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Avelumab in Combination with Axitinib as First-Line Treatment in Patients with Advanced Hepatocellular Carcinoma: Results from the Phase 1b VEGF Liver 100 Trial

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Keywords
Hepatocellular carcinoma · Immune checkpoint inhibitor · Vascular endothelial growth factor receptor tyrosine kinase inhibitor · Avelumab · Axitinib

Abstract
Introduction: Combining an immune checkpoint inhibitor with a targeted antiangiogenic agent may leverage complementary mechanisms of action for the treatment of advanced/metastatic hepatocellular carcinoma (aHCC). Avelumab is a human anti-PD-L1 IgG1 antibody with clinical activity in various tumor types; axitinib is a selective tyrosine kinase inhibitor of vascular endothelial growth factor receptors 1, 2, and 3. We report the final analysis from VEGF Liver 100 (NCT03289533), a phase 1b study evaluating safety and efficacy of avelumab plus axitinib in treatment-naive patients with aHCC. ***Methods:*** Eligible patients had confirmed aHCC, no prior systemic therapy, ≥1 measurable lesion, Eastern Cooperative Oncology Group performance status ≤1, and Child-Pugh class A disease. Patients received avelumab 10 mg/kg intravenously every 2 weeks plus axitinib 5 mg orally twice daily until progression, unacceptable toxicity, or withdrawal. Endpoints included safety and investigator-assessed objective response per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and modified RECIST (mRECIST) for HCC. ***Results:*** Twenty-two Japanese patients were enrolled and treated with avelumab plus axitinib. The minimum follow-up was 18 months as of October 25, 2019 (data cutoff). Grade 3 treatment-related adverse events (TRAEs) occurred in 16 patients (72.7%); the most common (≥3 patients) were hypertension (n = 11 [50.0%]), palmar-plantar erythrodysesthesia syndrome (n = 5 [22.7%]), and decreased appetite (n = 3 [13.6%]). No grade 4 TRAEs or treatment-related deaths occurred. Ten patients (45.5%) had an immune-related AE (irAE) of any grade; 3 patients (13.6%) had an infusion-related reaction (IRR) of any grade, and no grade ≥3 irAE and IRR were observed. The objective response rate was 13.6% (95% CI: 2.9–34.9%) per RECIST 1.1 and 31.8% (95% CI: 13.9–54.9%) per mRECIST for HCC. ***Conclusion:*** Treatment with avelumab plus axitinib was associated with a manageable toxicity profile and showed antitumor activity in patients with aHCC.

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Introduction

Liver cancer is the fourth most common cause of cancer-related deaths worldwide [1], with approximately 782,000 deaths occurring in 2018 [2]. In Japan, liver cancer was projected to cause approximately 27,000 deaths in 2018 [3]. Hepatocellular carcinoma (HCC) is the most common type of liver cancer, accounting for >80% of liver cancer diagnoses worldwide [4]. First-line systemic therapy with the oral multikinase inhibitors sorafenib or lenvatinib is the current standard of care for advanced HCC [5]; however, both are associated with considerable toxicities [6–8]. Therefore, treatments that are more efficacious and less toxic than the currently available options are needed. PD-1/PD-L1 pathway inhibitors have shown clinical activity and tolerable safety profiles in patients with advanced HCC. Based on results from the phase 1/2 CheckMate 040 study [9] and phase 2 KEYNOTE-224 study [10], nivolumab (anti-PD-1) and nivolumab plus ipilimumab (anti-CTLA-4) and pembrolizumab (anti-PD-1) were granted accelerated US Food and Drug Administration (FDA) approval for patients with HCC previously treated with sorafenib [11, 12].

Combining a PD-1/PD-L1 pathway inhibitor with a vascular endothelial growth factor receptor (VEGFR) inhibitor has the potential for a complementary mechanism of action: VEGF pathway inhibitors normalize blood vessels in tumors to increase the infiltration of immune cells and anticancer agents, potentially improving the effectiveness of immunotherapy [13, 14]. The combination of an immunotherapeutic agent and a VEGF pathway inhibitor enhances efficacy in murine tumor models [15, 16]. In the phase 3 IMbrave150 trial [17], atezolizumab (anti-PD-L1) was assessed in combination with bevacizumab (anti-VEGF) as first-line treatment in unresectable or metastatic HCC and showed superior overall survival (OS) and progression-free survival (PFS) versus sorafenib. These results subsequently led to the FDA approval of first-line atezolizumab and bevacizumab in this treatment setting [18].

