Atezolizumab plus bevacizumab versus active surveillance in patients with resected or ablated high-risk hepatocellular carcinoma (IMbrave050): a randomised, open-label, multicentre, phase 3 trial

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Summary

Background No adjuvant treatment has been established for patients who remain at high risk for hepatocellular carcinoma recurrence after curative-intent resection or ablation. We aimed to assess the efficacy of adjuvant atezolizumab plus bevacizumab versus active surveillance in patients with high-risk hepatocellular carcinoma.

Methods In the global, open-label, phase 3 IMbrave050 study, adult patients with high-risk surgically resected or ablated hepatocellular carcinoma were recruited from 134 hospitals and medical centres in 26 countries in four WHO regions (European region, region of the Americas, South-East Asia region, and Western Pacific region). Patients were randomly assigned in a 1:1 ratio via an interactive voice–web response system using permuted blocks, using a block size of 4, to receive intravenous 1200 mg atezolizumab plus 15 mg/kg bevacizumab every 3 weeks for 17 cycles (12 months) or to active surveillance. The primary endpoint was recurrence-free survival by independent review facility assessment in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, NCT04102098.

Findings The intention-to-treat population included 668 patients randomly assigned between Dec 31, 2019, and Nov 25, 2021, to either atezolizumab plus bevacizumab (n=334) or to active surveillance (n=334). At the prespecified interim analysis (Oct 21, 2022), median duration of follow-up was 17·4 months (IQR 13·9–22·1). Adjuvant atezolizumab plus bevacizumab was associated with significantly improved recurrence-free survival (median, not evaluable [NE]; [95% CI 22·1–NE]) compared with active surveillance (median, NE [21·4–NE]; hazard ratio, 0·72 [adjusted 95% CI 0·53–0·98]; p=0·012). Grade 3 or 4 adverse events occurred in 136 (41%) of 332 patients who received atezolizumab plus bevacizumab and 44 (13%) of 330 patients in the active surveillance group. Grade 5 adverse events occurred in six patients (2%, two of which were treatment related) in the atezolizumab plus bevacizumab group, and one patient (<1%) in the active surveillance group. Both atezolizumab and bevacizumab were discontinued because of adverse events in 29 patients (9%) who received atezolizumab plus bevacizumab.

Interpretation Among patients at high risk of hepatocellular carcinoma recurrence following curative-intent resection or ablation, recurrence-free survival was improved in those who received atezolizumab plus bevacizumab versus active surveillance. To our knowledge, IMbrave050 is the first phase 3 study of adjuvant treatment for hepatocellular carcinoma to report positive results. However, longer follow-up for both recurrence-free and overall survival is needed to assess the benefit–risk profile more fully.

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Introduction

Hepatocellular carcinoma accounts for approximately 80% of primary liver cancers, and is the fourth leading cause of cancer-related death worldwide. An estimated 72% of cases arise in Asia, with more than half occurring in China.[1] The incidence of and mortality related to hepatocellular carcinoma are rising in the USA and Europe.[1] It is estimated that the number of cases and deaths from liver cancer will increase by more than 50% over the next 20 years.[2] Hepatocellular carcinoma usually occurs in the setting of liver cirrhosis as a result of chronic hepatitis B or C infections, non-alcoholic steatohepatitis, alcohol consumption, or diabetes.[3] Hepatocellular carcinoma with non-viral causes is becoming more frequent in western countries.[3]

Surgical resection or local ablation are cornerstones of curative-intent treatment for hepatocellular carcinoma. However, rates of postoperative recurrence following resection or ablation are reported to exceed 70% within 5 years following resection or ablation, even in patients

