preceded DT treatment, 58 patients in this study subsequently received DT treatment following AB treatment. The efficacy of sequential treatment with ICI in HCC remains unexplored. Few studies have demonstrated that re-induction of ICI may be effective in some malignant tumors, including HCC; however, these studies included only a small number of patients [18–20]. A prospective randomized phase 3 trial comparing atezolizumab plus cabozantinib with cabozantinib alone after progression with prior ICI (anti-PD-L1 or anti-PD-1) in renal cell carcinoma, involving 522 patients, demonstrated that no additional treatment effect was observed with the addition of atezolizumab, and an increase in side effects was noted [21]. In this study, we demonstrated that administering DT treatment subsequent to AB treatment, a sequential regimen involving ICI, significantly diminished both treatment response and PFS. Our study results suggest that the effectiveness of this sequential treatment may be limited. Baseline patient characteristics (age, gender, etiology, BCLC stage and Child–Pugh Grade) were not associated with treatment response and prior AB treatment was the only factor associated with DT treatment response. Therefore, more clinical data are needed on the effectiveness of re-induction of ICI.

The clinical trial for DT treatment has only included cases introduced as first-line treatment. In clinical practice, DT treatment is sometimes initiated after second or subsequent lines of therapy. It is crucial to verify the effectiveness of DT post second-line treatment, an area that remains underexplored. In this study, we demonstrated that the response to second-line treatment in patients not receiving AB therapy was comparable to that observed in those undergoing first-line treatment. Therefore, regardless of when treatment is initiated, DT therapy can provide significant therapeutic benefits in cases without prior AB treatment.

Strengths and limitations

This is a nationwide, multicenter, prospective study that includes 85 patients undergoing DT treatment. However, many patients underwent DT treatment as a second or later line, while the number of cases receiving first-line DT treatment remained small. In addition, the number of cases with second-line or later DT treatment without AB treatment was also small. Thus, future studies should expand the sample size to validate the efficacy of DT treatment. Of the patients excluded from the study (absence of imaging study), 3 patients had rapid progression of disease. All

these patients received DT treatment in second or later line with AB treatment. Therefore, the overall results do not change for patients receiving DT in first-line treatment and second-line treatment without AB therapy, but this point should be noted.

Future implications

Both AB and DT treatments are recommended as first-line treatments in guidelines. There are no trials comparing the effectiveness of AB and DT treatments, nor are there clear criteria for choosing between these drugs. Nevertheless, the findings of this study indicate that the impact of sequencing treatments on DT following AB treatment is limited. Conversely, CTLA-4 inhibitors activate memory T cells, potentially enhancing the effects of sequential therapy [22, 23]. A randomized Phase 3 trial comparing nivolumab with chemotherapy following CTLA-4 inhibitor progression in melanoma demonstrated superior therapeutic efficacy of nivolumab [24]. Therefore, the efficacy of AB sequencing therapy following DT treatment in HCC requires further validation. Currently, the appropriate drug should be selected based on the tumor status and individual patient complications.

In conclusion, although the efficacy of DT sequencing following AB therapy was limited, even after second-line treatment, the therapeutic outcomes may be comparable to those of first-line treatments in patients without prior AB treatment. Thus, prior treatment history should be taken into account when initiating DT treatment.

Author contributions Author contribution: Study concept and design: NM, NT and MK; data collection and interpretation: all authors; drafting of the manuscript: NM and NT; critical revision of the manuscript: all authors; statistical analysis: NM and NT; study supervision: NI and MK; obtained funding: NT, YY and MK. All authors had access to the study data and reviewed and approved the final manuscript.

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Data availability The data presented in this study are available upon request from the corresponding author.

Declarations

Competing interests Masayuki Kurosaki and Kaoru Tsuchiya received lecture fee from AstraZeneca and Chugai. Other authors have no conflicts of interest to declare related to the study.

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