Avelumab is a human anti-PD-L1 monoclonal antibody that binds PD-L1 and inhibits the PD-1/PD-L1 pathway [19]. Due to its unmodified IgG1 isotype, avelumab has the potential to engage Fc receptors and elicit effector functions, as has been shown in vitro [20]. Avelumab has shown acceptable safety and durable antitumor activity in multiple tumor types [19, 21–24] and has been approved in various countries for the treatment of urothelial carcinoma that has progressed following platinum-containing therapy and as maintenance for disease that has not progressed following platinum-containing chemotherapy and metastatic Merkel cell carcinoma [25]. Avelumab also received regulatory approval in Japan in 2017 for the treatment of curatively unresectable Merkel cell carcinoma [26].

Axitinib is a potent, selective tyrosine kinase inhibitor of VEGFRs 1, 2, and 3. It is approved multinationally for the treatment of advanced renal cell carcinoma (RCC) after failure of 1 prior systemic therapy (indication varies according to region/country) and has shown single-agent antitumor activity and a manageable safety profile in Japanese patients with metastatic RCC in both the first- and second-line settings [27–31]. In a randomized phase 2 trial in advanced HCC, second-line treatment with axitinib plus best supportive care resulted in significantly longer PFS and time to progression and a higher clinical benefit rate versus placebo plus best supportive care, with an acceptable safety profile [32]. Although the primary OS endpoint had not been met in this study, a subset of Japanese patients showed favorable OS outcomes compared with patients from other countries [33].

The randomized phase 3 JAVELIN Renal 101 trial of first-line avelumab plus axitinib versus sunitinib in advanced RCC demonstrated significantly improved PFS with the combination [34], including in Japanese patients [35], leading to regulatory approval of avelumab in combination with axitinib in the USA, European Union, and Japan for the first-line treatment of advanced RCC [25, 36, 37].

Here, we report results from the final analysis of the phase 1b VEGF Liver 100 trial evaluating the safety and efficacy of avelumab in combination with axitinib in treatment-naive patients with HCC.

Patients and Methods

Study Design and Patients

VEGF Liver 100 (NCT03289533) was an open-label, multicenter, phase 1b trial. Eligible patients were adults aged ≥20 years who had not received prior systemic therapy and had histologically or cytologically confirmed, measurable, locally advanced or metastatic HCC. Other eligibility criteria included Eastern Cooperative Oncology group performance status (ECOG PS) of 0 or 1, Child-Pugh class A disease, and Barcelona Clinical Liver Cancer (BCLC) stage B (unresectable, not amenable to local therapy, or refractory to local therapy) or C disease.

Procedures

Patients received avelumab 10 mg/kg intravenously every 2 weeks and axitinib 5 mg twice daily (BID) until disease progression, unacceptable toxicity, or withdrawal. All patients received premedication with an antihistamine and acetaminophen (modified based on local treatment standards and guidelines) 30–60 min

before the first 4 infusions and then based on clinical judgment thereafter. Intrapatient axitinib dose escalation was permitted for an increase of +1 and +2 dose levels (7 and 10 mg BID, respectively), and axitinib treatment could be adjusted by dose interruption with or without dose reduction by −1 and −2 dose levels (3 and 2 mg BID, respectively; 1 dose level decrease at a time) depending on the type and severity of toxicity encountered. Management of patients requiring >2 dose reductions of axitinib was permitted based on discussions with the trial's medical monitor.

Adverse events (AEs) and laboratory abnormalities were graded by National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Clinical activity was assessed every 8 weeks by investigators using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and modified RECIST (mRECIST) for HCC [38].

Outcomes

The primary objective was to evaluate the safety and tolerability of avelumab in combination with axitinib. Secondary endpoints included PFS, objective response (OR), disease control (DC), time to tumor response (TTR) and duration of response (DOR) by RECIST 1.1, and OS. Predefined exploratory endpoints included PFS, OR, DC, TTR, and DOR by mRECIST for HCC.

PD-L1 Immunohistochemistry

PD-L1 expression was assessed in formalin-fixed paraffin-embedded sections from pretreatment specimens at a central laboratory with the use of the Ventana PD-L1 (SP263) assay (Ventana Medical Systems, Oro Valley, AZ, USA). The immune cell score is a relative area estimate of the tumor area that is covered by PD-L1+ immune cells (<1 or ≥1%).

Statistical Analysis

A target sample size of 20 patients was planned to provide at least 88% probability to observe at least one AE if the true incidence of the AE in the population was ≥10%. Clinical activity and safety were analyzed in all patients who received ≥1 dose of the study drug. PFS, DOR, and OS were evaluated using the Kaplan-Meier method. TTR was summarized using simple descriptive statistics. The rates of OR (ORR) and DC (DCR) were calculated along with corresponding exact 2-sided 95% CI using the Clopper-Pearson method.

