Lenvatinib plus pembrolizumab versus lenvatinib plus placebo for advanced hepatocellular carcinoma (LEAP-002): a randomised, double-blind, phase 3 trial

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Research in Context (322/350)

Evidence before this study

We searched PubMed from inception to January 31, 2023, to identify articles published in English for first-line systemic treatment options for unresectable hepatocellular carcinoma using the search terms ("hepatocellular carcinoma" OR "HCC") AND ("first-line" OR "untreated") AND "systemic" AND "treatment." Several treatment options for patients with advanced hepatocellular carcinoma have been evaluated and include sorafenib, lenvatinib, pembrolizumab, atezolizumab plus bevacizumab, durvalumab plus tremelimumab, and in China, donafenib, an oxaliplatin-based regimen, sintilimab plus a bevacizumab biosimilar (IBI305), and camrelizumab plus rivoceranib. Although treatments have evolved over time and survival outcomes have improved, many patients are unable to tolerate or are ineligible for these treatments, often because of existing conditions that may put them at higher risk of adverse events. Therefore, additional treatment options are needed.

Added value of this study

The LEAP-002 study suggested the activity of pembrolizumab added to lenvatinib when compared to lenvatinib alone in the first-line treatment of patients with advanced hepatocellular carcinoma but did not meet prespecified statistical significance superiority criteria for the dual primary endpoints overall survival and progression-free survival compared with lenvatinib plus placebo. Median overall survival observed with lenvatinib plus pembrolizumab was 21·2 months. Additionally, lenvatinib alone showed the longest overall survival reported for a single agent in this setting (median, 19·0 months), supporting it as a standard of care for patients treated with single agents in first-line hepatocellular carcinoma.

Implications of all the available evidence

Although lenvatinib plus pembrolizumab did not significantly improve overall survival and progression-free survival compared with lenvatinib plus placebo as a first-line therapy for advanced hepatocellular carcinoma, the study suggested the activity of pembrolizumab when added to lenvatinib compared to lenvatinib alone in patients with hepatocellular carcinoma, and underpins the importance of evaluating this treatment regimen in combination with chemoembolization in patients with intermediate stage hepatocellular carcinoma, such as in the ongoing phase 3 LEAP-012 study (lenvatinib plus pembrolizumab plus TACE *vs* TACE in intermediate stage HCC).

Abstract (519/300 words)

BACKGROUND: This study evaluated the addition of pembrolizumab to standard of care lenvatinib in the first-line setting for unresectable hepatocellular carcinoma.

METHODS: In this global, double-blind, phase 3 study, adults with unresectable hepatocellular carcinoma, Child Pugh class A liver disease, an Eastern Cooperative Oncology Group performance status of 0 or 1, and no prior systemic treatment were enroled. Patients were randomly assigned 1:1 using a central interactive voice-response system (block size of 4) to receive lenvatinib (body weight <60 kg, 8 mg/day; body weight ≥60 kg, 12 mg/day) plus pembrolizumab (200 mg every 3 weeks) or lenvatinib plus placebo. Randomisation was stratified by geographic region, macrovascular portal vein invasion or extrahepatic spread or both, α-fetoprotein level, and ECOG performance status. Dual primary endpoints were overall survival (superiority threshold at final overall survival analysis: 0·019, one-sided) and progression-free survival (superiority threshold: 0·002, one-sided) in the intention-to-treat population. Results from the final analysis are reported.

FINDINGS: Between January 17, 2019, and April 28, 2020, 794 patients (644 [81%] male, 150 [19%] female) were randomly assigned to lenvatinib plus pembrolizumab (n=395) or lenvatinib plus placebo (n=399). In this population, 345 (43%) were Asian, 345 (43%) were White, 22 (3%) were multiple races, 21 (3%) were American Indian/Alaska Native, 21 (3%) were Native Hawaiian/other Pacific Islander, 13 (2%) were Black/African American, and 46 (6%) did not have available race data; 683 (86%) were not Hispanic/Latino, 8 (11%) were Hispanic/Latino, and 13 (2%) were of unknown ethnicity. Median time from randomisation to data cutoff for final analysis (June 21, 2022) was 32·1 months (IQR 29·4–35·3). Median overall survival was 21·2 months (95% CI 19·0–23·6; 252 [64%] of 395 died) with lenvatinib