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See Online for appendix

Research in context

Evidence before this study

Liver resection or local ablation are potentially curative options for patients with hepatocellular carcinoma. However, recurrence rates within 5 years following resection or ablation have been reported to exceed 70%. Currently, there is no globally recognised standard of care for adjuvant therapy in patients with hepatocellular carcinoma after potentially curative treatment. Atezolizumab plus bevacizumab is the standard of care for first-line treatment of unresectable hepatocellular carcinoma, based on the results of the IMbrave150 study. IMbrave150 demonstrated superior overall survival, progression-free survival, and objective response rate compared with sorafenib. We searched PubMed for full manuscripts published between Jan 1, 2010, and Jan 1, 2023 that described results of randomised trials in the adjuvant setting after complete resection or ablation of early-stage hepatocellular carcinoma. Combined search terms, restricted to English, included "hepatocellular carcinoma," "HCC," "systemic," "adjuvant," "sorafenib," "PD-1 inhibitor," "PD-L1 inhibitor," "atezolizumab," "pembrolizumab," "durvalumab," and "nivolumab". We also assessed major clinical practice guidelines for hepatocellular carcinoma and associated references. Multiple treatment modalities have been evaluated in randomised phase 2 or 3 studies as adjuvant treatment for hepatocellular carcinoma. Early studies of adjuvant treatment following curative-intent treatment for hepatocellular carcinoma focused on antiviral agents, including interferon-α and nucleotide analogues. In a meta-analysis of nine randomised trials and five cohort studies, interferon-α treatment reduced recurrence rates in patients with hepatitis C-related hepatocellular carcinoma, but not those with hepatitis B-related disease. Nucleotide analogues have been shown to reduce tumour recurrence and improve survival of patients with hepatitis B-related hepatocellular carcinoma. Two phase 3 studies have evaluated antiangiogenic agents as adjuvant therapy. Muparfostat (a heparinase inhibitor) did not improve disease-free survival compared with placebo in Asian patients with hepatitis-related hepatocellular carcinoma. In a global phase 3 study (STORM), adjuvant sorafenib following resection or ablation did not improve recurrence-free survival relative to placebo. A series of investigator-led randomised studies evaluating adoptive immunotherapy conducted in South Korea demonstrated improved recurrence-free survival and, in some cases, overall survival. Before the opening of IMbrave050, three global phase 3 trials of adjuvant immunotherapy after surgical resection or ablation of hepatocellular carcinoma were ongoing, including CheckMate 9DX (nivolumab; NCT03383458), KEYNOTE-937 (pembrolizumab; NCT03867084), and EMERALD-2 (durvalumab with or without bevacizumab; NCT03847428).

Added value of this study

To our knowledge, IMbrave050 is the first positive phase 3 trial for adjuvant treatment in hepatocellular carcinoma. The results of IMbrave050 indicate that dual inhibition of programmed death-ligand 1 and vascular endothelial growth factor signalling, compared with active surveillance, significantly improves recurrence-free survival in patients at high risk of recurrence following either liver resection or thermal ablation. The results of IMbrave050 provide a new reference on which to base further treatment advances for early-stage hepatocellular carcinoma in the future.

Implications of all the available evidence

The results of IMbrave050 support the use of adjuvant atezolizumab plus bevacizumab in patients with hepatocellular carcinoma at high risk of disease recurrence. These results could be a practice-changing adjuvant treatment option for patients with hepatocellular carcinoma at high risk of recurrence and could lead to new considerations in indications for surgical resection. However, longer follow-up for both recurrence-free and overall survival is needed to assess the benefit–risk profile more fully.

who are considered optimal candidates for curative treatment.[4] In patients undergoing curative-intent therapy with a more advanced tumour burden, the risk of hepatocellular carcinoma recurrence is further amplified.[5,6] The risk of hepatocellular carcinoma recurrence follows a bimodal distribution, and is highest within 1–2 years of either resection or ablation.[7–9] Early recurrence is generally attributed to occult micrometastases from the primary tumour, whereas late recurrence, which peaks at between 4 and 5 years after curative treatment, is related to de-novo tumours associated with underlying liver disease.[9] Risk factors for early recurrence are driven mainly by aggressive characteristics of the primary tumour, such as tumour size, multiplicity, vascular invasion, high histological grade, and higher serum α fetoprotein level.[5] Early recurrence of hepatocellular carcinoma often has a more aggressive biology and is associated with poorer long-term clinical outcomes than late recurrence.[10]

Adjuvant therapy has the potential to prevent or delay recurrence by eradicating micrometastatic tumour deposits. The growing global incidence of hepatocellular carcinoma, coupled with the high probability of tumour recurrence after curative-intent treatment, highlights the need for effective adjuvant treatment options. Multiple systemic and local treatment modalities have been evaluated as adjuvant therapy for hepatocellular carcinoma, including antiangiogenic agents and immunotherapy.[11] Two randomised phase 3 trials of adjuvant anti-angiogenic therapy have been conducted, both of which did not meet their respective primary endpoints. The STORM trial compared adjuvant sorafenib with placebo following either curative-intent resection or ablation, and did not show improvement in

recurrence-free survival (RFS).[12] In the phase 3 PATRON trial, adjuvant muparfostat (a heparinase inhibitor) did not improve disease-free survival (DFS) compared with placebo in Asian patients with viral hepatocellular carcinoma, despite encouraging phase 2 data.[13,14] Adoptive immunotherapy with autologous cytokine-induced killer cells was shown to improve RFS and—in some cases—overall survival (OS) in a series of studies conducted in Japan and South Korea, indicating the potential utility of adjuvant immunotherapy for hepatocellular carcinoma.[15] To date, however, no adjuvant treatment has proven effective in a global phase 3 study, and there is no standard-of-care adjuvant treatment option for patients with hepatocellular carcinoma.[16]

Atezolizumab (anti-programmed death-ligand 1 [PD-L1]) combined with bevacizumab (anti–vascular endothelial growth factor) is the first-line standard of care for unresectable hepatocellular carcinoma based on results from the IMbrave150 study, which showed superior OS, progression-free survival, and objective response rates with atezolizumab plus bevacizumab compared with sorafenib.[17,18] These data provide a rationale for exploring this combination regimen in an earlier treatment setting.