Results

Patient Characteristics and Treatment

Between September 8, 2017, and January 30, 2018, 22 patients were enrolled at 7 sites across Japan and treated with avelumab plus axitinib. Baseline patient and disease characteristics are listed in Table 1. The proportion of patients with BCLC stage C disease was higher than that of patients with stage B disease (59.1 vs. 40.9%). The proportion of patients with baseline alpha-fetoprotein (AFP) levels <400 ng/mL was higher than that of patients with ≥400 ng/mL (59.1 vs. 40.9%). Vascular invasion was present in 6 patients (27.3%). Eight patients (36.4%) had both intra-

Table 1. Baseline patient and disease characteristics

Characteristics	*N* = 22
Age, median (range), years	68.5 (20–84)
<65 years, *n* (%)	7 (31.8)
≥65 years, *n* (%)	15 (68.2)
Sex, *n* (%)	
Male	20 (90.9)
Female	2 (9.1)
Weight, median (range), kg	61.9 (40–87)
Racial designation, *n* (%)	
Japanese	22 (100.0)
ECOG PS, *n* (%)	
0	21 (95.5)
1	1 (4.5)
BCLC staging classification, *n* (%)	
B	9 (40.9)
C	13 (59.1)
Factor of carcinogenesis (history of diseases, not ongoing), *n* (%)	4 (18.2)
Hepatitis B	1 (4.5)
Hepatitis C	3 (13.6)
Factor of carcinogenesis (ongoing medical history), *n* (%)	14 (63.6)
Alcoholic hepatitis	3 (13.6)
Nonalcoholic steatohepatitis	2 (9.1)
Hepatitis B	7 (31.8)
Hepatitis C	2 (9.1)
Baseline AFP level, *n* (%)	
<400 ng/mL	13 (59.1)
≥400 ng/mL	9 (40.9)
Vascular invasion, *n* (%)	
Yes	6 (27.3)
No	16 (72.7)
Extrahepatic/intrahepatic status, *n* (%)	
Both	8 (36.4)
Extrahepatic only	3 (13.6)
Intrahepatic only	11 (50.0)
None	0
Patients with ≥1 prior anticancer locoregional therapy, *n* (%)	19 (86.4)
Transcatheter arterial embolization	5 (22.7)
Transarterial chemoembolization	16 (72.7)
Radiofrequency ablation	5 (22.7)
Others	1 (4.5)
PD-L1 expression status (percent PD-L1+ infiltrating immune cells), *n* (%)	
≥1%	17 (77.3)
<1%	3 (13.6)
Not evaluable	2 (9.1)

AFP, alpha-fetoprotein; BCLC, Barcelona Clinical Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2. TRAEs of any grade in ≥2 patients or any grade ≥3 TRAE (*N* = 22)

Preferred term	Any grade, *n* (%)	Grade ≥3, *n* (%)
Any TRAE	21 (95.5)	16 (72.7)
Hypertension	17 (77.3)	11 (50.0)
Decreased appetite	12 (54.5)	3 (13.6)
Dysphonia	11 (50.0)	0
PPE syndrome	11 (50.0)	5 (22.7)
Stomatitis	9 (40.9)	2 (9.1)
Hypothyroidism	7 (31.8)	0
Malaise	7 (31.8)	0
Weight decreased	7 (31.8)	0
Diarrhea	6 (27.3)	1 (4.5)
Dysgeusia	6 (27.3)	0
Proteinuria	6 (27.3)	1 (4.5)
Rash	6 (27.3)	0
Fatigue	3 (13.6)	2 (9.1)
Hyperthyroidism	3 (13.6)	0
Nausea	3 (13.6)	0
Pruritus	3 (13.6)	0
Abdominal discomfort	2 (9.1)	0
Abdominal distension	2 (9.1)	0
Adrenal insufficiency	2 (9.1)	0
Anal erosion	2 (9.1)	0
Arthralgia	2 (9.1)	0
Blood bilirubin increased	2 (9.1)	0
Epistaxis	2 (9.1)	0
Glossitis	2 (9.1)	0
Headache	2 (9.1)	1 (4.5)
Hematuria	2 (9.1)	0
Infusion-related reaction	2 (9.1)	0
Paronychia	2 (9.1)	0
Peripheral edema	2 (9.1)	0
Transaminases increased	2 (9.1)	0
Amylase increased	1 (4.5)	1 (4.5)
Diverticulum intestinal hemorrhage	1 (4.5)	1 (4.5)
Mouth ulceration	1 (4.5)	1 (4.5)

TRAE, treatment-related adverse event; PPE, palmar-plantar erythrodysesthesia.

and extrahepatic disease, 3 (13.6%) had extrahepatic disease only, and 11 (50.0%) had intrahepatic disease only.