plus pembrolizumab versus 19·0 months (95% CI 17·2–21·7; 282 [71%] of 399 died) with lenvatinib plus placebo (hazard ratio, 0·84; 95% CI 0·71–1·00; stratified log-rank p=0·023). Median progression-free survival was 8·2 months (95% CI 6·4–8·4; 270 events occurred) with lenvatinib plus pembrolizumab versus 8·0 months (95% CI 6·3–8·2; 301 events occurred) with lenvatinib plus placebo (hazard ratio, 0·87; 95% CI 0·73–1·02; stratified log-rank p=0·047). The most common treatment-related grade 3/4 adverse events were hypertension (69 [17%] of 395 patients) and increased aspartate aminotransferase (27 [7%]) in the lenvatinib plus pembrolizumab group and hypertension (68 [17%] of 395 patients) in the lenvatinib plus placebo group. Treatment-related deaths occurred in 4 (1%) of 395 patients treated with lenvatinib plus pembrolizumab (due to gastrointestinal haemorrhage and hepatorenal syndrome, [n=1 each] and hepatic encephalopathy [n=2]) and in 3 (1%) of 399 patients treated with lenvatinib plus placebo (due to gastrointestinal haemorrhage, hepatorenal syndrome, and cerebrovascular accident [n=1 each]).

INTERPRETATION: Lenvatinib plus pembrolizumab did not meet prespecified statistical significance for improved overall survival and progression-free survival versus lenvatinib plus placebo as first-line therapy for advanced hepatocellular carcinoma. Results suggest the activity of pembrolizumab when added to lenvatinib compared to lenvatinib alone as seen in early studies but do not support a change in clinical practice.

FUNDING: Eisai Inc., Nutley, NJ, USA, and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Clinical Trial Registration: ClinicalTrials.gov; NCT03713593.

Introduction

Patients with hepatocellular carcinoma (HCC) are often diagnosed at advanced stages, and their life expectancy has improved with targeted and immune therapies.[1,2] Systemic therapies approved for first-line treatment of advanced HCC include monotherapy with the oral multikinase inhibitors sorafenib,[3] lenvatinib,[4] and donafenib (China only),[5] chemotherapy with an oxaliplatin-based regimen (China only),[6] and combination therapy with the anti–programmed death ligand 1 antibodies atezolizumab plus bevacizumab (anti–vascular endothelial growth factor antibody),[7] durvalumab plus tremelimumab (cytotoxic T lymphocyte–associated antigen 4 inhibitor),[8] sintilimab plus a bevacizumab biosimilar (IBI305; China only),[9]and camrelizumab plus rivoceranib (vascular endothelial growth factor receptor 2 inhibitor; China only).[10]

In the phase 3 REFLECT study, lenvatinib demonstrated non-inferiority compared with sorafenib in overall survival and a statistically significant clinically meaningful improvement in progression-free survival, time to progression, objective response, and delayed deterioration in quality-of-life in patients with previously untreated unresectable HCC.[4] Based on these results lenvatinib is included in treatment guidelines as a standard-of-care first-line treatment option for patients who are not candidates for atezolizumab and/or bevacizumab.[11,12] Pembrolizumab (anti–PD-1 antibody) received accelerated approval from the US Food and Drug Administration for patients with advanced HCC previously treated with sorafenib based on findings of the phase 2 KEYNOTE-224 study.[13] In KEYNOTE-240, pembrolizumab showed a favourable benefit-to-risk profile but narrowly missed prespecified statistical significance for overall survival and progression-free survival,[14] whereas a similar study, KEYNOTE-394, conducted in Asia significantly prolonged overall survival and progression-free survival.[15] Pembrolizumab also demonstrated durable antitumour activity

and promising overall survival in patients with advanced HCC in a front-line cohort of the KEYNOTE-224 study.[16]

Lenvatinib plus pembrolizumab showed promising antitumour activity in the first-line setting in the phase 1b Study 116/KEYNOTE-524, with an objective response rate of 36·0% (95% CI 26·6–46·2%) and median duration of response of 12·6 months per Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST v1.1) in patients with unresectable HCC.[17] In these patients, median overall survival of 22·0 months, median progression-free survival of 8·6 months, and manageable safety were also observed.[17] Additionally, this combination has demonstrated survival benefits in phase 3 studies in advanced renal cell carcinoma[18] and endometrial carcinoma.[19]

We conducted the LEAP-002 study to assess whether adding pembrolizumab to lenvatinib would improve efficacy versus lenvatinib alone in first-line therapy for advanced HCC and further define the safety of this combination.

