Liver Cancer

Brief Report

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A Phase 1b Study of Lenvatinib plus Pembrolizumab in Patients with Unresectable Hepatocellular Carcinoma: Extended Analysis of Study 116

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Keywords
Hepatocellular carcinoma · Lenvatinib · Pembrolizumab · Progression-free survival · Overall survival

Abstract

Introduction: Lenvatinib (dosing for patients who weigh ≥60 kg was 12 mg/day; for patients who weigh <60 kg, the dose was 8 mg/day) plus pembrolizumab 200 mg once every 3 weeks demonstrated antitumor activity and a manageable safety profile in patients with first-line unresectable hepatocellular carcinoma (uHCC) in the open-label phase 1b Study 116/KEYNOTE-524 (primary analysis data cutoff date: October 31, 2019; median follow-up: 10.6 months). This analysis (updated data cutoff date: March 31, 2021) reports efficacy results from 17 months of additional follow-up time.

Methods: 100 patients with uHCC were included in the primary analysis (median follow-up: 27.6 months). Endpoints included overall survival (OS), investigator-assessed progression-free survival (PFS), objective response rate (ORR), and duration of response (DOR) per modified RECIST.

Clinical Trial Information: NCT03006926 (https://clinicaltrials.gov/ct2/show/NCT03006926).

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Landmark analyses of OS by the best response at 3 and 9 months were performed. Pembrolizumab antidrug antibodies (ADAs) and concentrations were also measured (cutoff date: August 7, 2020). ***Results:*** ORR was 43.0% (95% CI 33.1–53.3%) and median DOR was 17.1 months (95% CI 6.9–19.3 months). Median PFS and OS were 9.3 months (95% CI 7.4–9.8 months) and 20.4 months (95% CI 14.4–25.9 months), respectively. No treatment-emergent ADAs were detected. ***Conclusion:*** Results show a sustained treatment effect with lenvatinib plus pembrolizumab in patients with uHCC in the first-line setting.

Introduction

Liver cancer is the sixth most common cancer diagnosis and third most common cause of cancer deaths worldwide [1]. Hepatocellular carcinoma (HCC) comprises 75% to 85% of liver cancer cases [2]. Lenvatinib (an oral multikinase inhibitor of vascular endothelial growth factor receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor α, RET, and KIT) [3–6] is approved for the first-line treatment of unresectable HCC (uHCC) in over 80 countries based on results of the phase 3 REFLECT trial [7, 8]. Additionally, pembrolizumab (an anti-programmed death receptor-1 monoclonal antibody [9]) is approved in the USA for the treatment of patients with HCC who have been previously treated with sorafenib [10].

In the open-label, multicenter, phase Ib Study 116/KEYNOTE-524 (ClinicalTrials.gov identifier: NCT03006926), lenvatinib plus pembrolizumab showed antitumor activity and a manageable safety profile in 100 patients with uHCC and no previous systemic therapy (data cutoff date: October 31, 2019; median follow-up: 10.6 months) [11]. The confirmed objective response rate (ORR) by the independent imaging review (IIR) per modified Response Evaluation Criteria in Solid Tumors (mRECIST) was 46.0% (95% CI 36.0–56.3%), and the confirmed ORR by IIR per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) was 36.0% (95% CI 26.6–46.2%). Median progression-free survival (PFS) by IIR was 9.3 months (95% CI 5.6–9.7) per mRECIST and 8.6 months (95% CI 7.1–9.7) per RECIST v1.1; median overall survival (OS) was 22.0 months (95% CI 20.4–not estimable). Overall, 67% of patients experienced grade ≥3 treatment-related adverse events. The present study reports extended follow-up survival analyses of Study 116 with updated data cutoff dates of August 7, 2020, and March 31, 2021 (about 9 and 17 additional months of follow-up from the primary analysis, respectively).

Materials and Methods

Study 116 procedures have been reported previously [11]. The open-label study had 2 phases: dose-limiting toxicity and expansion. This extended follow-up analysis reports data from the 100 patients who participated in the expansion phase (which included 2 patients from the dose-limiting toxicity phase). Eligible patients had uHCC; were stage B (not suitable for transarterial chemoembolization) or C per the Barcelona Clinic Liver Cancer staging system; had ≥1 measurable target lesion according to mRECIST per investigator assessment; and had a Child-Pugh class A score of 5–6, Eastern Cooperative Oncology Group performance status of 0 or 1, and no prior systemic therapy. Patients with gastric or esophageal bleeding varices, HCC with ≥50% liver occupation, clear invasion into the bile duct, or main portal vein invasion (Vp4) were excluded. Patients received lenvatinib based on body weight (if ≥60 kg, 12 mg; if <60 kg, 8 mg) orally once daily and pembrolizumab 200 mg intravenously on day 1 of a 21-day cycle. The primary endpoints were ORR and duration of response (DOR) by mRECIST and RECIST v1.1 per IIR.