As of October 25, 2019 (data cutoff; minimum follow-up, 18 months), all 22 patients had discontinued study treatment. Avelumab was discontinued due to progressive disease in 18 patients (81.8%) and AE and withdrawal of consent in 2 patients (9.1%) each. Axitinib was discontinued due to progressive disease in 17 patients (77.3%), AE in 3 patients (13.6%), and withdrawal of consent in 2 patients (9.1%). Patients received avelumab for a median duration of 20.0 weeks (range 5.9–80.0 weeks), and the median relative dose intensity of avelumab was 100.7% (range 49.4–104.9%). Patients received axitinib for a median duration of 19.9 weeks (range 4.4–79.3 weeks). Thirteen patients (59.1%) had ≥1 dose reduction; 13 patients had dose reduction to 3 mg BID, and 4 patients (18.2%) had dose reduction to 2 mg BID. One patient had received 1 mg BID axitinib in error. No patient had an axitinib dose escalation. Nineteen patients (86.4%) were reported to have ≥1 axitinib dose interruption, and the median relative dose intensity of axitinib was 69.7% (range 32.7–100.0%)

Safety

Treatment-related AEs (TRAEs) occurred in 21 patients (95.5%) (shown in Table 2). The most common

Table 3. All irAEs and IRRs ($N = 22$)[a]

Preferred term	Any grade, *n* (%)
Any irAE[b]	10 (45.5)
Hypothyroidism	7 (31.8)
Hyperthyroidism	3 (13.6)
Adrenal insufficiency	2 (9.1)
Pruritus	2 (9.1)
Rash	2 (9.1)
Rash maculo-papular	1 (4.5)
Thyroiditis chronic	1 (4.5)
Any IRR[c]	3 (13.6)
IRR	2 (9.1)
Chills	1 (4.5)

AE, adverse event; irAE, immune-related adverse event; IRR, infusion-related reaction. [a] No grade ≥3 or serious irAE or IRR occurred, and no patient discontinued treatment due to an irAE or IRR. [b] irAEs were programmatically identified using a prespecified list of adverse events and followed by a comprehensive medical review. [c] IRR was defined as a treatment-emergent AE coded under the preferred terms of IRR, drug hypersensitivity, hypersensitivity, anaphylactic reaction, type I hypersensitivity, chills, pyrexia, back pain, dyspnea, hypotension, flushing, urticaria, wheezing, and abdominal pain according to a predefined case definition.

Table 4. Confirmed OR by investigator assessment per RECIST 1.1 and mRECIST for HCC ($N = 22$)

	RECIST 1.1	mRECIST for HCC
Best overall response, *n* (%)		
Complete response	0	2 (9.1)
Partial response	3 (13.6)	5 (22.7)
Stable disease	12 (54.5)	8 (36.4)
Progressive disease	6 (27.3)	6 (27.3)
Not evaluable	1 (4.5)[a]	1 (4.5)[a]
ORR (95% CI), %	13.6 (2.9–34.9)	31.8 (13.9–54.9)
DCR (95% CI), %	68.2 (45.1–86.1)	68.2 (45.1–86.1)

DCR, disease control rate; HCC, hepatocellular carcinoma; (m) RECIST, (modified) Response Evaluation Criteria in Solid Tumors; OR(R), objective response (rate). [a] No postbaseline assessment.

TRAEs (≥10 patients) were hypertension (*n* = 17 [77.3%]), decreased appetite (*n* = 12 [54.5%]), dysphonia (*n* = 11 [50.0%]), and palmar-plantar erythrodysesthesia (PPE) syndrome (*n* = 11 [50.0%]). Grade 3 TRAEs occurred in 16 patients (72.7%). The most common grade 3 TRAEs (≥3 patients) were hypertension (*n* = 11 [50.0%]), PPE syndrome (*n* = 5 [22.7%]), and decreased appetite (*n* = 3 [13.6%]). No patient experienced a grade 4 TRAE, and there were no treatment-related deaths.