Methods

STUDY DESIGN AND PARTICIPANTS

In this global, multicentre, double-blind, phase 3 study, patients were randomly assigned in a 1:1 ratio to receive lenvatinib plus pembrolizumab versus lenvatinib plus placebo. At the time of the study design, single-agent multikinase inhibitor therapy with sorafenib or lenvatinib was considered the standard of care for the first-line treatment of hepatocellular carcinoma. Eligible patients were 18 years of age or older, had histologically, cytologically, or radiographically confirmed HCC, measurable disease per RECIST v1.1 that was not

amenable to curative or loco-regional therapies or that had progressed thereafter, no prior systemic therapy for advanced disease, Child-Pugh class A liver disease,[20] Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1,[21] adequately controlled blood pressure, and oesophagogastroduodenoscopy within 3 months of randomisation. Patients were also eligible regardless of tumour liver volume or biliary tract invasion. Contraception was required; pregnant and breastfeeding participants were excluded from the study because of the fetotoxicity of lenvatinib. Key exclusion criteria included oesophageal or gastric variceal bleeding, main portal vein invasion, inferior vena cava involvement, or cardiac involvement of HCC based on imaging. Full eligibility criteria are provided in the Protocol (Section 5), available with the full text of this article.

The trial protocol and all amendments were approved by the appropriate institutional review boards or independent ethics committees at each study site. This study was conducted in accordance with the Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. Data were collected by the investigators and monitored by an independent, external data monitoring committee.

RANDOMISATION AND MASKING

Patients were enroled by delegated investigators. The funder randomly assigned patients (1:1) using a stratified permuted block randomisation sequence using SAS version 9.4 with a block size of 4 to receive lenvatinib plus pembrolizumab or lenvatinib plus placebo in a double-blind design. A randomisation list was generated using the funder's Clinical Schedule Generation System (CSGS) platform. Randomisation was performed centrally through an interactive response technology system (IXRS®3; Almac Clinical Technologies; Souderton, PA, USA) by assigning patients a randomisation number and treatment group from the

randomisation list based on the lowest available randomisation number within the patient's stratum. This was stratified by geographic region (Asia without Japan *vs* Western regions and Japan), macrovascular portal vein invasion or extrahepatic spread or both (yes *vs* no), α-fetoprotein level (≤400 *vs* >400 ng/mL), and ECOG performance status (0 *vs* 1). Allocation concealment was secured by an online system; investigators and trial protocol personnel did not have access to the randomisation list generated by the CSGS platform. All patients, investigators, and protocol personnel involved in study treatment administration or clinical evaluation of the patients were masked to the treatment group assignment. Pembrolizumab and placebo (normal saline) were packaged identically by a site pharmacist to maintain masking.

PROCEDURES

Patients received lenvatinib at a dose of 8 mg (body weight <60 kg) or 12 mg (body weight ≥60 kg), administered orally once daily, plus pembrolizumab at a dose of 200 mg or matching placebo, administered intravenously every 3 weeks. Patients received their assigned drugs for a maximum of 35 cycles (approximately 2 years) or until unacceptable toxicity occurred, or disease progression was radiographically documented and verified by blinded independent central review. An exception to continue assigned drugs after confirmed radiographic disease progression was made in patients who achieved clinically meaningful benefit after physicians consulted with the sponsor. There was no crossover between treatment groups after disease progression. Dose interruptions and reductions for lenvatinib treatment-related toxicity are described in table S1 of the appendix (p 12; further details in Section 6 of the Protocol), and details regarding discontinuation of study treatment are provided in the appendix (p 6; further details in Section 7 of the Protocol). No concurrent

anticancer therapies were permitted during the study. Subsequent anticancer therapies were allowed following discontinuation of study intervention.

