# Nivolumab plus ipilimumab versus lenvatinib or sorafenib as first-line treatment for unresectable hepatocellular carcinoma (CheckMate 9DW): an open-label, randomised, phase 3 trial

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## Summary

**Background** Patients with unresectable hepatocellular carcinoma have a poor prognosis, and treatments with long-term benefits are needed. We report results from the preplanned interim analysis of the CheckMate 9DW trial assessing nivolumab plus ipilimumab versus lenvatinib or sorafenib for unresectable hepatocellular carcinoma in the first-line setting.

**Methods** This open-label, randomised, phase 3 trial enrolled patients aged 18 years or older with unresectable hepatocellular carcinoma without previous systemic therapy at 163 hospitals and cancer centres across 25 countries in Asia, Australia, Europe, North America, and South America. Patients had at least one measurable untreated lesion per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, a Child–Pugh score of 5 or 6, and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were randomly assigned (1:1) via an interactive response technology system to receive nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) intravenously every 3 weeks for up to four doses, followed by nivolumab 480 mg every 4 weeks or investigator's choice of either oral lenvatinib (8 mg or 12 mg mg daily depending on bodyweight) or oral sorafenib (400 mg twice daily). Randomisation was stratified by aetiology; the presence of macrovascular invasion, extrahepatic spread, or both; and baseline alpha-fetoprotein concentration. The primary endpoint was overall survival, which was assessed in all randomly assigned patients; safety was an exploratory endpoint and was assessed in all randomly assigned patients who received at least one dose of study medication. This trial is registered with ClinicalTrials.gov, NCT04039607 (ongoing).

**Findings** Between Jan 6, 2020, and Nov 8, 2021, 668 patients were randomly assigned to nivolumab plus ipilimumab (n=335) or lenvatinib or sorafenib (n=333). Early crossing of the overall survival Kaplan–Meier curves reflected a higher number of deaths during the first 6 months after randomisation with nivolumab plus ipilimumab (hazard ratio 1·65 [95% CI 1·12–2·43]) but was followed by a sustained separation of the curves thereafter in favour of nivolumab plus ipilimumab (0·61 [0·48–0·77]). After a median follow-up of 35·2 months (IQR 31·1–39·9), overall survival was significantly improved with nivolumab plus ipilimumab versus lenvatinib or sorafenib (median 23·7 months [95% CI 18·8–29·4] vs 20·6 months [17·5–22·5]; hazard ratio 0·79 [0·65–0·96]; two-sided stratified log-rank p=0·018); respective overall survival rates were 49% (95% CI 44–55) versus 39% (34–45) at 24 months and 38% (32–43) versus 24% (19–30) at 36 months. Overall, 137 (41%) of 332 patients receiving nivolumab plus ipilimumab and 138 (42%) of 325 patients receiving lenvatinib or sorafenib had grade 3–4 treatment-related adverse events. 12 deaths were attributed to treatment with nivolumab plus ipilimumab and three were attributed to treatment with lenvatinib or sorafenib.

**Interpretation** Nivolumab plus ipilimumab showed a significant overall survival benefit versus lenvatinib or sorafenib and manageable safety in patients with previously untreated unresectable hepatocellular carcinoma. These results support nivolumab plus ipilimumab as a first-line treatment in this setting.

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## Introduction

Liver cancer is the sixth most common cancer and the third leading cause of cancer-related death worldwide, accounting for almost 800 000 deaths in 2022; globally, new cases per year are predicted to increase by 55% between 2020 and 2040.[1–3] Hepatocellular carcinoma accounts for 75–85% of cases of liver cancer; the 5-year survival rate for advanced disease has typically been

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## Research in context

### Evidence before this study

We searched PubMed for randomised controlled trials published between Oct 24, 2019, and Oct 21, 2024, using the terms "unresectable hepatocellular carcinoma" OR "advanced hepatocellular carcinoma" AND "phase 3" OR "phase III" in the title or abstract. No language restriction was applied. Among the identified randomised phase 3 studies of unresectable or advanced hepatocellular carcinoma in the first-line setting, the investigated systemic treatments included immunotherapy alone (nivolumab in CheckMate 459 and tislelizumab in RATIONALE-301), immunotherapy combined with anti-angiogenic therapy (atezolizumab plus bevacizumab in IMbrave150 and camrelizumab plus rivoceranib in CARES-310), immunotherapy combined with targeted agents (atezolizumab plus cabozantinib in COSMIC-312 and pembrolizumab plus lenvatinib in LEAP-002), and dual immunotherapy regimens (durvalumab plus tremelimumab in HIMALAYA). The comparator group in all phase 3 studies was sorafenib, with the exception of one that had lenvatinib as the comparator (LEAP-002). Additionally, IMbrave152/SKYSCRAPER-14 (NCT05904886) is currently recruiting patients to assess the efficacy of the atezolizumab, bevacizumab, and tiragolumab combination versus atezolizumab plus bevacizumab plus placebo. TRIPLET HCC (NCT05665348) is also currently recruiting patients to assess the effectiveness of adding ipilimumab to the combination atezolizumab plus bevacizumab versus atezolizumab plus bevacizumab alone. Although some of these treatments have shown improved efficacy compared with single-agent tyrosine kinase inhibitors (sorafenib or lenvatinib), responsiveness to treatment, long-term benefit, and safety and tolerability are suboptimal, and therefore additional treatment options are needed. In the phase 2 CheckMate 040 trial, nivolumab plus ipilimumab showed long-term efficacy and manageable safety in patients with advanced hepatocellular carcinoma previously treated with sorafenib, providing the rationale to investigate this treatment in the first-line setting.

### Added value of this study

The CheckMate 9DW trial met the primary endpoint of overall survival for nivolumab plus ipilimumab versus lenvatinib or sorafenib in the first-line setting for patients with unresectable hepatocellular carcinoma. To our knowledge, the median overall survival of 23·7 months in the nivolumab plus ipilimumab group, along with overall survival rates of 49% at 24 months and 38% at 36 months, are the longest and highest reported for the approved systemic treatments in this setting. Additionally, CheckMate 9DW is the first trial to show improved overall survival with an immunotherapy-based regimen versus both lenvatinib and sorafenib individually. Nivolumab plus ipilimumab also showed a higher objective response rate by blinded independent central review versus lenvatinib or sorafenib (36% vs 13%) and durable responses (median duration of response 30·4 months vs 12·9 months). Additionally, many patients receiving nivolumab plus ipilimumab remained in response after discontinuing treatment, with 47% of responders having an ongoing response at 36 months. The regimen had a manageable safety profile, and no new safety concerns were identified. These results are consistent with previous findings for this treatment in the second-line setting.

### Implications of all the available evidence

In CheckMate 9DW, nivolumab plus ipilimumab showed a significant survival benefit over lenvatinib or sorafenib as first-line treatment in patients with unresectable hepatocellular carcinoma. The safety profile was manageable and consistent with that previously reported for the regimen in second-line hepatocellular carcinoma and for other indications, with no new safety concerns. These results support nivolumab plus ipilimumab as a first-line treatment option for patients with unresectable hepatocellular carcinoma.

below 5%.[2,4] Multikinase inhibitors, including sorafenib and lenvatinib, are first-line treatment options for patients with unresectable hepatocellular carcinoma; however, they provide modest improvements in median overall survival (ranging from 12 months to 14 months), along with unsatisfactory safety outcomes.[5,6] PD-L1 inhibitor-based regimens received approvals in 2020 (atezolizumab plus bevacizumab) and 2022 (tremelimumab plus durvalumab) as first-line treatment options for unresectable hepatocellular carcinoma after showing improved outcomes over sorafenib, with median overall survival ranging from 16 months to 19 months.[7–10] The response rate was 20% with durvalumab plus tremelimumab and 30% with atezolizumab plus bevacizumab, with median duration of response ranging from 18 months to 22 months.[7–10] Despite these advances in the past 5 years, the long-term prognosis for patients with unresectable hepatocellular

carcinoma remains poor, and there is a need for alternative therapies.