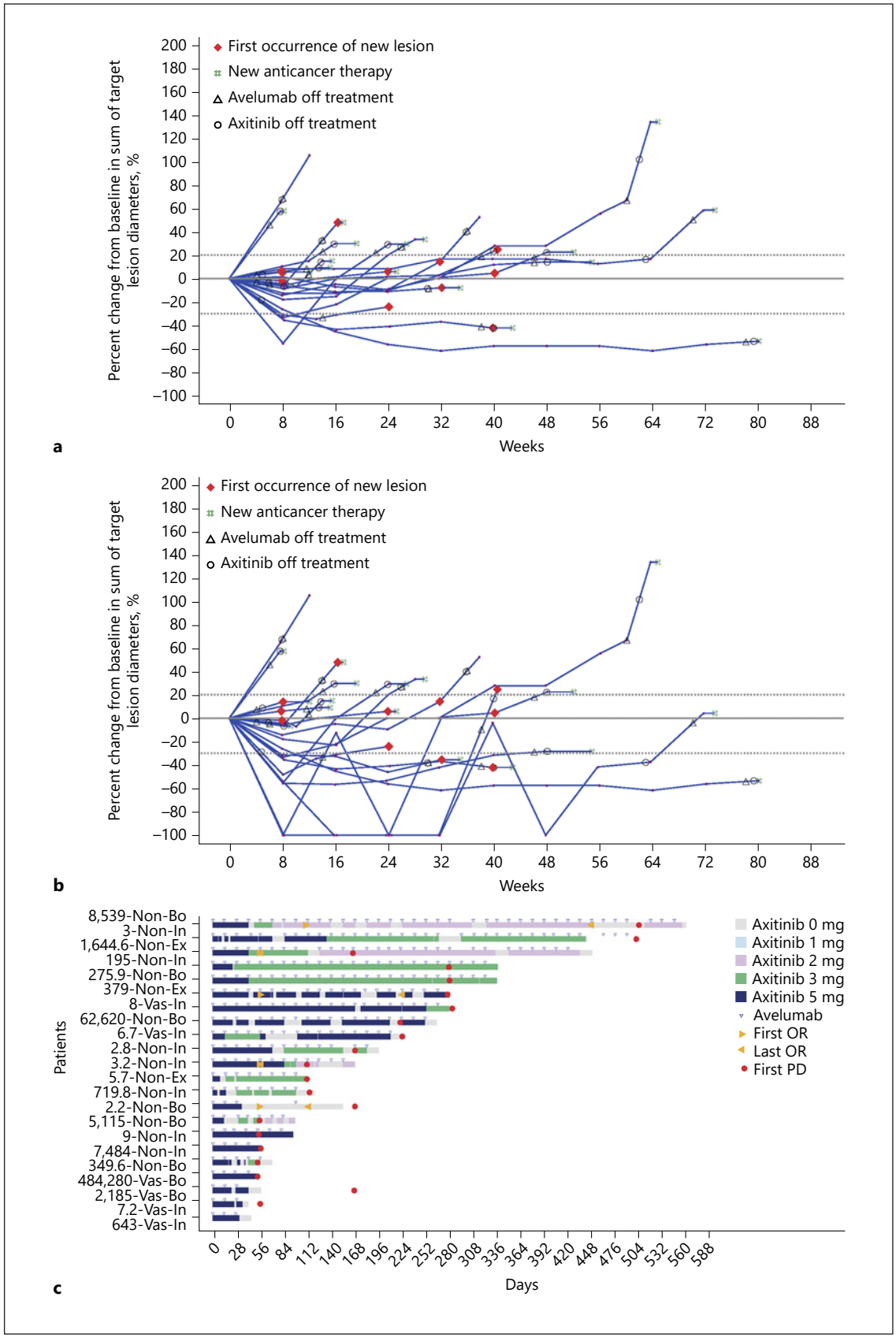
Ten patients (45.5%) had an immune-related AE (irAE) of any grade (shown in Table 3). The most common irAEs were immune-related thyroid disorders; those occurring in ≥10% of patients were hypothyroidism (*n* = 7 [31.8%]) and hyperthyroidism (*n* = 3 [13.6%]). Two patients (9.1%) received systemic corticosteroids for irAE management, none of which received a dose exceeding ≥40 mg. Three patients (13.6%) had an infusion-related reaction (IRR) of any grade (shown in Table 3). No grade ≥3 or serious irAE or IRR occurred, and no patient discontinued treatment due to an irAE or IRR.

Clinical Activity

Of 22 patients assessed for response by investigator assessment per RECIST 1.1, 3 patients (13.6%) had a partial response and 12 (54.5%) had stable disease (shown in Table 4). The ORR and DCR were 13.6% (95% CI: 2.9–34.9%) and 68.2% (95% CI: 45.1–86.1%). All patients were also assessed for response per mRECIST for HCC (shown in Table 4), and the ORR and DCR were 31.8% (95% CI: 13.9–54.9%) and 68.2% (95% CI: 45.1–86.1%). The change from baseline in target lesions for 21 evaluable patients according to RECIST 1.1 and mRECIST for HCC is shown in Fig. 1a and b and online suppl. Fig. 1 (see www.karger.com/doi/10.1159/000514420 for all online suppl. material). Median TTR and DOR per RECIST 1.1 was 1.9 months (range 1.9–3.7 months) and 7.3 months (95% CI: 3.7–12.9 months) (shown in Fig. 1c). Median TTR and DOR per mRECIST for HCC was 1.9 months (range 1.8–3.7 months) and 7.3 months (95% CI: 1.9–7.5 months) (shown in online suppl. Fig. 2). Median PFS was 5.5 months (95% CI: 1.9–7.4 months) per RECIST 1.1 (shown in online suppl. Fig. 3a) and 3.8 months (95% CI: 1.9–7.3 months) per mRECIST for HCC (shown in online suppl. Fig. 3b). Median OS was 14.1 months (95% CI: 8.0 months–not estimable [NE]), and the 1-year OS rate was 54.5% (95% CI: 32.1–72.4%) (shown in Fig. 2a).