Tumour imaging was assessed by computed tomography or magnetic resonance imaging at screening and every 9 weeks after randomisation. RECIST v1.1 by blinded independent central review was used for assessment of tumour response and disease progression. Survival status was ascertained every 12 weeks during the follow-up period. Adverse events were assessed every week during the first cycle, every 2 weeks during the second cycle, and then every cycle thereafter. Serious adverse events were reported within 24 hours of occurrence. Adverse events were monitored up to 90 days after the last dose or 30 days after the last dose for participants who initiated a new anticancer therapy. Severe adverse events were monitored up to 120 days after the last dose or 30 days after the last dose if the participant started a new antineoplastic therapy. Adverse events were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Clinically significant adverse events (CSAEs) are those associated with class effects and were identified based on a prespecified list of preferred terms maintained by Eisai and Merck & Co., Inc., Rahway, NJ, USA, to consistently characterise the safety of lenvatinib across the clinical programs (further details in Section 6 of the Protocol). Health-related quality-of-life questionnaires were administered before drug administration, adverse event evaluation, and disease status notification, at baseline, on day 1 of every subsequent treatment cycle up to cycle 10, and on day 1 of every second treatment cycle thereafter up to 1 year or end of treatment, whichever came first.

OUTCOMES

The dual primary endpoints were overall survival (the time from randomisation to death from any cause) and progression-free survival (the time from randomisation to disease progression per RECIST v1.1 by blinded independent central review, or death from any cause, whichever occurred first). Secondary endpoints included the objective response rate (percentage of patients with a confirmed complete or partial response), duration of response (the time from first documented complete or partial response to disease progression or death due to any cause, whichever occurs first), disease control rate (percentage of patients with a confirmed complete or partial response or stable disease after ⩾6 weeks), and time to progression (time from randomisation to first documented disease progression), all per RECIST v1.1 and HCC-specific modified RECIST (mRECIST)[22] by blinded independent central review, progression-free survival per mRECIST by blinded independent central review,[22] and safety. Exploratory endpoints included progression-free survival, objective response rate, duration of response, disease control rate, and time to progression per RECIST v1.1 and RECIST v1.1 modified for immune-based therapeutics (iRECIST) by investigator review. Analysis per iRECIST is not reported herein and will be reported at a later date. Assessment of health-related quality of life was included as an exploratory endpoint, and the results have been reported elsewhere.[23]

STATISTICAL ANALYSIS

Efficacy analysis was conducted in all randomly assigned patients (the intention-to-treat population). Safety analyses were conducted in all randomly assigned patients who received ≥1 dose of study treatment (all-participants-as-treated population). Immunogenicity status was analysed in all patients assigned to lenvatinib plus pembrolizumab who had a pre-dose anti–drug-antibody sample and at least one anti–drug-antibody sample available after treatment with pembrolizumab (n=312). Event rates over time were estimated using the

Kaplan-Meier method. The comparison of progression-free survival and overall survival for lenvatinib plus pembrolizumab versus lenvatinib plus placebo was performed using the stratified log-rank test. Hazard ratios were estimated using a stratified Cox regression model with the Efron method for handling ties. Percentage of patients with a confirmed complete or partial response was compared between treatment groups using the stratified Miettinen and Nurminen method.[24] All stratified analyses used the same factors applied for randomisation, with small strata pooled per prespecified rules. In total, 10 strata were used and are provided in the Protocol (Section 3), available with the full text of this article. Subgroup analyses of efficacy were prespecified. Prespecified subgroups were geographic region (Asia without Japan *vs* Japan and Western regions), macroscopic portal vein invasion or extrahepatic spread or both (yes *vs* no), α-fetoprotein level (≤400 *vs* >400 ng/mL), ECOG performance status (0 *vs* 1), age category (<65 *vs* ≥65 years), sex (female *vs* male), hepatitis C virus (HCV) aetiology (yes *vs* no), hepatitis B virus (HBV) aetiology (yes *vs* no), viral aetiology (yes *vs* no), macrovascular invasion (yes *vs* no), extrahepatic spread (yes *vs* no), overall BCLC stage (B *vs* C), and Child-Pugh score (5 *vs* 6). All prespecified subgroups were analysed, and no additional subgroups were included *post hoc*. No formal analyses of subgroups were performed; results were summarised descriptively.

Post hoc analysis of the immunogenicity of pembrolizumab was also performed. The presence of anti–drug antibody for pembrolizumab was assayed using a validated electrochemiluminescence immunoassay on the MesoScale Discovery platform, and details are provided in the appendix (p 6).