Nivolumab, a PD-1 inhibitor, in combination with ipilimumab, a CTLA-4 inhibitor, has shown favourable efficacy outcomes and manageable safety profiles across multiple tumour types.[11–15] In the phase 2 CheckMate 040 trial, nivolumab plus ipilimumab showed long-term efficacy and manageable safety in patients with advanced hepatocellular carcinoma previously treated with sorafenib, leading to accelerated approval in the USA in this population.[14,15] Conversely, monotherapy with nivolumab in CheckMate 459[16] and tislelizumab, another PD-1 inhibitor, in RATIONALE-301[17] did not show overall survival benefits versus sorafenib as first-line treatments for advanced or unresectable hepatocellular carcinoma.

We report the results from the preplanned interim analysis of CheckMate 9DW, which is evaluating the efficacy and safety of nivolumab plus ipilimumab versus

investigator's choice of lenvatinib or sorafenib as first-line systemic therapy for patients with unresectable hepatocellular carcinoma.

## Methods

### Study design and participants

In this open-label, randomised, phase 3 trial, patients were enrolled at 163 hospitals and cancer centres across 25 countries in Asia, Australia, Europe, North America, and South America (listed in the appendix p 3). We recruited adult patients (aged ≥18 years) with histologically confirmed advanced hepatocellular carcinoma, defined as either not eligible for curative surgical or locoregional therapy or having progressed after surgical or locoregional therapy. Patients had not received previous systemic therapy for advanced hepatocellular carcinoma; had at least one measurable untreated lesion per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1; a Child–Pugh score of 5 or 6; and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were excluded from the study if they had known fibrolamellar hepatocellular carcinoma, sarcomatoid hepatocellular carcinoma, or mixed cholangiocarcinoma and hepatocellular carcinoma; previous liver transplant; episodes of hepatic encephalopathy (grade ≥2) within 12 months before randomisation; or clinically significant ascites. Patients with main portal vein invasion (Vp4) and active co-infection with both hepatitis B virus (HBV) and hepatitis C virus (HCV) or both HBV and hepatitis D virus were also excluded. Full eligibility criteria are listed in the protocol (appendix pp 116–123). Sex data were self-reported by the trial participants, with male or female options provided for participant's sex at birth.

CheckMate 9DW was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and the principles of the Declaration of Helsinki. The protocol was approved by the institutional review board or independent ethics committee at each site (listed in the appendix pp 4–21). All patients provided written informed consent. An independent data monitoring committee provided trial oversight. During the study, compliance with the protocol and Good Clinical Practice was reviewed by the site monitors on an ongoing basis; relevant protocol deviations were defined as deviations that might substantially affect the completeness, accuracy, and reliability of the study data or that might substantially affect a participant's rights, safety, or wellbeing. Between April 1, 2019, and Feb 1, 2023, two protocol amendments were made, which included changes in the statistical assumptions to preserve study power with the increased number of events. Full details of the revisions are available in the protocol (appendix pp 50–53). This trial is registered with ClinicalTrials.gov, NCT04039607.

### Randomisation and masking

CheckMate 9DW is an open-label trial; however, patients were randomly assigned (1:1) to receive nivolumab plus ipilimumab followed by nivolumab monotherapy or investigator's choice of lenvatinib or sorafenib via an interactive response technology system. The Bristol Myers Squibb (Princeton, NJ, USA) interactive response technology group created the computer-generated randomisation schedule; study investigators screened patients at each site and an interactive response system was used to complete the random assignment to trial groups. Patients were stratified according to aetiology (HBV *vs* HCV *vs* uninfected); macrovascular invasion, extrahepatic spread, or both (present *vs* absent); and baseline alpha-fetoprotein concentration (<400 ng/mL *vs* ≥400 ng/mL). Randomisation was done via permuted blocks within each stratum using a block size of four.

See **Online** for appendix

### Procedures

Patients received nivolumab 1 mg/kg and ipilimumab 3 mg/kg intravenously every 3 weeks for up to four doses, followed by nivolumab 480 mg monotherapy every 4 weeks, or lenvatinib 8 mg daily (if bodyweight was <60 kg) or 12 mg daily (if bodyweight was ≥60 kg) or sorafenib 400 mg twice a day orally. Treatments continued until disease progression (treatment beyond progression was allowed after assessment of clinical benefit by an investigator), unacceptable toxicity, withdrawal of consent (applicable to both treatment groups), or a maximum of 2 years (applicable to nivolumab plus ipilimumab only). A minimum of one dose of nivolumab plus ipilimumab was required before proceeding to nivolumab monotherapy; patients experiencing adverse events related to nivolumab plus ipilimumab combination therapy that did not meet treatment discontinuation criteria were allowed to proceed to nivolumab monotherapy dosing without completing all four combination doses on a case-by-case basis. No dose escalations or reductions were allowed for nivolumab or ipilimumab. Dose reductions were allowed for lenvatinib or sorafenib for the management of suspected adverse treatment reactions. Dose delays were permitted for nivolumab, ipilimumab, or both due to adverse events. Patients receiving nivolumab plus ipilimumab who had treatment-related toxicities that met the criteria for dose delay had both nivolumab and ipilimumab delayed until retreatment criteria were met, regardless of whether the event was attributed to only one of the treatments (nivolumab or ipilimumab). Lenvatinib or sorafenib dose reduction or interruption was based on instructions in the approved product label and were considered for any severe or intolerable drug-related adverse events. Before resuming therapy after a dose interruption, criteria for dose reduction or discontinuation were considered and applied in accordance with the summary of product characteristics or locally approved product label information. Tumour assessments for all participants continued per protocol even if dosing was delayed or

interrupted. Additional details on dose modification criteria are in the protocol (appendix pp 128–137).

Tumour assessments were done by contrast-enhanced CT of the chest and CT or MRI of the abdomen and pelvis, including required triphasic CT or MRI of the liver, and all other known or suspected sites of disease. Baseline tumour assessments were performed within 28 days before randomisation. Patients were evaluated for tumour response 9 weeks (±1 week) from the date of randomisation, at week 16 (±1 week), and every 8 weeks (±1 week) up to 48 weeks, then every 12 weeks (±1 week) until disease progression (unless treatment beyond progressive disease was permitted), treatment discontinuation (including treatment beyond progressive disease), or initiation of subsequent therapy, whichever occurred later. Change in tumour measurements and tumour response to guide ongoing study treatment decisions were assessed by the investigator using RECIST version 1.1. For assessment of PD-L1 expression status, fresh or archived formalin-fixed, paraffin-embedded tissue sections were stained for PD-L1 using PD-L1 IHC 28-8 pharmDx assay (Agilent/Dako, Santa Clara, CA, USA) and designated a combined positive score (CPS). The PD-L1 CPS was defined as the number of PD-L1 staining cells (tumour cells, lymphocytes, and macrophages) divided by the total number of viable tumour cells, multiplied by 100.

## Outcomes

The primary endpoint was overall survival. Overall survival was defined as the time from randomisation to the date of death due to any cause. Patients who were alive were censored at the last known alive dates. Overall survival was censored at the date of randomisation for patients who were randomly assigned but had no follow-up.

Secondary endpoints were objective response rate, duration of response, and time to symptom deterioration. Objective response rate was defined as the proportion of patients whose best overall response was either a confirmed complete response or a partial response per blinded independent central review (BICR) using RECIST version 1.1. Best overall response was defined as the best response designation recorded between the date of randomisation and the date of first objectively documented progression or the date of subsequent anticancer therapy, whichever occurred first. Duration of response was defined as the time between the date of first confirmed documented response of complete response or partial response and the date of the first documented tumour progression or death due to any cause, whichever occurred first. Patients who started any subsequent anticancer therapy without a previous reported progression were censored at the last evaluable tumour assessment before initiation of the subsequent anticancer therapy. Patients who died without a reported previous progression were considered to have progressed

on the date of their death. Patients who did not progress or died were censored on the date of their last evaluable tumour assessment. Time to symptom deterioration was defined as the time from randomisation until a clinically meaningful decline (at least a 6-point decrease from baseline) in the hepatobiliary cancer subscale (HCS) score of the Functional Assessment of Cancer Therapy Hepatobiliary Cancer (FACT-Hep). Patients who did not deteriorate were censored at the time of their last valid HCS score. Patients without a valid HCS score at baseline or who were never treated were censored on the randomisation date. Death or disease progression were not included as symptom deterioration events in these analyses. Additional details on FACT-Hep assessments are in the appendix (p 22).