The composition of the tumour microenvironment is an important determinant of hepatocellular carcinoma recurrence.[19] In resected hepatocellular carcinoma, reciprocal interactions occur between the immune and angiogenic milieu, which affects both DFS and OS.[20] In advanced hepatocellular carcinoma, bevacizumab has been shown to augment anticancer immunity and enhance PD-L1 blockade through inhibition of angiogenesis, regulatory T-cell proliferation, and myeloid cell inflammation.[21] Along with tumour factors, these immunological mechanisms are strongly implicated in hepatocellular carcinoma recurrence, thus providing a mechanistic rationale to explore atezolizumab plus bevacizumab as an adjuvant treatment.[22–24]

We conducted IMbrave050 to evaluate the efficacy and safety of adjuvant atezolizumab plus bevacizumab versus active surveillance in patients with hepatocellular carcinoma at high risk of tumour recurrence following curative-intent resection or ablation.

Methods

Study design and participants

This phase 3, randomised, open-label study was conducted in 134 hospitals and medical centres in 26 countries and four regions (European Region, Region of the Americas, South-East Asia Region, and Western Pacific Region; appendix pp 4–6).

Eligible patients were aged 18 years or older at the time of recruitment, had a first diagnosis of hepatocellular carcinoma, and had undergone either complete surgical resection (R0, grossly and microscopically negative margins) or ablation (microwave or radiofrequency ablation with complete response on imaging) within 4–12 weeks of random allocation. Patients had Child-Pugh class A liver function (a three-category scale of A, B, or C, in which C is the most severe compromise of liver function) with adequate haematological and organ function, and an Eastern Cooperative Oncology Group performance status score of 0 or 1 (on a five-point scale, with higher scores indicating greater disability). One cycle of transarterial chemoembolisation following resection was permitted if indicated by local treatment guidelines. Patients at high risk of tumour recurrence following resection or ablation were eligible. For resection, recurrence risk was defined with composite criteria that included tumour size; tumour number; and the presence of microvascular invasion or segmental portal vein invasion (segmental portal vein invasion [Vp1] or right anterior or posterior portal vein [Vp2] according to Liver Cancer Study Group of Japan classification),[25] poorly differentiated microscopic appearance (histological grade 3 or 4), or both. For ablation, recurrence risk was based on tumour size and number. Further details on high-risk criteria are in the panel.

Key exclusion criteria included any previous treatment for hepatocellular carcinoma, infection with both hepatitis B and hepatitis C virus, and untreated or incompletely treated oesophageal or gastric varices (assessed per oesophagogastroduodenoscopy and treated per local clinical practice) with bleeding or at high risk for bleeding. Full eligibility criteria are provided in the trial protocol, available in the appendix (pp 68–76). All patients gave written informed consent to participate in IMbrave050. IMbrave050 was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki. Protocol approval was obtained from institutional review boards or ethics committees for each site. The redacted protocol and list of protocol deviations are available in the appendix (p 15).

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to receive open-label atezolizumab plus bevacizumab or active surveillance. Random allocation was performed via an interactive voice–web response system using permuted blocks, using a block size of 4, stratified by geographical region (Asia-Pacific excluding Japan *vs* rest of world) and a composite stratification factor including number of high-risk features (one *vs* two or more), curative procedure (ablation *vs* resection), and use of adjuvant transarterial chemoembolisation (yes *vs* no; appendix p 2). Japan was excluded from Asia-Pacific, as the main cause of hepatocellular carcinoma is the hepatitis B virus in most of Asia, but the heptatitis C virus in Japan.

Despite patients, investigators, and some study staff not being masked to treatment allocation, study data were handled by the sponsor as if the study was masked—ie, data cleaning and query resolution was performed regardless of treatment assignment. Analyses presented

***Panel*: Criteria for high risk of hepatocellular carcinoma recurrence by curative treatment**

Resection

- Up to three tumours, with largest tumour >5 cm regardless of vascular invasion (microvascular invasion or segmental portal vein invasion—Vp1 or Vp2), or poor tumour differentiation (grade 3 or 4)*
- Four or more tumours, with largest tumour ≤5 cm regardless of vascular invasion (microvascular invasion or segmental portal vein invasion—Vp1 or Vp2), or poor tumour differentiation (grade 3 or 4)*
- Up to three tumours, with largest tumour ≤5 cm with vascular invasion (microvascular invasion or segmental portal vein invasion—Vp1 or Vp2), with or without poor tumour differentiation (grade 3 or 4)*

Ablation†

- Single tumour >2 cm but ≤5 cm
- Multiple tumours (up to four tumours), all ≤5 cm

Vp1=segmental portal vein invasion. Vp2=right anterior or posterior portal vein. *In cases in which a patient has evidence of mixed tumour differentiation, the worst differentiation status rather than the predominant differentiation status should be used to characterise high-risk criteria. †Ablation must be radiofrequency ablation or microwave ablation.

in this manuscript were conducted by the sponsor after unmasking.