The final IIR analysis (data cutoff date: August 7, 2020) assessed OS, ORR, and PFS (per RECIST v1.1), and ORR and PFS (per mRECIST). At an extended follow-up analysis (data cutoff date: March 31, 2021), OS, PFS, ORR, and DOR (per mRECIST by the investigator) were assessed. OS, PFS, and DOR were estimated using the Kaplan-Meier method. ORR was calculated with 95% CI using the Clopper-Pearson method. Additionally, landmark analyses of OS were conducted for patients alive at each respective landmark time and classified by patients' best responses (BRs) by 3 and 9 months after starting study treatment. BR was assessed on August 7, 2020 (per mRECIST and RECIST v1.1 by IIR) and on March 31, 2021 (per mRECIST by the investigator). Immunogenicity assessments including pembrolizumab antidrug antibodies (ADAs) and concentration were performed (data cutoff date: August 7, 2020).

This study was approved by each research site's Institutional Review Board or independent Ethics Committee; the name of the Ethics Committee at a leading recruitment site was UCLA Office of the Human Research Protection Program (approval number 17-000943-CR-00005). A list of participating sites is included in the online supplementary (for all online suppl. material, see https://doi.org/10.1159/000535154). Written informed consent was obtained from all patients.

Results

Patients

Baseline characteristics are summarized in Table 1. At the updated data cutoff date of March 31, 2021, median follow-up was 27.6 months, 38 (38%) patients were alive, and 10 (10%) patients were on study treatment. During the survival follow-up, most patients did not receive subsequent anticancer medication or undergo an anticancer procedure (additional details on patient procedures during the follow-up are in online suppl. Table 1).

Table 1. Baseline characteristics [11]

Characteristics	Lenvatinib + pembrolizumab (*N* = 100)
Age, years, median (range)	66.5 (47–86)
Sex, %	
Male	81
Female	19
Body weight, kg	
<60	19
≥60	81
Race, %	
White	51
Asian	28
Black/African American	2
Other	5
Missing	14
ECOG PS, %	
0	62
1	38
BCLC stage, %	
B	29
C	71
Patients with serum AFP level, %[a]	
<400 ng/mL	67
≥400 ng/mL	30
Patients with Child-Pugh score, %	
5	71
6	27
7[b]	2
Etiology, %[c]	
HBV	19
HCV	36
Alcohol	28
Other	22
Patients with macroscopic portal vein invasion and/or extrahepatic spread, %[d]	62
Patients with radiological presence of cirrhosis, %[e]	52
Patients with involved disease sites, %[d,f]	
Liver	93
Lung	18
Lymph node	30
Bone	10
Other	20
Number of involved disease sites per patient, %[d]	
1	46
2	41
≥3	13

AFP, alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus. [a]AFP measurements were missing for 3 patients. [b]These 2 patients had protocol deviations. [c]Based on the medical history, patients could be counted in multiple categories. [d]Per investigator assessment. [e]Per independent imaging review. [f]Patients could have had more than 1 involved disease site.

Efficacy

Results of the final IIR analysis (data cutoff date: August 7, 2020) are reported in the online supplementary material. At the later, updated, data cutoff date (March 31, 2021), ORR per mRECIST by the investigator assessment was 43.0% (95% CI 33.1–53.3), with 6 complete and 37 partial responses (Table 2; online suppl. Fig. 1). The median DOR was 17.1 months (95% CI 6.9–19.3),

Table 2. Summary of tumor response by mRECIST per investigator assessment

Characteristics	Lenvatinib + pembrolizumab (*N* = 100)
Best overall response, %	
CR	6
PR	37
SD	43
PD	7
Not evaluable[a]	7
ORR (CR + PR), % (95% CI)	43 (33.1–53.3)
Disease control rate (CR + PR + SD), % (95% CI)	86 (77.6–92.1)
Median duration of response, months (95% CI)	17.1 (6.9–19.3)
Duration of response range, months	2.7–31.0

CR, complete response; mRECIST, modified Response Evaluation Criteria In Solid Tumors; PD, progressive disease; PR, partial response; SD, stable disease. [a]Five patients had no postbaseline tumor assessments; 1 patient had ≥1 lesion that was not evaluable; and 1 patient was assessed as having SD at <5 weeks.

with the upper range of DOR exceeding 2.5 years (range, 2.7–31.0 months) (Table 2; online suppl. Fig. 2). The median PFS per mRECIST by investigator assessment was 9.3 months (95% CI 7.4–9.8); the median OS was 20.4 months (95% CI 14.4–25.9) (shown in Fig. 1). At 12 months, 64.9% of patients were alive; at 18 months, 53.7% of patients were alive. Results of all landmark analyses of OS, irrespective of RECIST (mRECIST vs. RECIST v1.1) or review (investigator vs. IIR), suggested an association between BR and OS (online suppl. Table 2; online suppl. Fig. 3).