Key prespecified exploratory endpoints included safety; progression-free survival and time to response per BICR and by investigator assessment using RECIST version 1.1; objective response rate and progression-free survival on next-line therapy by investigator assessment; health-related quality of life, as measured with the FACT-Hep and EQ-5D-3L; and influence of PD-L1 on overall survival. Progression-free survival was defined as the time from randomisation to the first documented disease progression or death due to any cause, whichever occurred first. Patients who received subsequent anticancer therapy before documented progression or death were censored at the date of the last evaluable tumour assessment conducted on or before the date of initiation of the subsequent anticancer therapy. Patients who did not have any evaluable on-study tumour assessments and did not die were censored on the randomisation date. Patients who did not progress or die were censored on the date of their last evaluable tumour assessment. Progression-free survival on next-line therapy was defined as the time from randomisation to documented progression, per investigator assessment, after the next-line therapy (ie, subsequent systemic anti-cancer therapy), to death from any cause, or to the start of second next-line systemic therapy, whichever occurred first. Patients who were alive and without progression after the next-line therapy were censored at last known alive date. Patients who had disease progression after the start of subsequent systemic anti-cancer therapy were considered as having the event on the date of the disease progression. Time to response was defined as the time from randomisation to the date of the first confirmed complete response or partial response. Supporting prespecified exploratory analyses were performed in the context of violation of the proportional hazard assumption (the unstratified MaxCombo test, the restricted mean survival time [different timepoints were explored post hoc], and the piecewise hazard ratio [HR]). The unstratified MaxCombo test was applied to estimate the difference in overall survival between treatment groups, the restricted mean survival time represents the area under the overall survival curve for each treatment

group, and the optimal cutoff timepoint for piecewise HR was determined using a grid of possible timepoints from 1 to minimum follow-up and obtained by maximising the partial log likelihood. Additional details on prespecified exploratory endpoints are in the appendix (p 22).

For assessment of safety, all adverse events were continuously assessed during the treatment period and for a minimum of 100 days following discontinuation of study treatment. Adverse events were defined and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0). Immune-mediated adverse events were defined as events consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory aetiologies have been ruled out.

The influence of baseline demographic and clinical characteristics on overall survival was assessed by exploratory subgroup analyses in all randomly assigned patients. Subgroups are described in the statistical analysis plan (appendix p 273) and included standard demographics and stratification factors (age, sex, region, baseline ECOG performance status, Child–Pugh score, aetiology, macrovascular invasion, extrahepatic spread, and baseline alpha-fetoprotein concentration, PD-L1 CPS, and baseline Barcelona Clinic Liver Cancer category). Full details on endpoints for the CheckMate 9DW trial are provided in the protocol (appendix pp 101–102).

### Statistical analysis

Sample size determination was based on overall survival comparison between groups. It was estimated that 650 patients randomly assigned in a 1:1 ratio and followed up until at least 520 overall survival events would provide approximately 87% power for an average HR of 0·74 with an overall two-sided type I error of 0·05. The interim analysis was planned when at least 416 overall survival events were observed (80%). Alpha allocation for the interim and final analyses was based on the Lan–DeMets alpha spending function approach using an O'Brien–Fleming stopping boundary controlling for a two-sided overall type I error of 0·05. For overall survival, distribution was compared in the two randomised treatment groups via a two-sided, stratified log-rank test. HRs and corresponding 95% CIs were estimated in stratified Cox proportional hazards models using randomised treatment group as a single covariate. Medians were estimated using Kaplan–Meier methods, and 95% CIs were calculated using a log–log transformation method. A competing risk analysis was conducted post hoc to show death occurring over time due to various causes. Specifically, a cumulative incidence function was used to estimate the probability of a specific cause or multiple causes of death over time, considering the deaths due to other reasons as competing events. The HR is estimated from the Fine and Gray subdistribution hazard model.

Overall survival, objective response rate, time to symptom deterioration, the unstratified MaxCombo test, the restricted mean survival time, piecewise HR, progression-free survival, and progression-free survival on next-line therapy were assessed in all randomly assigned patients. Duration of response, based on Kaplan–Meier estimates, and time to response, summarised using descriptive statistics, were assessed in patients with a confirmed complete or partial response. The objective response rate was compared between the two randomised groups using a two-sided Cochran–Mantel–Haenszel test, stratified by the stratification factors; two-sided 95% CIs were calculated based on the Clopper and Pearson method. Maximum change from baseline in the sum of diameters of target lesions (based on an evaluation of target lesions at baseline and at least one on-study assessment of all baseline target lesions) was assessed by aetiology in response-evaluable patients. Safety was assessed in all randomly assigned patients who received at least one dose of study medication.

Additional details of the statistical analysis, including those related to the prespecified hierarchical testing procedures and boundaries for statistical significance, are provided in the appendix (pp 22–23, the protocol [pp 163–167], and the statistical analysis plan [pp 230–304]).

Statistical analyses were performed using SAS software (version 9.4).

### Role of the funding source

The funder of the study provided the trial agents and collaborated with the academic authors on the trial design and on the collection, analysis, and interpretation of the data. Medical writing support, including development of the first draft of the manuscript under the guidance of the authors, was funded by the funder.

### Results

Between Jan 6, 2020, and Nov 8, 2021, 668 patients were randomly assigned to receive nivolumab plus ipilimumab (335 patients) or lenvatinib or sorafenib (333 patients; figure 1). Of these patients, 657 were treated (332 in the nivolumab plus ipilimumab group and 325 in the lenvatinib or sorafenib group); among the 325 patients treated with lenvatinib or sorafenib, 275 (85%) received lenvatinib and 50 (15%) received sorafenib. A summary of relevant protocol deviations is provided in the appendix (p 24). At clinical cutoff (Jan 31, 2024), all 332 (100%) treated patients in the nivolumab plus ipilimumab group and 310 (95%) of 325 treated patients in the lenvatinib or sorafenib group had discontinued study treatment; overall, 133 (40%) of 332 treated patients versus 224 (69%) of 325 treated patients discontinued study treatment due to disease progression (figure 1). Baseline characteristics are shown in table 1.