Procedures

Treatment was 1200 mg intravenous atezolizumab plus intravenous bevacizumab (both Genentech [San Francisco, CA, USA]) 15 mg/kg every 3 weeks for up to 12 months or 17 cycles, whichever occurred first. Patients randomly allocated to active surveillance were permitted to receive crossover treatment with atezolizumab plus bevacizumab at investigator discretion on independent review facility confirmation of disease recurrence. Resection or ablation of recurrent lesions was allowed before crossover treatment.

Outcomes

The primary endpoint was RFS (time from randomisation to disease recurrence per independent review facility, or death from any cause, whichever occurred first). Intrahepatic and extrahepatic recurrence were defined according to European Association for the Study of the Liver criteria and Response Evaluation Criteria in Solid Tumours version 1.1, respectively.[16,26] The primary endpoint was based on a centrally based independent review facility. Recurrence was assessed and recorded locally.

Secondary endpoints were OS; investigator-assessed RFS; investigator-assessed and independent review facility-assessed time to recurrence and RFS rate at 24 months and 36 months; OS rate at months 24 and 36; investigator-assessed time to extrahepatic spread or macrovascular invasion; and investigator-assessed and independent review facility-assessed RFS among patients in the PD-L1-high subgroup. Secondary endpoints reported in this paper are investigator-assessed RFS, investigator-assessed and independent review facility-assessed time to recurrence, and OS. Data for secondary endpoints that are not reported here will be reported in future publications when the data are mature.

Safety assessment included the nature, frequency, and severity of adverse events according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 until the data cutoff date. The full list of endpoints is available in the appendix (pp 28–30).

Disease recurrence was evaluated with contrast-enhanced CT or MRI at baseline, every 12 weeks (±7 days) from the date of random allocation for the first 3 years, and every 24 weeks thereafter (±10 days), regardless of treatment delays, until confirmation of disease recurrence by an independent review facility (see appendix pp 2–3). Following disease recurrence, patients were contacted approximately every 12 weeks until death or the end of study, whichever occurred first, for information on follow-up therapy and survival status.

Adverse events were assessed throughout the trial treatment period and during follow-up. An independent data monitoring committee reviewed unmasked safety and study conduct data approximately every 6 months. The independent data monitoring committee also reviewed efficacy data at the prespecified interim analysis.

Statistical analysis

We estimated that a sample size of 662 patients, targeting 323 independent review facility-assessed RFS events, would provide 80% power to detect a hazard ratio (HR) of 0·73 favouring atezolizumab plus bevacizumab versus active surveillance using a stratified log-rank test at a two-sided 0·05 significance level. The minimum detectable difference for RFS was an HR of 0·8. The dropout rate was assumed to be 15% for the atezolizumab plus bevacizumab group and 20% for the active surveillance group over 12 months (see appendix p 2). The key secondary endpoint of OS was to be tested using a stratified log-rank test with a two-sided significance level of 0·05 if statistical significance was reached for independent review facility-assessed RFS.

A group sequential design was implemented for testing the independent review facility-assessed RFS to account for conducting one interim analysis. The interim analysis of RFS, as assessed by an independent review facility, was to be conducted when approximately 236 RFS events had occurred. By Oct 21, 2022, a total of 243 RFS events had occurred. On the basis of the observed number of RFS events, the multiplicity-adjusted, two-sided α level for the first interim analysis of independent review facility-assessed RFS was 0·0195. The final analysis of RFS was planned to be conducted when approximately 323 independent review facility-assessed RFS events had occurred. If the study was positive at the RFS interim analysis, the final RFS analysis would be descriptive in

nature and would complement the current analysis by examining the sustainability of the treatment effect of atezolizumab plus bevacizumab with longer term follow-up. Additional details (including for the OS analyses) are in the appendix (pp 3, 39–42). To minimise bias, the primary endpoint of RFS was assessed by an independent review facility to enable centralised independent reviews of images (for details of screening assessments see appendix pp 2–3). Summaries and analyses for the planned interim independent review facility-assessed RFS analysis were first prepared by an independent Data Coordinating Centre and reviewed by the independent Data Monitoring Committee. The sponsor was unmasked after the independent Data Monitoring Committee indicated that the study had met its primary endpoint, and recommended that the study be fully analysed.