Antidrug Antibody Status and Pembrolizumab Concentration

Of 79 patients who were evaluable for immunogenicity assessments, no patients had treatment-emergent ADAs. Three patients were ADA-positive prior to pembrolizumab administration; thus, they were nontreatment-emergent positive. The extent of pembrolizumab exposure was comparable for patients treated with the same regimen who were ADA-positive versus those who were ADA-negative (online suppl. Fig. 4).

Discussion

This extended follow-up analysis of Study 116/KEYNOTE-524 (median follow-up: 27.6 months; 17 months of additional follow-up from the primary analysis) continued to show deep and durable responses, with an ORR of 43% and median DOR of 17.1 months by mRECIST per investigator, a high disease control rate of 86%, and a low progressive disease rate of 7%. Compared with the 5 complete responses observed in the primary analysis [11], 1 additional complete response per mRECIST by investigator review was observed. The combination continued to show compelling PFS (mRECIST by the investigator review; median, 9.3 months) and OS (median, 20.4 months) benefits that were consistent with the original analysis (median PFS per mRECIST by investigator review, 8.2 months [95% CI 7.4–9.7]; median OS, 22.0 months [95% CI 20.4–not estimable]) [11]. OS results were similar to those obtained in the lenvatinib plus pembrolizumab arm of the phase 3 LEAP-002 study of lenvatinib plus pembrolizumab versus lenvatinib monotherapy in the first-line treatment of patients with advanced HCC (median OS, 21.2 months [95% CI 19.0–23.6]). Although the lenvatinib plus pembrolizumab arm of LEAP-002 yielded the longest median OS ever reported in a first-line phase 3 study of patients with HCC, the primary endpoints of LEAP-002 (OS and PFS) did not meet the prespecified statistical significance threshold [12]. Results of the landmark analyses of OS by BR at 3 and 9 months suggested an association between OS and BR regardless of landmark time, RECIST (mRECIST vs. RECIST v1.1), or review (investigator vs. IIR). Results of the landmark analysis at 9 months showed that median OS among patients with a complete or partial response was not reached. Notably, most patients did not receive subsequent anticancer medications or procedures; however, 4 out of 13 patients who completed 2 years of pembrolizumab treatment