With a median follow-up of 35·2 months (IQR 31·1–39·9), nivolumab plus ipilimumab showed a
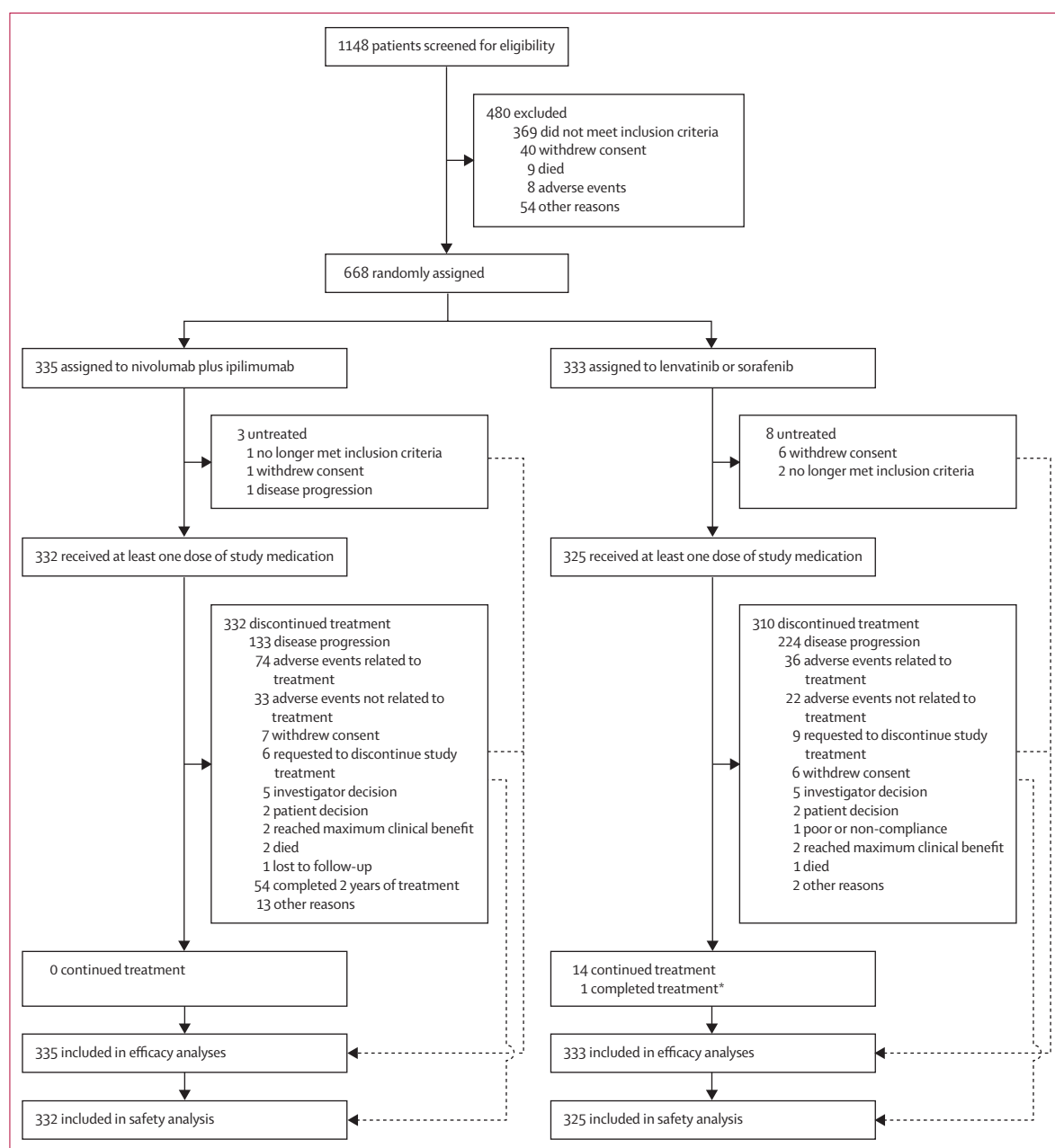
**Figure 1: Trial profile**
*Reported as "treatment completed" due to Russia's exit from the trial.

significant improvement in overall survival versus lenvatinib or sorafenib (23·7 months [95% CI 18·8–29·4] vs 20·6 months [17·5–22·5]; HR 0·79 [95% CI 0·65–0·96], two-sided stratified log-rank p=0·018; figure 2). Overall survival at 24 months was 49% (95% CI 44–55) with nivolumab plus ipilimumab versus 39% (34–45) with lenvatinib or sorafenib; 36-month overall survival was 38% (32–43) versus 24% (19–30), respectively. As the proportional hazards assumption was violated, additional supporting analyses were conducted using

restricted mean survival time, piecewise HRs, and the MaxCombo test (appendix p 25). Due to the early crossing of the Kaplan–Meier curves, the restricted mean survival time was similar between the treatment groups at 26 months and 36 months; however, at 47 months (after nearly all overall survival follow-up time had been captured), the estimated restricted mean survival time was 25·8 months (95% CI 23·9–27·8) with nivolumab plus ipilimumab versus 23·0 months (21·3–24·8) with lenvatinib or sorafenib, with a between-treatment

difference of 2·8 months (0·2–5·4). In the prespecified analysis of piecewise HRs, an increased risk of death was observed with nivolumab plus ipilimumab versus lenvatinib or sorafenib within the first 6 months after randomisation (HR 1·65 [95% CI 1·12–2·43]), but a reversed trend was observed thereafter (0·61 [0·48–0·77]). Additionally, the prespecified MaxCombo test of overall survival was consistent with the primary analysis (p<0·0001). In a post-hoc analysis, nivolumab plus ipilimumab showed overall survival benefit versus patients treated with lenvatinib (HR 0·77 [95% CI 0·62–0·95]) or with sorafenib (0·42 [0·24–0·73]; appendix pp 39–40), with consistent results observed in supporting analyses conducted in the context of violation of the proportional hazards assumption (appendix p 26). In exploratory subgroup analyses, overall survival favoured nivolumab plus ipilimumab over lenvatinib or sorafenib across clinically relevant subgroups (figure 2B); overall survival across the evaluated PD-L1 CPS expression levels is shown in the appendix (p 41).

The proportion of patients with a confirmed objective response was significantly higher in the nivolumab plus ipilimumab group than in the lenvatinib or sorafenib group (121 [36%; 95% CI 31–42] of 335 vs 44 [13%; 10–17] of 333; p<0·0001); complete responses were observed in 23 (7%) versus six (2%) patients (table 2). Median duration of response was 30·4 months (95% CI 21·2–not estimable) with nivolumab plus ipilimumab versus 12·9 months (10·2–31·2) with lenvatinib or sorafenib; 55% (95% CI 44–64) versus 35% (17–53) of patients had an ongoing response at 24 months, respectively, and only patients in the nivolumab plus ipilimumab group had an ongoing response at 36 months (47% [34–59]; table 2; figure 3A). Objective response rates by BICR were consistent with those by investigator assessment (appendix p 27). In a post-hoc analysis, reductions in the sum of the longest diameters of tumour target lesions seemed to occur independent of aetiology; median reduction in the sum of the longest diameters of tumour target lesions was –27·6% (IQR –65·3 to 0·0) in the nivolumab plus ipilimumab group and –13·2% (–25·8 to 0·0) in the lenvatinib or sorafenib group (figure 3B, C).

Median progression-free survival by BICR was 9·1 months (95% CI 6·6–10·5) for the nivolumab plus ipilimumab group versus 9·2 months (7·9–11·1) for the lenvatinib or sorafenib group (HR 0·87 [0·72–1·06]; appendix p 42). Progression-free survival at 18 months was 34% (95% CI 28–39) in the nivolumab plus ipilimumab group versus 18% (13–24) in the lenvatinib or sorafenib group; 24-month progression-free survival was 28% (23–34) versus 12% (8–17). Progression-free survival trends were consistent with those by investigator assessment (appendix p 42). Results were also consistent with those observed in supporting analyses conducted in the context of violation of the proportional hazards assumption (appendix p 28).

| | Nivolumab plus ipilimumab group (n=335) | Lenvatinib or sorafenib group (n=333) |
|---|---|---|
| Age, years | 65 (59–71) | 66 (59–73) |
| Sex | | |
| Male | 271 (81%) | 277 (83%) |
| Female | 64 (19%) | 56 (17%) |
| Race | | |
| White | 179 (53%) | 174 (52%) |
| Asian | 140 (42%) | 152 (46%) |
| Black | 11 (3%) | 4 (1%) |
| Other | 5 (1%) | 3 (1%) |
| Geographical region | | |
| Europe or North America | 144 (43%) | 145 (44%) |
| Asia | 133 (40%) | 147 (44%) |
| Rest of the world | 58 (17%) | 41 (12%) |
| Aetiology† | | |
| HBV | 114 (34%) | 115 (35%) |
| HCV | 90 (27%) | 96 (29%) |
| Uninfected | 124 (37%) | 119 (36%) |
| HBV and HCV‡ | 7 (2%) | 3 (1%) |
| ECOG performance status | | |
| 0 | 233 (70%) | 243 (73%) |
| 1 | 102 (30%) | 89 (27%) |
| Missing | 0 | 1 (<1%) |
| Child–Pugh score | | |
| 5 | 254 (76%) | 263 (79%) |
| 6 | 72 (21%) | 58 (17%) |
| ≥7 | 9 (3%) | 11 (3%) |
| Missing | 0 | 1 (<1%) |
| BCLC stage | | |
| 0 or A | 28 (8%) | 21 (6%) |
| B | 61 (18%) | 67 (20%) |
| C | 246 (73%) | 242 (73%) |
| Unknown | 0 | 3 (1%) |
| Macrovascular invasion, extrahepatic spread, or both† | 221 (66%) | 217 (65%) |
| Macrovascular invasion | 77 (23%) | 92 (28%) |
| Extrahepatic spread | 188 (56%) | 172 (52%) |
| Alpha-fetoprotein concentration, ng/mL | | |
| <400 | 227 (68%) | 220 (66%) |
| ≥400 | 108 (32%) | 113 (34%) |
| Previous local non-systemic therapy | 142 (42%) | 158 (47%) |