Efficacy was assessed in all patients who had been randomly assigned to either treatment or active surveillance (intention-to-treat population), with patients grouped according to the treatment assigned at randomisation. Patients who had not had disease recurrence or had died at the time of analysis were censored at the date of the last assessment for hepatocellular carcinoma occurrence. Patients with no post-baseline radiographic assessment were censored at the date of randomisation. In the rare event that the independent review facility identified baseline disease, this patient was assessed as having a recurrence event at the time of randomisation. The two-sided stratified log-rank test was used as the primary method to compare RFS between the two groups. A stratified Cox proportional hazards model was used to estimate the HR and its 95% CI, and the Kaplan-Meier method was used to estimate the median RFS for each group. Unstratified analysis was used for other important subgroups due to the potentially small number of patients in each subgroup.

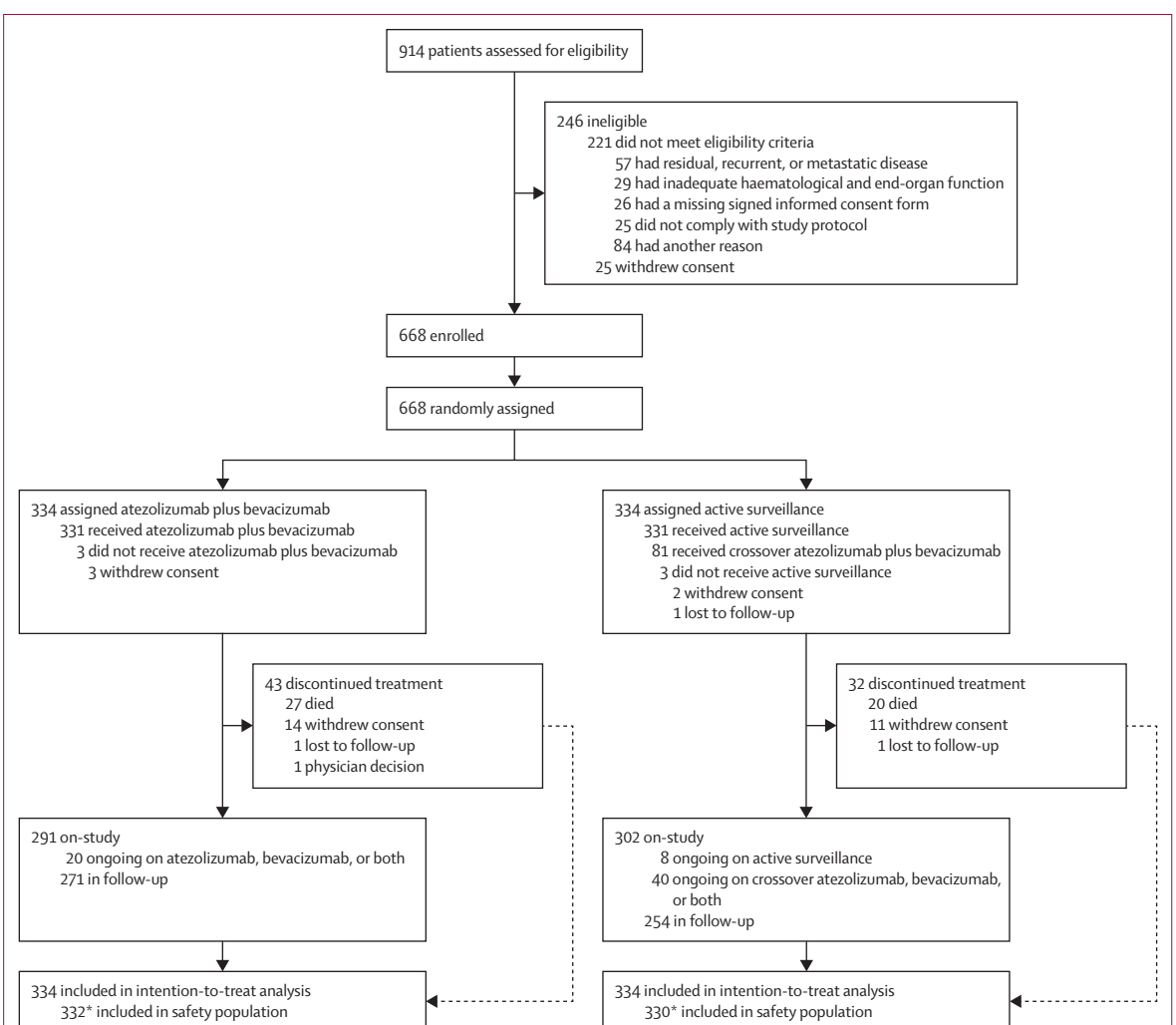

Figure 1: **Trial profile**

*One patient was assigned to the active surveillance group and mistakenly received treatment with atezolizumab plus bevacizumab. This patient is included under the atezolizumab plus bevacizumab group in the safety population.