We estimated that a sample size of ~750 patients would provide 92% power to detect a hazard ratio of 0·70 at a one-sided 0·002 significance level with 571 events for progression-free survival and 90% power to detect a hazard ratio of 0·75 at a one-sided 0·023 significance level with 532 events for overall survival. Sample size calculations and assumptions of overall survival and progression-free survival superiority were based on preliminary objective response rate data from the first 30 patients enroled in the phase 1b single-arm KEYNOTE-524/Study 116 (NCT03006926).[17]

The protocol specified two interim analyses and a final analysis. The overall type I error (0·025) was strongly controlled using a graphic approach for multiplicity strategy[25] (figure S1 in the appendix [p 7]). The first interim analysis, second interim analysis, and final analysis of overall survival were planned to occur when ~335, ~452, and ~532 deaths accrued, respectively. The data monitoring committee reviewed unblinded data from the first interim analysis and the second interim analysis and recommended continuation of the study. The first interim analysis of overall survival was also the final analysis of progression-free survival because the prespecified number of progression-free survival events (571) was reached before the first interim analysis. The analysis of progression-free survival at the time of the final overall survival analysis was *post hoc*. The timing of analyses for secondary and exploratory endpoints that are not included in the multiplicity for Type I error control was not prespecified, and the analyses were performed at the final analysis. Overall survival superiority boundary was calculated using the Lan-DeMets O'Brien-Fleming spending function.

SAS version 9.4 was used for all statistical analyses. This trial is registered with ClinicalTrials.gov, NCT03713593.

ROLE OF THE FUNDING SOURCE

The academic authors and employees of Eisai Inc. and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (the study funders) participated in protocol design, data analysis and interpretation, and writing of this paper. The study sponsor maintained the study database. Editorial assistance was provided by a medical writer employed by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. All authors had access to the data and had final responsibility to submit this paper for publication. The data were verified by Josep M. Llovet, MD, Leonid Dubrovsky, MD, and Abby B. Siegel, MD.

Results

A total of 1309 patients were screened for enrolment. Between January 17, 2019, and April 28, 2020, 794 patients from 172 global sites were randomly assigned to lenvatinib plus pembrolizumab (n=395) or lenvatinib plus placebo (n=399) (figure 1). Median (IQR) time from randomisation to data cutoff for final analysis (June 21, 2022) was 32·1 (29·4–35·3) months. Baseline demographic and disease characteristics were generally balanced between the groups (table 1) and representative of patients in the first-line treatment setting of advanced HCC. Of the 794 patients enroled, 395 patients in each group received at least one dose of treatment. At the time of data cutoff, 36 (9%) of 395 patients in the lenvatinib plus pembrolizumab group and 24 (6%) of 395 patients in the lenvatinib plus placebo group were still receiving the assigned treatment. The primary reason for treatment discontinuation in any group was disease progression (figure 1). In the intention-to-treat population, 174 (44%) of 395 patients in the lenvatinib plus pembrolizumab group and 208 (52%) of 399 patients in the

lenvatinib plus placebo group had received at least one subsequent systemic anticancer therapy (table S2 in the appendix [p 13]).

As of the data cutoff date for the final analysis, 534 patients had died (lenvatinib plus pembrolizumab, 252; lenvatinib plus placebo, 282; hazard ratio for death 0·840; 95% CI 0·708–0·997, stratified log-rank p=0·023; superiority boundary of one-sided p=0·019 not crossed; figure 2A). The median overall survival for lenvatinib plus pembrolizumab was 21·2 months (95% CI 19·0–23·6) versus 19·0 months (95% CI 17·2–21·7) for lenvatinib plus placebo. Outcomes were generally consistent across prespecified subgroups (figure S3 in the appendix [p 9]).

At the first interim analysis, median (IQR) time from randomisation to data cutoff (April 5, 2021) was 17·6 (14·9–20·7) months. Median progression-free survival was 8·2 months (95% CI 6·4–8·4, 270 events occurred) with lenvatinib plus pembrolizumab versus 8·0 months (95% CI 6·3–8·2, 301 events occurred) with lenvatinib plus placebo, and the hazard ratio was 0·867 (95% CI 0·734–1·024, stratified log-rank p=0·047; superiority boundary of one-sided p=0·002 not crossed; figure S4 in the appendix [p 10]). At the final *post hoc* analysis of progression-free survival, the hazard ratio for progression-free survival was 0·834 (95% CI 0·712–0·978; 293 events occurred with lenvatinib plus pembrolizumab, and 336 events occurred with lenvatinib plus placebo) (figure 2B).