Data are median (IQR) or n (%). Percentages might not sum to 100 because of rounding. BCLC=Barcelona Clinic Liver Cancer. ECOG=Eastern Cooperative Oncology Group. HBV=hepatitis B virus. HCV=hepatitis C virus. *Randomisation was stratified according to aetiology (HBV vs HCV vs uninfected); macrovascular invasion, extrahepatic spread, or both (present vs absent); and alpha-fetoprotein concentration (<400 ng/mL vs ≥400 ng/mL). †Per case report form. ‡These patients did not have active co-infection with HBV and HCV.

*Table 1:* Baseline demographics and disease characteristics in all randomly assigned patients*

Subsequent systemic anticancer therapies were received by 128 (38%) of 335 patients in the nivolumab plus ipilimumab group versus 172 (52%) of 333 patients in the lenvatinib or sorafenib group, with 44 (13%) versus 115 (35%) receiving immunotherapy, respectively (appendix p 29). Median progression-free survival on

**A** — Kaplan–Meier estimates of overall survival

Nivolumab plus ipilimumab: median overall survival 23·7 months (95% CI 18·8–29·4); 194 events
Lenvatinib or sorafenib: median overall survival 20·6 months (95% CI 17·5–22·5); 228 events
HR 0·79 (95% CI 0·65–0·96); two-sided stratified log-rank p=0·018

**Number at risk (number censored)**

| | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 | 45 | 48 | 51 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab plus ipilimumab | 335 (0) | 300 (3) | 264 (5) | 239 (9) | 220 (11) | 206 (15) | 179 (19) | 162 (21) | 150 (22) | 137 (24) | 104 (51) | 71 (79) | 42 (103) | 24 (119) | 11 (132) | 8 (133) | 0 (141) | 0 (141) |
| Lenvatinib or sorafenib | 333 (0) | 310 (7) | 280 (11) | 245 (15) | 216 (20) | 194 (23) | 164 (25) | 144 (27) | 116 (28) | 106 (31) | 76 (48) | 44 (67) | 34 (75) | 20 (88) | 4 (102) | 3 (102) | 1 (104) | 0 (105) |

*Figure 2:* **Kaplan–Meier estimates of overall survival among all randomly assigned patients and subgroup analysis of overall survival**
(A) Overall survival in all randomly assigned patients. Vertical lines and circles indicate censored data. (B) Subgroup analysis of overall survival. BCLC=Barcelona Clinic Liver Cancer. ECOG=Eastern Cooperative Oncology Group. HBV=hepatitis B virus. HCV=hepatitis C virus. HR=hazard ratio. NE=not estimable. *The HR was not computed for subset categories with ten or fewer patients per treatment group. †15 patients in the nivolumab plus ipilimumab group and five in the lenvatinib or sorafenib group were from North America. ‡Not reported for one patient in the lenvatinib or sorafenib group. §Nine patients in the nivolumab plus ipilimumab group and 11 in the lenvatinib or sorafenib group had a score of 7 or higher, and the score was not reported for one patient in the lenvatinib or sorafenib group. ¶Per case report form. ‖Seven patients in the nivolumab plus ipilimumab group and three in the lenvatinib or sorafenib group were reported as having both HBV and HCV; these patients did not have active co-infection. **BCLC was unknown for three patients in the lenvatinib or sorafenib group.

**B**

| | Patients | Median overall survival (95% CI), months — Nivolumab plus ipilimumab | Median overall survival (95% CI), months — Lenvatinib or sorafenib | Unstratified HR* (95% CI)† |
|---|---|---|---|---|
| **Age, years** | | | | |
| <65 | 311 | 26·8 (23·0–33·0) | 22·7 (19·1–26·2) | 0·78 (0·58–1·04) |
| ≥65 | 357 | 18·8 (15·7–27·1) | 18·2 (15·6–21·5) | 0·81 (0·63–1·05) |
| **Sex** | | | | |
| Male | 548 | 23·0 (17·9–29·3) | 21·1 (17·8–23·0) | 0·83 (0·68–1·03) |
| Female | 120 | 26·9 (19·6–NE) | 17·3 (11·6–23·3) | 0·63 (0·39–1·00) |
| **Region‡** | | | | |
| Asia | 280 | 34·0 (20·5–NE) | 22·5 (19·1–30·0) | 0·75 (0·54–1·03) |
| Europe or North America† | 289 | 22·9 (14·6–29·3) | 19·8 (16·3–22·5) | 0·83 (0·62–1·10) |
| Rest of the world | 99 | 18·8 (15·3–26·9) | 12·4 (6·4–20·5) | 0·67 (0·43–1·06) |
| **ECOG performance status‡** | | | | |
| 0 | 476 | 27·9 (23·1–34·0) | 22·5 (20·1–25·1) | 0·78 (0·62–0·98) |
| 1 | 191 | 16·4 (10·0–23·0) | 15·3 (10·3–17·4) | 0·78 (0·55–1·09) |
| **Child–Pugh score§** | | | | |
| 5 | 517 | 27·9 (23·0–35·4) | 23·2 (21·2–25·4) | 0·80 (0·64–1·01) |
| 6 | 130 | 18·3 (8·8–25·8) | 10·3 (5·9–15·4) | 0·61 (0·41–0·91) |
| **Aetiology¶‖** | | | | |
| HBV | 229 | 23·5 (18·0–37·8) | 22·3 (19·8–24·0) | 0·84 (0·60–1·17) |
| HCV | 186 | 33·0 (18·8–NE) | 17·8 (14·0–23·8) | 0·68 (0·46–1·00) |
| Uninfected | 243 | 19·3 (15·5–26·9) | 18·4 (15·8–23·3) | 0·84 (0·63–1·14) |
| **Macrovascular invasion¶** | | | | |
| Yes | 169 | 22·9 (15·2–NE) | 15·4 (10·3–20·1) | 0·59 (0·40–0·87) |
| No | 499 | 23·9 (18·8–29·4) | 21·9 (19·3–23·9) | 0·89 (0·71–1·11) |
| **Extrahepatic spread¶** | | | | |
| Yes | 360 | 18·7 (15·6–24·8) | 16·6 (14·0–20·3) | 0·82 (0·64–1·05) |
| No | 308 | 33·5 (23·0–NE) | 22·5 (20·5–28·3) | 0·72 (0·53–0·97) |
| **Macrovascular invasion, extrahepatic spread, or both¶** | | | | |
| Yes | 438 | 19·4 (16·2–25·9) | 17·7 (15·2–20·9) | 0·80 (0·64–1·01) |
| No | 230 | 33·5 (23·1–NE) | 23·0 (20·3–30·0) | 0·74 (0·52–1·04) |
| **Baseline alpha-fetoprotein, ng/mL** | | | | |
| <400 | 447 | 25·9 (22·0–33·5) | 23·8 (21·2–29·1) | 0·86 (0·68–1·10) |
| ≥400 | 221 | 16·4 (10·3–25·5) | 12·1 (8·7–16·3) | 0·69 (0·50–0·95) |
| **BCLC at baseline**** | | | | |
| 0 or A | 49 | 42·6 (31·2–NE) | 31·6 (11·6–NE) | 0·44 (0·17–1·12) |
| B | 128 | 26·8 (15·7–37·8) | 23·0 (20·5–30·6) | 0·92 (0·59–1·44) |
| C | 488 | 20·3 (16·9–25·8) | 17·8 (15·5–21·1) | 0·81 (0·65–1·01) |
| **Overall** | **668** | **23·7 (18·8–29·4)** | **20·6 (17·5–22·5)** | **0·79 (0·65–0·96)** |

Favours nivolumab plus ipilimumab ← → Favours lenvatinib or sorafenib

next-line therapy per investigator assessment was 19·3 months (95% CI 16·2–24·5) with nivolumab plus ipilimumab versus 15·4 months (13·8–17·0) with lenvatinib or sorafenib (HR 0·70 [0·58–0·84]; appendix p 43), with consistent results observed in supporting analyses conducted in the context of violation of the proportional hazards assumption (appendix p 30).