	Atezolizumab plus bevacizumab (n=334)	Active surveillance (n=334)
Age, years	60 (52–68)	59 (50–70)
Sex		
Male	277 (83%)	278 (83%)
Female	57 (17%)	56 (17%)
Race*		
Asian	276 (83%)	269 (81%)
White	35 (10%)	41 (12%)
Other	23 (7%)	24 (7%)
Geographical region		
Asia-Pacific, excluding Japan	237 (71%)	238 (71%)
Rest of world	97 (29%)	96 (29%)
ECOG performance status score†		
0	258 (77%)	269 (81%)
1	76 (23%)	65 (19%)
PD-L1 status‡	285	270
≥1%	154/285 (54%)	140/270 (50%)
<1%	131/285 (46%)	139/270 (50%)
Cause of hepatocellular carcinoma		
Hepatitis B	209 (63%)	207 (62%)
Hepatitis C	34 (10%)	38 (11%)
Non-viral	45 (13%)	38 (11%)
Unknown	46 (14%)	51 (15%)
Barcelona Clinic Liver Cancer stage at initial diagnosis		
0	2 (1%)	3 (1%)
A	287 (86%)	277 (83%)
B	25 (7%)	32 (10%)
C	20 (6%)	22 (7%)
D	0	0
Resection	293 (88%)	292 (87%)
Longest diameter of the largest tumour at diagnosis, cm§	5·3 (3·3–8·0)	5·9 (3·5–9·0)
Number of tumours		
1	266/293 (91%)	260/292 (89%)
2	20/293 7%)	29/292 (10%)
3	4/293 (1%)	2/292 (1%)
≥4	3/293 (1%)	1/292 (<1%)
Adjuvant TACE following resection		
Yes	32/293 (11%)	34/292 (12%)
No	261/293 (89%)	258/292 (88%)
Any tumours >5 cm		
Yes	152/293 (52%)	175/292 (60%)
No	141/293 (48%)	117/292 (40%)
Microvascular invasion present		
Yes	178/293 (61%)	176/292 (60%)
No	115/293 (39%)	116/292 (40%)
Segmental portal vein invasion (Vp1 or Vp2) present		
Yes	22/293 (8%)	17/292 (6%)
No	271/293 (92%)	275/292 (94%)
Poor tumour differentiation (grade 3 or 4)		
Yes	124/293 (42%)	121/292 (41%)
No	169/293 (58%)	171/292 (59%)
Ablation	41 (12%)	42 (13%)
Longest diameter of the largest tumour at diagnosis, cm	2·5 (2·3–3·0)	2·6 (2·3–3·0)
Number of tumours		
1	29/41 (71%)	31/42 (74%)
2	11/41 (27%)	8/42 (19%)
3	1/41 (2%)	3/42 (7%)

Data are median (IQR), n (%), or n/N (%). ECOG=Eastern Cooperative Oncology Group. PD-L1=programmed death-ligand 1. TACE=transarterial chemoembolisation. Vp1=segmental portal vein invasion. Vp2=right anterior or posterior portal vein. *Race was reported by the patients. †ECOG performance status scores range from 0 to 5, with higher scores indicating greater disability. ‡PD-L1 expression was determined with the use of the PD-L1 SP263 immunohistochemical assay (Ventana Medical Systems, Tucson, AZ, USA). §One patient in the atezolizumab plus bevacizumab group was excluded from the calculation due to a data entry error.

Table 1: **Baseline characteristics, including curative procedures, cause, and disease characteristics, in the intention-to-treat population**

Confidence intervals were not adjusted for multiplicity in these subgroup analyses.

Safety assessment was conducted in the safety-evaluable population, defined as all patients randomly allocated to atezolizumab plus bevacizumab who received at least one full or partial dose of study treatment, and all patients allocated to active surveillance who underwent at least one post-baseline safety assessment.

This trial is registered with ClinicalTrials.gov, NCT04102098.

Role of the funding source

F Hoffmann-La Roche/Genentech sponsored the study; provided the study drugs; and collaborated with an academic steering committee on study design and data collection, data analysis, and data interpretation. All drafts of the manuscript were prepared by the authors.

Results

Between Dec 31, 2019, and Nov 25, 2021, 668 patients were randomly assigned to receive atezolizumab plus bevacizumab (334 [50%] of 668 patients) or active surveillance (334 [50%] of 668 patients), and were included in the intention-to-treat population (figure 1).