Subgroup Analyses

Twenty patients were evaluable for PD-L1 expression, of which 17 patients (85.0%) were PD-L1+ (based on a cutoff of ≥1% of immune cells expressing PD-L1). In patients with PD-L1+ and PD-L1− tumors, the ORR per RECIST 1.1 was 17.6% (95% CI: 3.8–43.4%) and 0% (95% CI: 0–70.8%) (shown in online suppl. Table 1); median PFS per RECIST 1.1 was 5.6 months (95% CI: 1.9–9.2 months) and 5.5 months (95% CI: 1.8–9.2 months), re-



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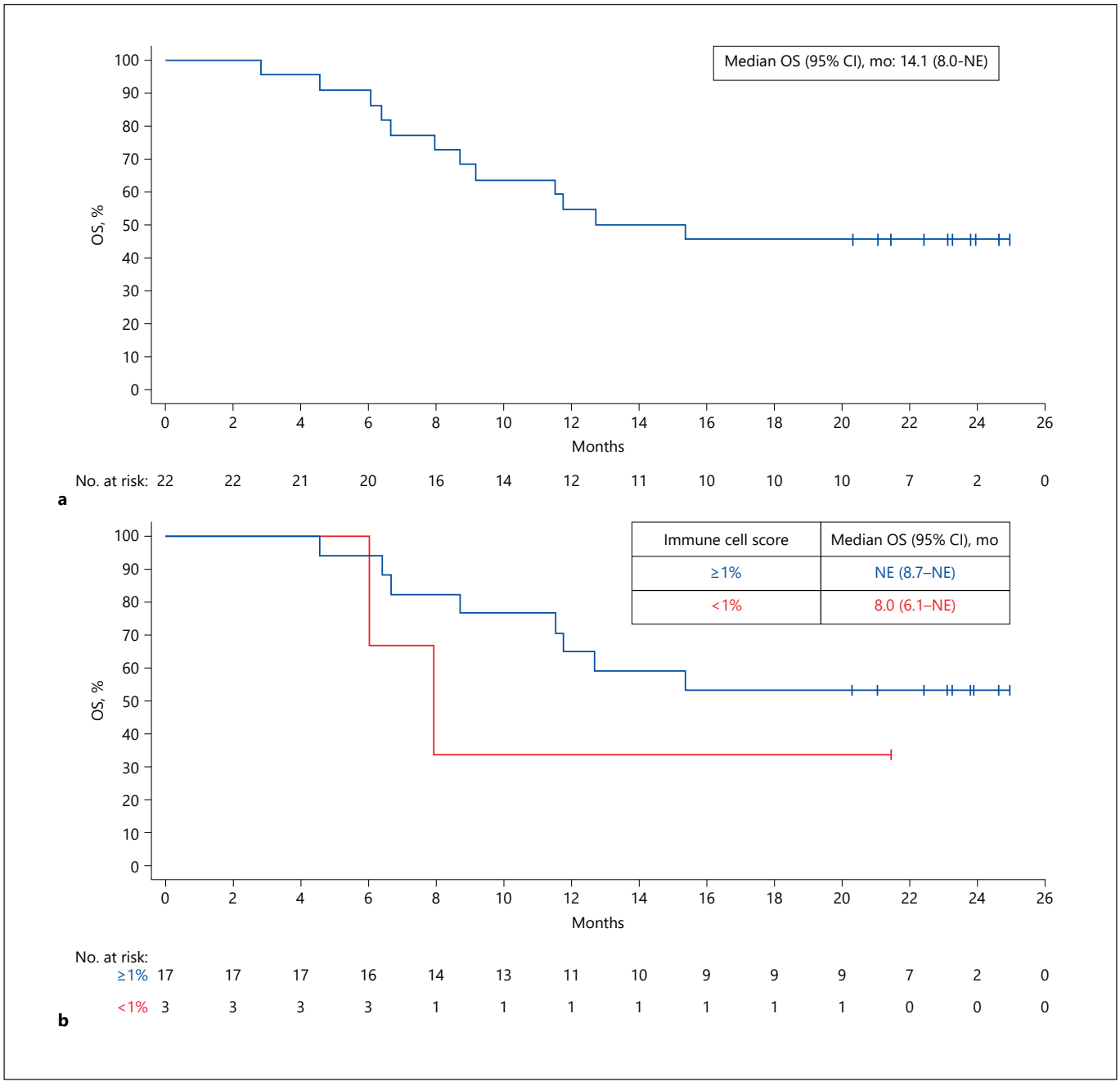