Among 657 treated patients, median duration of treatment was 4·7 months (IQR 1·4–15·7) with nivolumab plus ipilimumab versus 6·9 months (3·5–14·0) with lenvatinib or sorafenib. Among 332 treated patients in the nivolumab plus ipilimumab group, the median number of doses received was 4 (range 1–4) for both nivolumab and ipilimumab during the combination phase; 300 (90%) of the patients received more than one dose of ipilimumab. 62 (19%) of 332 patients in the nivolumab plus ipilimumab group and 157 (48%) of 325 patients in the lenvatinib or sorafenib group were treated beyond progression (defined as patients whose last available dose date was after the date of radiographic progression per investigator using RECIST version 1.1).

Treatment-related adverse events of any grade occurred in 278 (84%) of 332 treated patients in the nivolumab plus ipilimumab group and 297 (91%) of 325 treated patients in the lenvatinib or sorafenib group. Grade 3–4 treatment-related adverse events occurred in 137 (41%) patients in the nivolumab plus ipilimumab group and 138 (42%) patients in the lenvatinib or sorafenib group (table 3). All grade 3–4 treatment-related adverse events are reported in the appendix (pp 31–34). Any-grade treatment-related adverse events leading to discontinuation occurred in 59 (18%) patients in the nivolumab plus ipilimumab group and 34 (10%) patients in the lenvatinib or sorafenib group, with grade 3–4 treatment-related adverse events leading to discontinuation in 44 (13%) and 21 (6%) patients, respectively (table 3). Treatment-related deaths were reported in 12 patients in the nivolumab plus ipilimumab group and three patients in the lenvatinib or sorafenib group. Treatment-related deaths in the nivolumab plus ipilimumab group were from immune-mediated hepatitis (four patients), hepatic failure (three patients), hepatic insufficiency (one patient), decompensated cirrhosis (one patient), diarrhoea-colitis (one patient), autoimmune haemolytic anaemia (one patient), and dysautonomia (one patient). Treatment-related deaths in the lenvatinib or sorafenib group were from hepatorenal syndrome (one patient), ischaemic stroke (one patient), and acute kidney injury (one patient). Among patients in the nivolumab plus ipilimumab group, two with hepatic-related causes of death died at least 90 days after the last dose of study treatment. Additionally, disease progression per BICR was confirmed in one patient (with hepatic failure as the cause of death) and was suspected by imaging tests in three additional patients (two with immune-mediated hepatitis as the cause of death, and

| | Nivolumab plus ipilimumab group (n=335) | Lenvatinib or sorafenib group (n=333) |
|---|---|---|
| Objective response rate* (%; 95% CI) | 121 (36%; 31–42) | 44 (13%; 10–17) |
| Best overall response† | | |
| Complete response | 23 (7%) | 6 (2%) |
| Partial response | 98 (29%) | 38 (11%) |
| Stable disease‡ | 108 (32%) | 205 (62%) |
| Progressive disease | 67 (20%) | 47 (14%) |
| Could not be evaluated§ | 39 (12%) | 37 (11%) |
| Median duration of response (95% CI), months¶ | 30·4 (21·2–NE) | 12·9 (10·2–31·2) |
| Patients with duration of response (%; 95% CI)¶ | | |
| ≥24 months | 55% (44–64) | 35% (17–53) |
| ≥36 months | 47% (34–59) | NA |
| Median time to response (IQR), months‖ | 2·2 (2·1–3·8) | 3·7 (2·1–5·6) |

NA=not applicable. NE=not estimable. *Patients who had confirmed complete response or partial response per Response Evaluation Criteria in Solid Tumours (version 1.1). The objective response rate 95% CI is based on the Clopper and Pearson method. The two-sided p value was less than 0·0001 and was calculated with a stratified Cochran–Mantel–Haenszel test. †Percentages might not sum to 100 because of rounding. ‡Includes patients with non-complete response or non-progressive disease (six [2%] in the nivolumab plus ipilimumab group and seven [2%] in the lenvatinib or sorafenib group). §Includes one patient from the lenvatinib or sorafenib group who did not have a baseline lesion per blinded independent central review and thus did not have their response evaluated. ¶Assessed in patients with a confirmed partial or complete response. Based on Kaplan–Meier estimates of duration of response. ‖Assessed in patients with a confirmed partial or complete response.

*Table 2:* Response outcomes, as assessed by blinded independent central review

one with hepatic cirrhosis as the cause of death). Deaths due to adverse events considered to be unrelated to study treatment per investigator assessment were reported in 35 patients in the nivolumab plus ipilimumab group and were mostly due to infection complications, including COVID-19 in seven patients, and in 14 patients in the lenvatinib or sorafenib group, which were mostly due to haemorrhagic or infection complications (appendix pp 35–37).

Early deaths (within 6 months after randomisation) due to adverse events unrelated to study treatment were reported in 18 (5%) of 335 patients in the nivolumab plus ipilimumab group and seven (2%) of 333 patients in the lenvatinib or sorafenib group; early deaths due to adverse events related to study treatment were reported in 11 (3%) patients versus one (<1%) patient (appendix p 35). When a competing risk analysis was performed to evaluate the effect of different causes of death on the early crossing of the overall survival Kaplan–Meier curves, deaths due to adverse events unrelated to study treatment emerged as a substantial contributor (appendix pp 44–45).

Immune-mediated adverse events of any grade occurred in 191 (58%) of 332 treated patients in the nivolumab plus ipilimumab group, with 93 (28%) having a grade 3–4 event. Overall, 96 (29%) of 332 treated patients received high-dose steroids and 42 (13%) patients discontinued treatment due to immune-mediated adverse events (appendix p 38).

FACT-Hep questionnaire completion rates were higher than 99% in both groups at baseline and higher than 85%

for most weeks during the treatment period. Median time to first symptom deterioration as measured by the HCS score was longer with nivolumab plus ipilimumab versus lenvatinib or sorafenib (2·6 months [95% CI 2·0–3·9] vs 2·1 months [1·6–2·8]), with a significantly reduced risk of symptom deterioration with nivolumab

plus ipilimumab (HR 0·76 [0·62–0·93]; p=0·0059; appendix p 46). Additionally, a trend for improvement in health-related quality of life was observed with nivolumab plus ipilimumab based on the FACT-Hep total scores and the EQ-5D-3L utility index; in the lenvatinib or sorafenib group, there was a decline in health-related