At final analysis, the confirmed objective response rate per RECIST v1.1 by blinded independent central review was 26% (103 of 395 patients) in the lenvatinib plus pembrolizumab group and 18% (70 of 399 patients) in the lenvatinib plus placebo group; the between-group difference was 8·5% (95% CI 2·8-14·2; nominal p=0·0018). The disease control rate was 81% (321 of 395 patients) in the lenvatinib plus pembrolizumab group and 78% (313 of 399 patients) in the lenvatinib plus placebo group. The median duration of

response was 16·6 months (range, 2·0+ to 33·6+) in the lenvatinib plus pembrolizumab group and 10·4 months (range, 1·9 to 35·1+) in the lenvatinib plus placebo group (plus signs in the ranges indicate no progressive disease at the time of the last disease assessment; figure S5A in the appendix [p 11]). Results for progression-free survival and objective response per RECIST v1.1 by investigator review were consistent with those by blinded independent central review (table 2). Response and duration of response per mRECIST are summarised in table 2 and figure S5B in the appendix (p 11).

The median (IQR) duration on therapy was 8·6 (4·2–18·0) months with lenvatinib plus pembrolizumab and 9·5 (4·4–15·9) months with lenvatinib plus placebo. Lenvatinib exposure is summarised in table S3 in the appendix (p 15). Median (IQR) relative dose intensity of lenvatinib as a percentage of planned starting dose was 81·2% (61·4–99·7) in the lenvatinib plus pembrolizumab group and 81·3% (61·9–98·4) in the lenvatinib plus placebo group. Lenvatinib dose reduction is summarised in table S4 in the appendix (p 16). Treatment-related adverse events occurred in 381 (96%) of the 395 patients in the lenvatinib plus pembrolizumab group and 378 (96%) of the 395 patients in the lenvatinib plus placebo group (grade 3/4, 62% [243 of 395] *vs* 57% [224 of 395]); grade 5 treatment-related adverse events occurred in 4 (1%) of 395 and 3 (1%) of 395 patients, respectively (tables 3 and S5 [appendix p 17]). The most common treatment-related adverse events in both groups were hypertension, diarrhoea, and hypothyroidism. The only grade 3/4 treatment-related adverse event that occurred in >10% of the patients was hypertension (17% [69 of 395 patients] in the lenvatinib plus pembrolizumab group and 17% [68 of 395] in the lenvatinib plus placebo group). Treatment-related serious adverse events occurred in 99 (25%) of the 395 patients in the lenvatinib plus pembrolizumab group and 65 (16%) of the 395 patients in the lenvatinib plus placebo group.

Common adverse events of any cause and those that led to death are summarised in tables S6 and S7 in the appendix (pp 18 and 19). Immune-mediated adverse events and infusion reactions are summarised in table S8 in the appendix (p 20) and are mostly grade 1/2 (grade 3/4, 9% [35 of 395 patients] *vs* 2% [9 of 395] for lenvatinib plus pembrolizumab *vs* lenvatinib plus placebo). CSAEs for lenvatinib are summarized in table S9 in the appendix (p 21). Systemic corticosteroid use for immune-mediated adverse events and infusion reactions was reported in 38 (10%) of 395 versus 7 (2%) of 395 patients, respectively.

Data on immunogenicity or anti–drug antibody for pembrolizumab were available in 312 patients in the lenvatinib plus pembrolizumab group. Treatment-emergent anti–drug-antibody positivity was observed in 8 (3%) of 312 patients (table S10 in the appendix [p 22]). One out of these 8 patients had antibodies with neutralizing capacity (treatment-emergent neutralizing antibody positivity, 0·3% [1 out of 312 patients]). No impact on pembrolizumab exposure by the presence of the anti–drug antibody was observed (figure S2 in the appendix [p 8]).

Discussion

The LEAP-002 study did not meet the prespecified significance boundary for superiority for the dual endpoints of overall survival and progression-free survival comparing lenvatinib plus pembrolizumab versus lenvatinib plus placebo in first-line advanced hepatocellular carcinoma. Nonetheless, the combination of lenvatinib and pembrolizumab achieved a median survival of 21·2 months whereas lenvatinib alone achieved a median overall survival of 19·0 months. Our results with lenvatinib plus pembrolizumab are consistent with those reported in the phase 1b Study 116/KEYNOTE-524.[17] Despite the encouraging survival

results for the combination, the lack of significant differences compared with lenvatinib plus placebo can have multiple explanations.