Baseline characteristics were generally well balanced between treatment groups (table 1). The intention-to-treat population was predominantly male (555 [83%] of

668 *vs* 113 [17%] female) with a median age of 59 years (IQR 51–68). Most patients were Asian (545 [82%] of 668), and were primarily recruited in mainland China, Hong Kong, Japan, South Korea, and Taiwan (515 [77%] of 668). Hepatitis B was the main underlying cause of hepatocellular carcinoma in both study groups (416 [62%] of 668). Most patients (564 [84%] of 668) had Barcelona Clinic Liver Cancer stage A disease. Most patients (585 [88%] of 668) underwent surgical resection; among these patients, median tumour size, based on the longest diameter of the largest tumour at diagnosis, was 5·5 cm (IQR 3·5–8·5) and 526 (90%) of 585 had a solitary tumour. Microvascular invasion was reported in 354 (61%) of 585 resected tumours and Vp1 or Vp2 portal vein invasion was noted in 39 (7%) of 585. Among patients who underwent ablation, most had a single tumour with a median size of 2·5 cm (IQR 2·3–3·0).

At the clinical data cutoff (Oct 21, 2022), the median duration of follow-up was 17·4 months (17·0 months [IQR 13·8–22·1] in the treatment group and 17·6 months [14·0–22·1] in the active surveillance group). A total of 110 patients (33%) of 334 in the atezolizumab plus bevacizumab group and 133 (40%) of 334 in the active surveillance group had recurrence per the independent