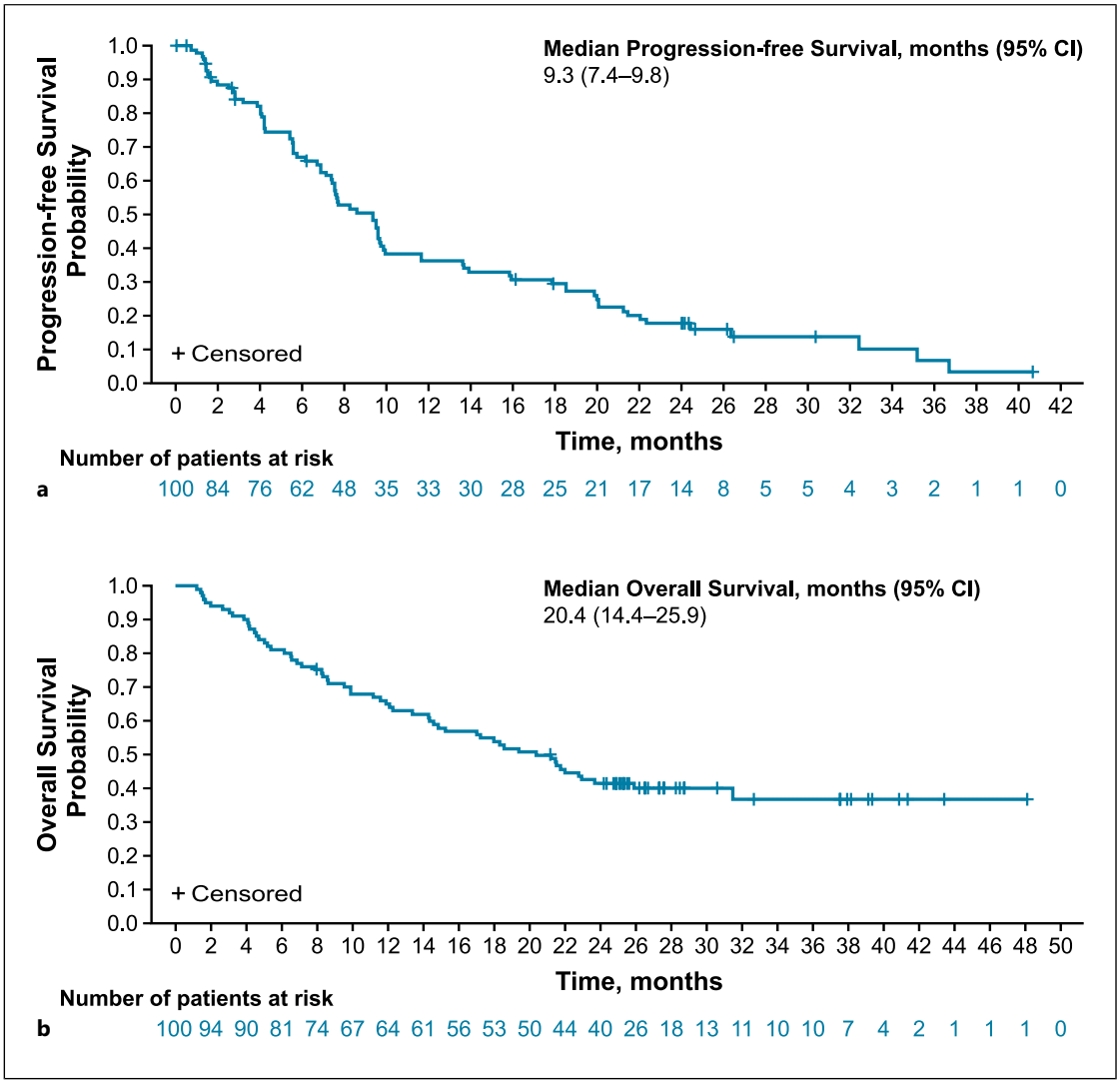

Fig. 1. Kaplan–Meier assessments of progression-free survival per mRECIST by the investigator assessment (**a**) and of OS (**b**). Median duration of follow-up: 27.6 months. mRECIST, modified Response Evaluation Criteria In Solid Tumors.

and continued in the study received retreatment with pembrolizumab upon disease progression, which was not counted as a second-line therapy because a pembrolizumab retreatment option was consistent with study procedures.

Consistent with the low immunogenicity of pembrolizumab [13] and other immune checkpoint inhibitor monotherapies [14, 15], lenvatinib plus pembrolizumab had limited potential to elicit the formation of ADAs. No treatment-emergent ADAs were detected, 3 patients had nontreatment-emergent ADAs, and, notably, none of them had antibodies with neutralizing capacity. Although Study 116 was limited by its single-arm design, results of our extended analysis (median follow-up: 27.6 months) demonstrate a sustained treatment effect with lenvatinib plus pembrolizumab in adult patients with uHCC who have not received prior systemic therapy.

Statement of Ethics

This study was approved by each research site's Institutional Review Board or independent Ethics Committee; the name of the Ethics Committee at a leading recruitment site was UCLA Office of the Human Research Protection Program (approval number: 17-000943-CR-00005). A list of participating sites is included in the supplement. Written informed consent was obtained from all patients.