***Figure 3:* Kaplan–Meier estimates of duration of response and change from baseline in all response-evaluable patients by aetiology**
(A) Kaplan–Meier estimates are based on all patients with a confirmed objective response per blinded independent central review using Response Evaluation Criteria in Solid Tumours version 1.1. Vertical lines and circles indicate censored data. (B) Waterfall plots represent best change from baseline in response evaluable patients by aetiology, defined as patients with a best overall response of complete response, partial response, stable disease, non-complete response or non-progressive disease, or progressive disease. Best change is maximum change in sum of diameters of target lesions (a negative value means true reduction, and a positive value means increase only observed over time) up to radiographic progression or start of subsequent systemic therapy date. Horizontal dashed lines indicate a 30% reduction consistent with response per Response Evaluation Criteria in Solid Tumours version 1.1. Asterisks represent confirmed responders. Square symbols represent percentage change truncated to 100%. Patients with HBV–HCV co-infection based on the case report form were categorised to HCV. HBV=hepatitis B virus. HCV=hepatitis C virus.
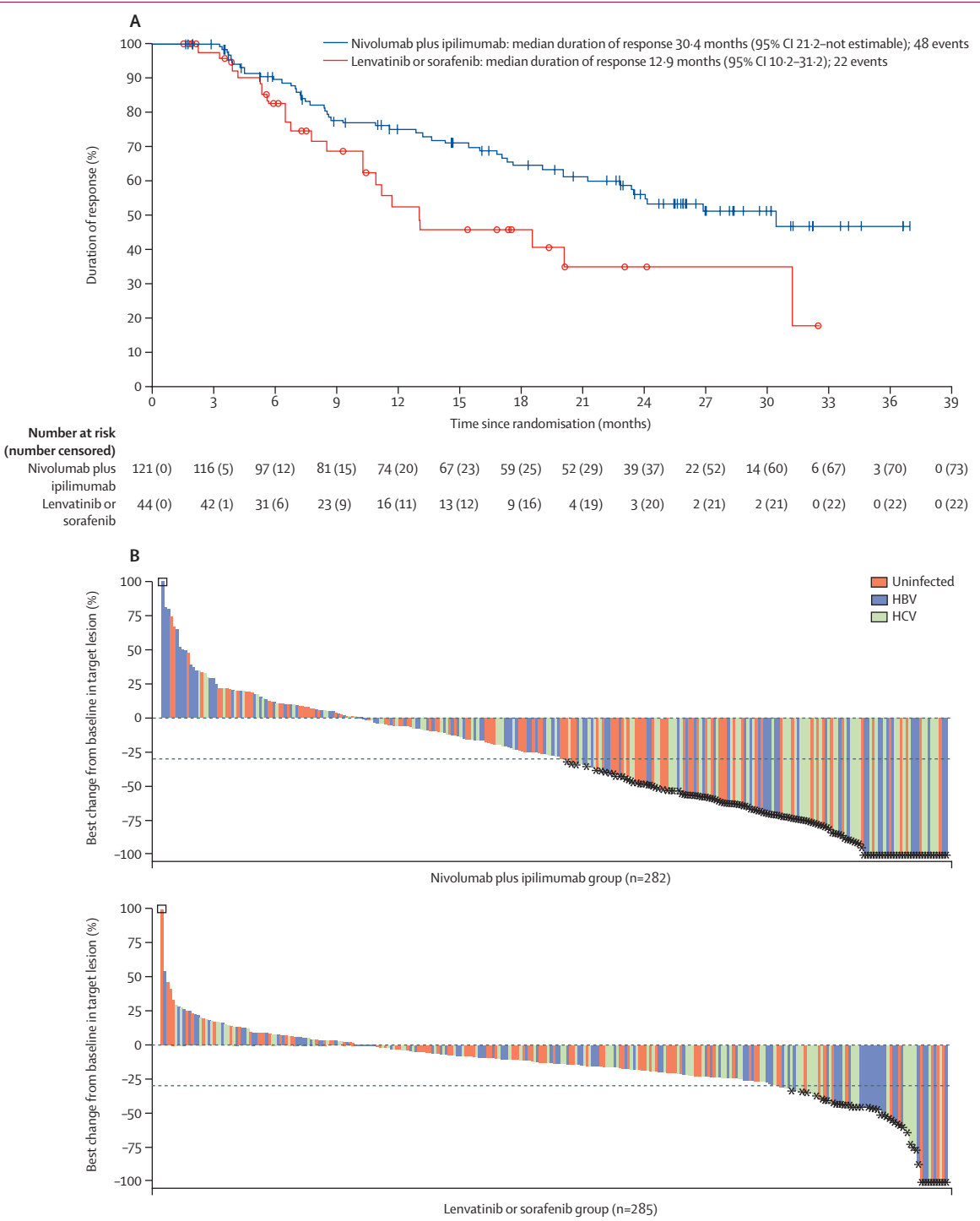
quality of life, with decreases from baseline reaching the minimally important differences in both scales (appendix p 47).

## Discussion

In CheckMate 9DW, nivolumab plus ipilimumab showed a significant overall survival benefit over lenvatinib or sorafenib in patients with unresectable hepatocellular carcinoma who had not received previous systemic treatment for advanced disease. This benefit was generally consistent across clinically relevant subgroups, including those based on disease aetiology. An early crossing of the overall survival Kaplan–Meier curves was observed, reflecting an increased incidence of early death during first 6 months after randomisation among patients who received nivolumab plus ipilimumab, but was followed by a sustained separation thereafter in favour of nivolumab plus ipilimumab. The cause of the early crossing of survival curves is probably multifactorial. A competing risk analysis suggested that it was substantially driven by an imbalance in deaths attributed to adverse events that were unrelated to study treatment, as assessed by investigators. Although deaths due to disease progression contributed minimally to the early crossing in CheckMate 9DW, a potential delayed treatment effect seen with immuno-oncology therapies compared with treatments such as lenvatinib, which have different response dynamics and a more immediate impact on tumour growth and progression than sorafenib, might explain why this phenomenon has not been seen in studies using sorafenib as the comparator.

Given the violation of the proportional hazards assumption, the treatment effect on overall survival should be evaluated using a comprehensive analysis of the data, including survival rates over time, restricted mean survival time, piecewise HRs, and the MaxCombo test, in addition to overall HR and median overall survival. These analyses provide insights into temporal changes in treatment effect and consistently support the overall treatment benefit of nivolumab plus ipilimumab over lenvatinib or sorafenib. Despite the initial crossing of the Kaplan–Meier curves, the sustained separation of the curves and supporting analyses indicate a long-term survival benefit with nivolumab plus ipilimumab in patients with unresectable hepatocellular carcinoma who had not received previous systemic treatment. Additionally, results from CheckMate 9DW further support the clinical benefits of nivolumab plus ipilimumab shown in the phase 2 CheckMate 040 trial in patients with advanced hepatocellular carcinoma previously treated with sorafenib.[14,15] In previously untreated patients with advanced hepatocellular carcinoma, the approved multikinase inhibitors lenvatinib and sorafenib have provided modest median overall survival benefits of 13·6 months (lenvatinib) and 12·3 months (sorafenib).[5,6] Although lenvatinib showed non-inferiority in overall survival versus sorafenib in the