Fig. 2. OS in all patients (**a**) and according to PD-L1 status (**b**). **b** The immune cell score is a relative area estimate of the tumor area that is covered by PD-L1+ immune cells (<1 or ≥1%). Patients with unknown PD-L1 status were not included. NE, not estimable; OS, overall survival.

Fig. 1. Percent change in target lesions from baseline in evaluable patients per RECIST 1.1 (**a**) and mRECIST for HCC (**b**) ($N = 21$) and TTR and DOR by investigator assessment per RECIST 1.1 (**c**) ($N = 22$). **a**, **b** Only includes patients with target lesions at baseline and ≥1 postbaseline assessment. The baseline measurement was the last measurement prior to the first dose of study treatment. **c** Vertical axis label: AFP value at screening (ng/mL)-vascular invasion status (Vas/Non)-extrahepatic/intrahepatic status (Ex/In/Bo). AFP, alpha-fetoprotein; Bo, both; DOR, duration of response; Ex, extrahepatic only; HCC, hepatocellular carcinoma; In, intrahepatic only; (m)RECIST, (modified) Response Evaluation Criteria in Solid Tumors; Non, no vascular invasion; OR, objective response; PD, progressive disease; TTR, time to response; Vas, vascular invasion.

spectively (shown in online suppl. Fig. 4); and median OS was not reached (95% CI: 8.7 months–NE) and 8.0 months (95% CI: 6.1 months–NE), respectively (shown in Fig. 2b). The ORR by investigator assessment per RECIST 1.1 and mRECIST for HCC and OS in HCC-specific subgroups including patients with and without vascular invasion, extrahepatic spread, intrahepatic tumor, and etiology are shown in online suppl. Table 2.

Discussion/Conclusion

In this phase 1b study of patients with locally advanced or metastatic HCC, avelumab in combination with axitinib had a manageable safety profile that was consistent with that of each treatment when administered as monotherapy or in combination [25, 34, 39, 40]. The TRAE profile was also consistent with that observed in the avelumab plus axitinib arm ($N = 434$) of the large, randomized, phase 3 JAVELIN Renal 101 trial, in which the most common grade ≥3 TRAEs were hypertension ($n = 106$ [24.4%]), PPE syndrome ($n = 25$ [5.8%]), diarrhea ($n = 22$ [5.1%]), and alanine aminotransferase increased ($n = 21$ [4.8%]) [34], as well as in the subgroup of Japanese patients enrolled in the trial [35]. In the phase 3 JAVELIN Renal 101 trial, an AE led to discontinuation of both avelumab and axitinib in 33 patients (7.6%) [34]. In this study, treatment was discontinued due to an AE in a comparable proportion of patients (avelumab, $n = 2$ [9.1%]; axitinib, $n = 3$ [13.6%]). Thyroid disorders were the most common irAEs observed in this study, including hypothyroidism ($n = 7$ [31.8%]) and hyperthyroidism ($n = 3$ [13.6%]), consistent with that reported with the same combination in advanced RCC [34, 40], and could be more frequent with the combination than with avelumab alone, which may be related to the known effect of axitinib on thyroid function. All irAEs and IRRs were nonserious and mild to moderate in severity (grade 1/2). Exposure to study drugs was also consistent between this study and in a subset of Japanese patients enrolled in the JAVELIN Renal 101 trial, for whom the median relative dose intensity of avelumab was 89.8% [35]. A total of 69.7% of Japanese patients had reduced axitinib dosing, and the median relative dose intensity of axitinib was 69.4% [35].

Avelumab plus axitinib showed clinical activity as first-line treatment for advanced HCC. In this study, the ORR was 13.6% (95% CI: 2.9–34.9%) per RECIST and 31.8% (95% CI: 13.9–54.9%; complete response in 9.1%) per mRECIST for HCC. The ORRs in this study appeared to be numerically lower compared to other similar trials in the first-line HCC setting; however, cross-trial comparisons should be interpreted with caution and in consideration of the limited patient numbers and differences in trial design. In a single-arm phase 1b study of first-line pembrolizumab (anti-PD-1 monoclonal antibody) in combination with lenvatinib (anti-VEGF multikinase inhibitor) in patients with unresectable HCC, ORRs were 36% per RECIST and 46% per mRECIST [41]. In another single-arm phase 1b study of atezolizumab (anti-PD-L1 monoclonal antibody) plus bevacizumab (anti-VEGF monoclonal antibody) as first-line treatment for patients with unresectable HCC, the ORRs were 36% per RECIST and 39% per mRECIST [42]. The randomized phase 3 IMbrave150 study was subsequently initiated to assess the safety and efficacy of first-line atezolizumab plus bevacizumab versus sorafenib [17, 43]; assessment by independent review per RECIST 1.1, which demonstrated an ORR of 27% in the combination arm versus 12% in the sorafenib arm.