The lenvatinib plus placebo group showed longer survival than expected. In the only other phase 3 study with lenvatinib as a comparator group, the REFLECT study, the median overall survival was 13·6 months with lenvatinib.[4] Potential reasons include the long treatment duration and the substantial use of effective second-line therapies, which have evolved since the REFLECT study and the initiation of LEAP-002. Patients were on lenvatinib plus placebo for a median of 9·5 months, longer than in other studies using front-line multikinase inhibitors,[3,4,7,8] possibly reflecting the acquired experience of physicians in managing adverse events compared with earlier trials, such as in the REFLECT trial.[4] Moreover, unlike other open-label front-line phase 3 studies in advanced HCC, the longer exposure can also be associated with the double-blind design of LEAP-002. This design prevents a potential bias in treatment management versus an open-label trial design, which has been recognized as a common limitation in recent phase 3 studies.[7,8,26] Finally, ~50% of patients in the lenvatinib plus placebo group received second-line therapies (including 23% using immunotherapies), in contrast to the 39% of second-line therapies in REFLECT. Overall, the results of the control group provide a new benchmark for survival estimates when using single-agent molecular therapies for first-line advanced hepatocellular carcinoma. In this regard, although no cross-trial comparisons are recommended, contemporary phase 3 studies using sorafenib as a comparator and sharing similar patient inclusion criteria as LEAP-002 reported a median survival of 13·2-15·5 months.[7,8,26]

Tyrosine kinase inhibitors and monoclonal antibodies against vascular endothelial growth factor can transform immunological *cold* tumours into *hot* tumours, thus expanding the

patient population responding to checkpoint inhibitors because of distinct immunomodulatory effects.[27] Experimental studies have shown that this for the combination of lenvatinib and pembrolizumab in HCC as a result of enhancing the CD8 T-cell population in the tumour and decreasing the regulatory T-cell population.[28] In LEAP-002, although the objective response rate was 17·5% for lenvatinib alone and 26·1% when pembrolizumab was added, the survival curves started separating only beyond the first year, in contrast to the data with atezolizumab plus bevacizumab versus sorafenib.[7] Of particular interest in this mature data set is that the probability of survival was 39% and 31% at 30 months for the combination therapy and lenvatinib alone, respectively. Similarly, delayed separation of survival curves also occurred in the trial comparing tremelimumab plus durvalumab versus sorafenib in patients with unresectable HCC; however, significant differences between the groups were observed in that study.[8]

Our study found low levels of treatment-emergent anti–drug-antibody positivity, with no impact on pembrolizumab exposure, in contrast to the higher level of anti–drug-antibody positivity reported with the treatment of atezolizumab and bevacizumab in patients with advanced HCC, which was associated with poor clinical outcomes.[29] The incidence and severity of adverse events observed with lenvatinib and pembrolizumab were consistent with the known safety profile reported in our previous study.[17] In the combination group, 71 (18%) of 395 patients discontinued any study treatment because of treatment-related adverse events versus 42 (11%) of 395 patients in the lenvatinib plus placebo group. The higher incidence of discontinuations in the combination group may have been caused by the greater proportion of patients with treatment-related grade 3/4 adverse events (62% [243 of 395 patients] *vs* 57% [224 of 395], respectively) and treatment-related serious adverse events (25% [99 of 395] *vs* 16% [65 of 395], respectively) compared with the lenvatinib plus placebo group. Treatment-

related adverse events leading to lenvatinib drug reductions were similar between both groups. Immune-mediated adverse events were mostly of grade 1/2 severity. Limitations of the study include the lack of enrolment of patients with main portal vein invasion, which has been common in contemporary trials of hepatocellular carcinoma.[8,26] The LEAP-002 study excluded patients with Vp4 main portal vein invasion, a well-known prognostic factor. These criteria are very common in most phase 3 trials for advanced HCC, such as REFLECT,[4] HIMALAYA,[8] RATIONALE-301,[30] and SHR-1210-III-310,[10] and may have implications for better outcome in patients in these studies. Additionally, the proportion of patients with macrovascular portal vein invasion in LEAP-002 was relatively low compared with the REFLECT[4] and HIMALAYA[8] studies and may have impacted the study results.