| | Nivolumab plus ipilimumab group (n=332) | | Lenvatinib or sorafenib group (n=325) | |
|---|---|---|---|---|
| | Grade 1–2 | Grade 3–4† | Grade 1–2 | Grade 3–4† |
| Any treatment-related adverse event | 141 (42%) | 137 (41%) | 159 (49%) | 138 (42%) |
| Treatment-related serious adverse event | 11 (3%) | 83 (25%) | 5 (2%) | 42 (13%) |
| Treatment-related adverse event leading to discontinuation‡ | 15 (5%) | 44 (13%) | 13 (4%) | 21 (6%) |
| Treatment-related adverse events§ | | | | |
| Pruritus | 88 (27%) | 5 (2%) | 10 (3%) | 0 |
| Rash | 58 (17%) | 6 (2%) | 26 (8%) | 3 (<1%) |
| ALT increased | 47 (14%) | 16 (5%) | 16 (5%) | 3 (<1%) |
| AST increased | 45 (14%) | 20 (6%) | 25 (8%) | 2 (<1%) |
| Diarrhoea | 43 (13%) | 4 (1%) | 104 (32%) | 10 (3%) |
| Hypothyroidism | 40 (12%) | 0 | 79 (24%) | 0 |
| Asthenia | 33 (10%) | 1 (<1%) | 46 (14%) | 5 (2%) |
| Hyperthyroidism | 32 (10%) | 2 (<1%) | 5 (2%) | 0 |
| Decreased appetite | 22 (7%) | 1 (<1%) | 65 (20%) | 5 (2%) |
| Lipase increased | 20 (6%) | 17 (5%) | 14 (4%) | 4 (1%) |
| Fatigue | 27 (8%) | 0 | 44 (14%) | 6 (2%) |
| Nausea | 19 (6%) | 0 | 29 (9%) | 2 (<1%) |
| Blood bilirubin increased | 13 (4%) | 1 (<1%) | 18 (6%) | 5 (2%) |
| Weight decreased | 7 (2%) | 0 | 32 (10%) | 5 (2%) |
| Colitis | 6 (2%) | 8 (2%) | 0 | 0 |
| PPE syndrome | 6 (2%) | 0 | 88 (27%) | 11 (3%) |
| Hypertension | 5 (2%) | 0 | 96 (30%) | 38 (12%) |
| Platelet count decreased | 4 (1%) | 0 | 17 (5%) | 5 (2%) |
| Hypertransaminasaemia | 2 (<1%) | 4 (1%) | 1 (<1%) | 1 (<1%) |
| Neutropenia | 2 (<1%) | 2 (<1%) | 4 (1%) | 5 (2%) |
| Immune-mediated hepatitis | 1 (<1%) | 7 (2%) | 0 | 0 |
| Autoimmune hepatitis | 1 (<1%) | 5 (2%) | 0 | 0 |
| Thrombocytopenia | 1 (<1%) | 1 (<1%) | 24 (7%) | 4 (1%) |
| Dysphonia | 1 (<1%) | 0 | 48 (15%) | 0 |
| Hepatic failure | 0 | 4 (1%) | 0 | 1 (<1%) |
| Proteinuria | 0 | 0 | 48 (15%) | 17 (5%) |

Data are n (%). ALT=alanine aminotransferase. AST=aspartate aminotransferase. PPE=palmar-plantar erythrodysesthesia. *Includes patients who received at least one dose of the study treatment. All events were reported between the first dose and 30 days after the last dose of study therapy. †No grade 5 treatment-related adverse events occurred in either treatment group. Note that only events that led to death within 24 h of onset were documented as grade 5; events leading to death more than 24 h after onset are reported at the worst grade before death. ‡This category refers to adverse events leading to discontinuation of any drug in the regimen. ¶Individual treatment-related adverse events that occurred at grade 1 or 2 in at least 10% of patients in either treatment group or at grade 3 or 4 in at least 1% of patients in either treatment group.

*Table 3:* **Treatment-related adverse events in all treated patients***

global, phase 3, multicentre REFLECT trial, lenvatinib showed significant improvements over sorafenib in progression-free survival, median time to progression, and objective response rate, in both global and Japanese populations.[6,18] With the introduction of PD-L1 inhibitors in this setting, survival benefits versus sorafenib were improved with a median overall survival of 19·2 months with atezolizumab plus bevacizumab,[9,10] 16·6 months with durvalumab monotherapy, and 16·4 months with tremelimumab plus durvalumab,[7,8] leading to regulatory approvals of both combination therapies in the first-line setting. Although the combination of camrelizumab

plus rivoceranib showed significant benefits over sorafenib in overall survival (median 23·8 months *vs* 15·2 months), 83% of patients in this study were from Asia, and the incidence of grade 3 or 4 treatment-related adverse events was high (81%) with this regimen.[19,20] In the COSMIC-312 trial, first-line cabozantinib plus atezolizumab resulted in progression-free survival benefit but not overall survival benefit versus sorafenib in this setting.[21] In the CheckMate 9DW trial, the median overall survival was 23·7 months with nivolumab plus ipilimumab compared with 20·6 months with lenvatinib or sorafenib. Moreover, the survival benefits observed with nivolumab plus ipilimumab are particularly compelling considering that the majority of the patients in the comparator group received lenvatinib (85%), and in a post-hoc analysis, nivolumab plus ipilimumab showed an overall survival benefit when separately compared with patients who received lenvatinib or who received sorafenib. By contrast, most of the previous phase 3 trials compared PD-1-based or PD-L1-based regimens with sorafenib, with the exception of the LEAP-002 trial, in which pembrolizumab plus lenvatinib did not show an overall survival benefit over lenvatinib plus placebo.[22]

In the current study, benefits of nivolumab plus ipilimumab over lenvatinib or sorafenib were further demonstrated by significant improvement in the objective response rate (36% *vs* 13%; p<0·0001) and durable responses, with a median duration of response of 30·4 months versus 12·9 months. Moreover, the objective response benefits observed with nivolumab plus ipilimumab appeared to be independent of disease aetiology. In IMbrave150, atezolizumab plus bevacizumab yielded an objective response rate of 30% and a median duration of response of 18·1 months.[10] In HIMALAYA, durvalumab plus tremelimumab yielded an objective response rate of 20% and median duration of response of 22·3 months.[7] In CheckMate 9DW, many patients receiving nivolumab plus ipilimumab remained in response even after discontinuing treatment, and 47% of responders had an ongoing response at 36 months, suggesting that therapeutic activity continued beyond treatment administration.

Efficacy of nivolumab plus ipilimumab over lenvatinib or sorafenib was also supported by numerically higher progression-free survival rates at 18 months (34% *vs* 18%) and 24 months (28% *vs* 12%). Additionally, patients in the nivolumab plus ipilimumab group showed a median progression-free survival on next-line therapy of 19·3 months (*vs* 15·4 months in the lenvatinib or sorafenib group) despite a higher proportion of patients in the lenvatinib or sorafenib group receiving subsequent systemic therapy, including immunotherapy.

Nivolumab plus ipilimumab had a similar incidence of grade 3–4 treatment-related adverse events as lenvatinib or sorafenib, and the safety profile was manageable and consistent with that previously reported for the regimen

in second-line hepatocellular carcinoma and for other indications.[11–14,23] Additionally, in CheckMate 9DW, the frequency of treatment-related grade 3–4 adverse events were similar to that described for the IMbrave 150 study (41% *vs* 43%), despite CheckMate 9DW having a longer median follow-up (35·2 months *vs* 15·6 months); the incidence of treatment-related discontinuations due to adverse events was 18% in CheckMate 9DW and 22% in the IMbrave 150 study.[10] Immune-mediated adverse events reported with nivolumab plus ipilimumab in CheckMate 9DW were manageable with established management algorithms; 29% of the patients required high-dose corticosteroids, and most events did not result in discontinuation. Among the 12 deaths considered by the investigator to be related to nivolumab plus ipilimumab treatment, 11 occurred within 6 months after randomisation, and nine were attributed to fatal hepatic events in patients with advanced underlying liver disease. Although hepatic events (including fatal events) are a known adverse reaction to immunotherapy, and hepatic failure is a common and life-threatening complication in patients with cirrhosis and hepatocellular carcinoma,[24,25] liver function should be closely monitored and treatment evaluated in case of liver function deterioration. An overall trend towards improved health-related quality of life and significantly reduced risk in the time to first symptom deterioration on the HCS with nivolumab plus ipilimumab versus lenvatinib or sorafenib was observed, supporting the tolerability of this regimen in patients with unresectable hepatocellular carcinoma.

Limitations of this trial include the exclusion of patients with Vp4 portal vein thrombosis and the open-label design. Although the overall survival endpoint was not biased by the assigned treatment, determination of adverse event causality and health-related quality of life might have been influenced by awareness of the treatment received. For endpoints such as objective response rates and progression-free survival, bias was mitigated by using BICR; however, similar results by investigatorassessment suggest that the open-label design potentially did not influence efficacy assessments.

In conclusion, nivolumab plus ipilimumab demonstrated a significant survival benefit over lenvatinib or sorafenib as first-line treatment in patients with unresectable hepatocellular carcinoma. The safety profile was manageable, and no new safety concerns were identified. These results support nivolumab plus ipilimumab as a first-line treatment option for patients with unresectable hepatocellular carcinoma.

reviewed and edited the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors reviewed the final version of the manuscript to be submitted and agree with its content and submission.

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