In our study, median PFS was 5.5 months (95% CI: 1.9–7.4 months) per RECIST 1.1 and 3.8 months (95% CI: 1.9–7.3 months) per mRECIST for HCC, and median OS was 14.1 months (95% CI: 8.0 months–NE). Prolongation of PFS and OS was not observed with the combination of avelumab plus axitinib compared with other single-agent therapies or combination therapies. Over half of the patients in our study required dose reduction and/or interruption of axitinib due to toxicity after an initial antitumor response, which may account for the comparatively less durable PFS observed according to mRECIST for HCC, which primarily reflects the effect of a VEGFR pathway inhibitor.

Although patient numbers were limiting, avelumab plus axitinib showed favorable efficacy in some subgroups in this study. Patients without baseline vascular invasion or with baseline extrahepatic spread showed a higher ORR per RECIST 1.1 and favorable OS, but the reason is unclear. Among 11 patients with extrahepatic spread, 8 patients had both intra- and extrahepatic tumors, and only 3 patients had extrahepatic tumors only. The small population of this study limited further exploration of this question.

The ORR by RECIST 1.1 was higher in patients with nonviral-associated disease than in those with hepatitis B or C. It has been reported that the efficacy was similar between patients with hepatitis B or C and uninfected patients in other studies of nivolumab or pembrolizumab in patients with advanced HCC [9, 10]. The small number of patients with each status of etiology in this study limits

the ability to discuss these differences compared with other immunotherapies.

The small number of patients with PD-L1− disease in this study limits the ability to draw conclusions; however, longer OS was observed in patients with PD-L1+ tumors compared with those with PD-L1− tumors. Preliminary results from a phase 2 study of pembrolizumab showed that PD-L1 expression assessed by tumor proportion score was not significantly associated with response, although PD-L1 expression assessed by the combined positive score was associated with the response [10]. In addition, an OR occurred regardless of PD-L1 expression on tumor cells in a phase 1/2 study of nivolumab [9]. Additional potential limitations of this study include the single-arm, open-label design.

In conclusion, treatment with avelumab plus axitinib was associated with a manageable toxicity profile and showed antitumor activity in patients with advanced HCC.

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Statement of Ethics

This trial was conducted at several study sites in accordance with the ethical principles of the Declaration of Helsinki and the International Council on Harmonization Guidelines on Good Clinical Practice. Patients provided written informed consent, and the study protocol was approved by the participating institutes' committee on human research. Thus, an ethics committee approval number is not applicable for this trial.

Conflict of Interest Statement

Masatoshi Kudo is the Editor-in-Chief of *Liver Cancer*. Kenta Motomura has received honoraria from Eisai Co. Ltd. Yoshiyuki Wada has nothing to disclose. Yoshitaka Inaba has nothing to disclose. Yasunari Sakamoto has nothing to disclose. Masayuki Kurosaki has served as a speaker and an advisory board member for Gilead, AbbVie, Eisai, and Bayer. Yoshiko Umeyama is an employee of Pfizer R&D Japan and owns stock in Pfizer. Yoichi Kamei is an employee of Pfizer R&D Japan. Junichiro Yoshimitsu is an employee of Pfizer R&D Japan. Yosuke Fujii is an employee of Pfizer R&D Japan. Mana Aizawa is an employee of Pfizer R&D Japan. Paul B. Robbins is an employee of Pfizer. Junji Furuse is an Editorial Board member of *Liver Cancer*.

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Author Contributions

Conception and design: M.K., J.F., Y.U., Y.K., J.Y., P.B.R., Y.F., and M.A. Provision of study materials or patients: M.K., K.M., Y.W., Y.I., Y.S., M.K., and J.F. Collection and assembly of data: Y.U., Y.K., and J.Y. Data analysis and interpretation: M.K., J.F., Y.U., Y.K., J.Y., P.B.R., Y.F., and M.A. Manuscript writing: all authors. Final approval of the manuscript: all authors. Accountable for all aspects of the work: all authors.

Availability of Data and Material

Upon request and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the USA and/or European Union or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

Prior Presentation

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