Conflict of Interest Statement

Masatoshi Kudo: honoraria – Eli Lilly, Bayer, Eisai, Chugai, Takeda, and AstraZeneca; grant – Taiho, Otsuka, EA Pharma, AbbVie, Eisai, Chugai, and GE Healthcare; and advisory consulting – Chugai, Roche, Eisai, and AstraZeneca. Richard S. Finn: consulting or advisory role – Pfizer, Bayer, Novartis, Bristol Myers Squibb, Merck, Eisai, Lilly, Genentech/Roche, AstraZeneca, Exelixis, and C Stone Pharma; research funding – Pfizer (Inst), Bayer (Inst), Novartis (Inst), Eisai (Inst), Lilly (Inst), Merck (Inst), Bristol Myers Squibb (Inst), and Roche/Genentech (Inst); and expert testimony – Novartis. Masafumi Ikeda: honoraria – Abbott Japan, Bayer Yakuhin, Bristol Myers Squibb Japan, Chugai Pharma, Eisai, Lilly Japan, Novartis, Taiho Pharmaceutical, Teijin Pharma, Yakult, Nihon Servier, AstraZeneca, MSD, Takeda, Astellas Pharma, AbbVie, Fujifilm Toyama Chemical, EA Pharma, Ono Pharmaceutical, Incyte Biosciences Japan, and Taisho Pharmaceutical; consulting or advisory role – Eisai, Novartis, Lilly Japan, Chugai Pharma, Ono Pharmaceutical, AstraZeneca, Nihon Servier, Takeda, and GlaxoSmithKline; and research funding – AstraZeneca (Inst), Bayer Yakuhin (Inst), Bristol Myers Squibb (Inst), Chugai Pharma (Inst), Eisai, Lilly Japan (Inst), Merck Biopharma (Inst), Delta-Fly Pharma (Inst), Novartis (Inst), Ono Pharmaceutical (Inst), Yakult (Inst), MSD (Inst), J-Pharma (Inst), Takeda (Inst), Pfizer (Inst), Chiome Bioscience (Inst), Merus N.V. (Inst), Nihon Servier (Inst), and Syneos Health (Inst). Max W. Sung: honoraria – Genentech and Bayer. Ari D. Baron: speakers' bureau – Bristol Myers Squibb, Merck, Lilly, Amgen, Eisai, Johnson & Johnson, and AbbVie. Takuji Okusaka: honoraria – Meiji Seika Kaisha, Merck Sharp & Dohme, Shire, AbbVie, Eisai, Ono Pharmaceutical, Daiichi Sankyo, Taiho Pharmaceutical, Takeda Pharmaceuticals, Teijin Pharma, Lilly, Nippon Shinyaku, Servier, Novartis, Bayer, Pfizer, and Mundipharma; consulting or advisory role – Taiho Pharmaceutical, Daiichi Sankyo, Dainippon Sumitomo Pharma, Bristol Myers Squibb, AstraZeneca, and Eisai; research funding – Novartis (Inst), Eisai (Inst), Dainippon Sumitomo Pharma (Inst), Baxter (Inst), Lilly (Inst), Taiho Pharmaceutical (Inst), AstraZeneca (Inst), Chugai Pharma (Inst), Bristol Myers Squibb, and Merck Sharp & Dohme (Inst); and travel, accommodations, and expenses – Takara Bio. Masahiro Kobayashi: honoraria – Eisai Japan. Hiromitsu Kumada: honoraria – Merck Sharp & Dohme, Dainippon Sumitomo Pharma, AbbVie, Gilead Sciences, and Eisai. Shuichi Kaneko: honoraria – Merck Sharp & Dohme, Eisai, Gilead Sciences, Dainippon Sumitomo Pharma, Bayer, Bristol Myers Squibb, and Lilly; consulting or advisory role – Bayer, Merck Sharp & Dohme, Lilly, and Eisai; research funding – Merck Sharp & Dohme (Inst), Bayer (Inst), Chugai Pharma (Inst), and Eisai (Inst). Marc Pracht: consulting – BMS and Ipsen. Tim Meyer: consulting – Eisai, BMS, Adaptimmune, Ipsen, Roche, and AstraZeneca; grant funding – MSD. Satoshi Nagao, Kalgi Mody, and Zahra Ramji: employment – Eisai. Kenichi Saito: employment – Eisai; and patents, royalties, and other intellectual property – applying for patent for pharmaceutical composition. Leonid Dubrovsky: employment – Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Josep M. Llovet: research support – Eisai, Bristol Myers Squibb, Bayer Pharmaceuticals, Boehringer-Ingelheim, and Ipsen; and consultancy – Eisai, Merck, Bayer Pharmaceuticals, Bristol Myers Squibb, Celsion Corporation, Eli Lilly, Roche, Genentech, Ipsen, Glycotest, Nucleix, Biopharma, Sirtex, and AstraZeneca.

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Author Contributions

Conception and design: Kenichi Saito. Collection and assembly of data: Masatoshi Kudo, Max W. Sung, Tim Meyer, and Marc Pracht. Data analysis and interpretation: Masatoshi Kudo, Max W. Sung, and Kenichi Saito. Manuscript writing, final approval of manuscript, and accountable for all aspects of the work: Masatoshi Kudo, Richard S. Finn, Masafumi Ikeda, Max W. Sung, Ari D. Baron, Takuji Okusaka, Masahiro Kobayashi, Hiromitsu Kumada, Shuichi Kaneko, Marc Pracht, Tim Meyer, Satoshi Nagao, Kenichi Saito, Kalgi Mody, Zahra Ramji, Leonid Dubrovsky, and Josep M. Llovet.

Data Availability Statement

The data will not be available for sharing at this time because the data are commercially confidential. However, Eisai will consider written requests to share the data on a case-by-case basis. Inquiries can be directed to the corresponding author.

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