In conclusion, the LEAP-002 study did not reach prespecified statistical significance criteria for improving overall survival and progression-free survival with lenvatinib plus pembrolizumab versus lenvatinib plus placebo as first-line therapy for advanced hepatocellular carcinoma. The study suggests the activity of the addition of pembrolizumab to lenvatinib when compared to lenvatinib alone as seen in early studies, and the ongoing phase 3 LEAP-012 study is evaluating this regimen in combination with chemoembolization in patients with the intermediate stage of the disease. Lenvatinib led to a median survival that supports this therapy as a guideline-endorsed standard of care[11,12] for patients treated with single agents in first-line hepatocellular carcinoma.

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Declaration of Interests

JML reports serving in a consulting or advisory role for AstraZeneca, Bayer HealthCare Pharmaceuticals, Bluejay, Boston Scientific, Bristol Myers Squibb, Captor Therapeutics, Eisai Inc, Exelixis, Genentech, Glycotest, Ipsen, Eli Lilly, Merck, MiNA Alpha, and Omega Therapeutics; receiving research funding paid to his institution from Bayer Pharmaceuticals, Bristol Myers Squibb, Eisai Inc, and Ipsen.

MK reports receiving honoraria from Bayer, Chugai/Roche, Eisai, Lilly Japan, Takeda and receiving research funding paid to his institution from AbbVie, Chugai/Roche, EA Pharma, Eisai, GE Healthcare, Otsuka, and Taiho Pharmaceutical.

PM reports serving in a consulting or advisory role for AstraZeneca, Bayer, Bristol Myers Squibb, Eisai, MSD, and Roche and receiving research funding from Ipsen.

TM reports serving in a consulting or advisory role for Bayer, Beigene, BTG, Eisai, Ipsen, MSD, and Roche and receiving research funding from Bayer, BTG, and Ipsen.

SQ has no disclosures to report.

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ABS is an employee of, has stock and other ownership interests in, and has received travel, accommodations, and expenses from Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

RSF reports serving in a consulting or advisory role for AstraZeneca, Bayer, Bristol Myers Squibb, CStone Pharmaceuticals, Eisai, Exelixis, Genentech/Roche, Hengrui Therapeutics, Lilly, Merck, Novartis, Pfizer; reports receiving research funding paid to his institution from Bayer, Bristol Myers Squibb, Eisai, Lilly, Merck, Novartis, Pfizer, Roche/Genentech; and providing expert testimony for Bayer.

Contributors

JML, TM, MI, B-YR, GM, HYL, KM, CD, SQ, PRG, and M Kudo were involved in the conceptualisation of the study. B-YR, HYL, CD, and M Kudo were involved with the data curation. Formal analysis was conducted by HYL, AW, and SQ. TM, JE, B-YR, HYL, JHK, VB, A-LC, KM, CD, LD, SQ, and M Kudo were involved in the investigation process. TM, MI, B-YR, and KM developed/designed the methodology. MI, HYL, and M Kudo were involved with the project administration. TM, JE, GM, HYL, JHK, A-LC, KM, and M Kudo provided study resources. TM, LD, and PRG provided supervision. B-YR, GM, HYL, and A-LC provided validation. HYL, KM, and M Kudo provided visualisation. JML and LD were involved drafting the manuscript. JML, TM, MI, JE, B-YR, GM, HYL, JHK, VB, A-LC, SQ, PRG, and M Kudo critically reviewed and edited the manuscript. All authors reviewed the final version of the manuscript to be submitted and agree with its content and submission. All authors had access to all the relevant study data and related analyses and vouch for the completeness and accuracy of the data presented. JML, HYL, LD, and ABS verified the data. JML had final responsibility for the decision to submit this manuscript for publication.

Data Sharing

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD), is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

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Figure Legends

Figure 1. Patient disposition in LEAP-002

Figure 2. Kaplan–Meier analysis of overall and progression-free survival at final analysis.
Kaplan–Meier estimates of overall survival (A) and progression-free survival per RECIST v1.1 by blinded independent central review (B) in the two treatment groups at the final analysis. Tick marks in Panel A indicate censoring of data. [a]Did not reach superiority threshold, one-sided α=0·019 using the stratified log-rank test. There was no statistical testing of progression-free survival at final analysis. Final analysis of progression-free survival was a post hoc *analysis.*