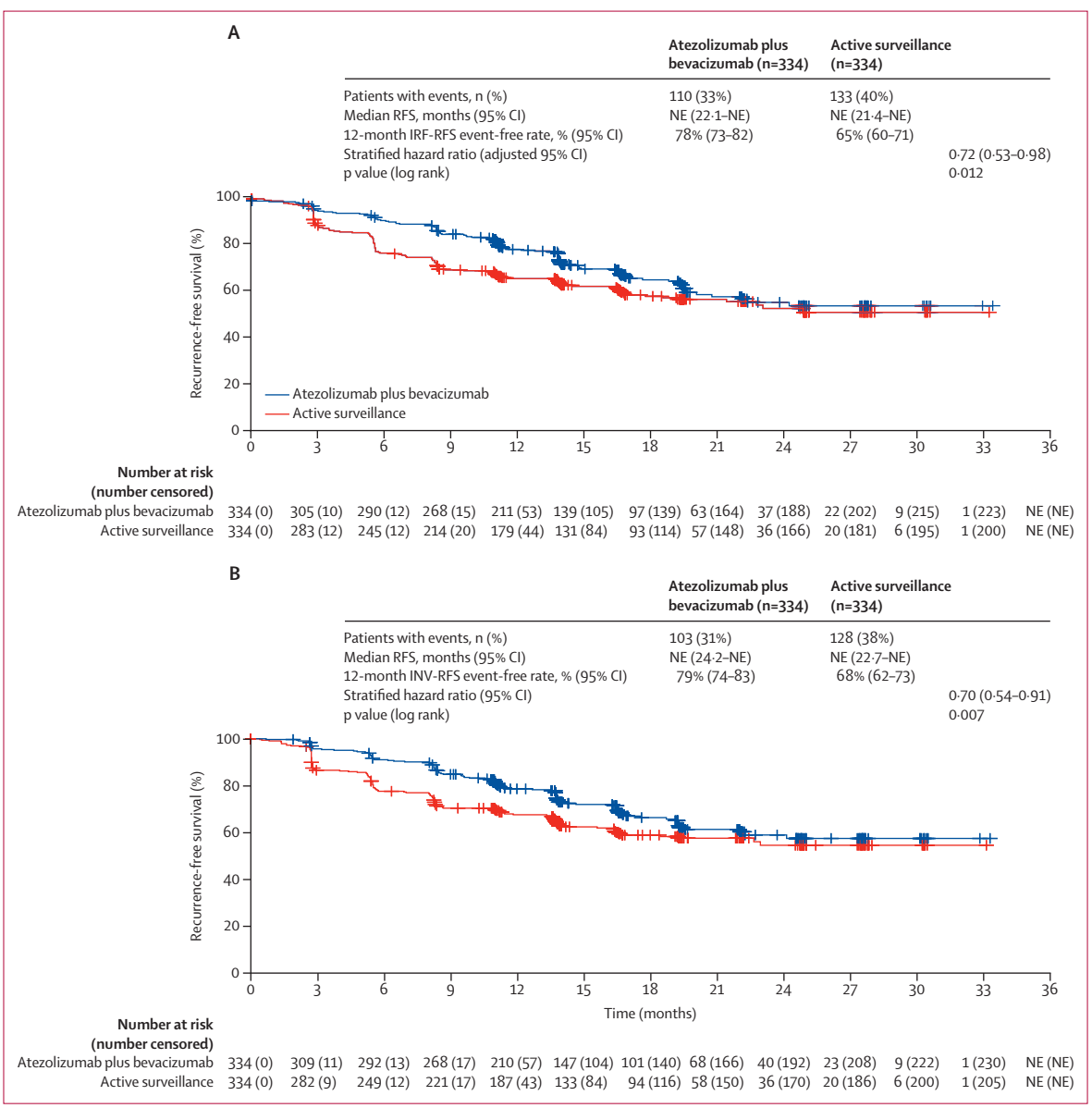

Figure 2: **Kaplan-Meier analysis of recurrence-free survival based on independent assessment (A) and investigator assessment (B)**
Kaplan-Meier estimates of IRF-assessed (A) and INV-assessed (B) RFS in patients in the intention-to-treat population. Stratified hazard ratios for recurrence or death are reported, along with p values. Stratification factors included in the stratified p value and Cox model are per interactive voice web response system. Censored events are indicated with a + symbol. IRF=independent review facility. INV=investigator. RFS=recurrence-free survival. NE=could not be evaluated.

review facility or had died. The risk of disease recurrence or death was 28% lower with adjuvant atezolizumab plus bevacizumab than with active surveillance (HR 0·72, adjusted 95% CI 0·53–0·98; p=0·012). The median RFS was not reached in either group (figure 2A). The difference in RFS event-free rates at 12 months was 13% (95% CI 6–20). The HR for RFS as assessed by study investigators (0·70, 95% CI 0·54–0·91; descriptive p=0·0070) was consistent with that from independent review facility assessment (figure 2B). Patients in the atezolizumab plus bevacizumab group had a 33% reduction in the risk of independent review facility-assessed disease recurrence compared with the active surveillance group (HR 0·67; 0·52–0·88; descriptive p=0·0030; appendix p 12). Among 231 patients (100 in the atezolizumab plus bevacizumab group and 131 in the active surveillance group) who developed recurrence, the majority were intrahepatic recurrences in both groups (67 [67%] of 100 and 86 [66%] of 131 respectively; appendix p 8). The proportion of patients experiencing extrahepatic or both intrahepatic and extrahepatic recurrence was similar in both groups (appendix p 8).

Prespecified subgroup analyses are shown in figure 3. HRs for disease recurrence or death favoured atezolizumab plus bevacizumab across most prespecified subgroups.

At the time of the RFS interim analysis, OS was very immature, with a 7% event-to-patient ratio. There were 47 deaths across the study, 27 (8%) with atezolizumab plus bevacizumab and 20 (6%) with active surveillance. Median OS was not reached in either group (appendix p 13). The HR for death was 1·42 (95% CI 0·80–2·54). In the atezolizumab plus bevacizumab group, 17 (63%) deaths were due to progressive disease, six (22%) due to adverse events, and four (15%) due to other causes. In the active surveillance group, 16 (80%) deaths were due to progressive disease, one (5%) due to adverse events, and three (15%) due to other causes. Within the first year after random allocation, there were three COVID-19-related deaths, all in the atezolizumab plus bevacizumab group.

Of the 133 patients with an RFS event during active surveillance, 81 (61%) crossed over to atezolizumab plus bevacizumab (appendix p 14). Of the patients who received crossover atezolizumab plus bevacizumab, 29 (36%) of 81 patients underwent a second ablation or resection before commencing treatment.

The safety-evaluable population included 332 patients in the atezolizumab plus bevacizumab and 330 in the active surveillance group. The median number of atezolizumab and bevacizumab cycles was 17 (IQR 10–17) and 15 (8–17), respectively. The median duration of treatment was 11·1 months (7·7–11·3) for atezolizumab and 11·0 months (5·6–11·2) for bevacizumab.

Adverse events of any cause occurred in 326 patients (98%) of 332 who received atezolizumab plus bevacizumab and 205 (62%) of 330 in the active surveillance group before crossover. The most common adverse events of any grade regardless of causality in the atezolizumab plus bevacizumab group were proteinuria, hypertension, and decreased platelet count (table 2). Most of these common adverse events were grade 1 or 2. Grade 3 or 4 adverse events occurred in 136 (41%) of 332 patients in the atezolizumab plus bevacizumab group and 44 (13%) of 330 patients in the active surveillance group. Grade 3–4 adverse events with a 2% or greater difference between the atezolizumab plus bevacizumab and the active surveillance group were hypertension, proteinuria, and decreased platelet count (table 2). Immune-mediated adverse events of any grade occurred in 208 (63%) of 332 patients in the atezolizumab plus bevacizumab group and 59 (18%) of 330 patients in the active surveillance group. These events were grade 3 or 4 in 32 patients (10%) and eight patients (2%) in each group, respectively (appendix pp 9–10). The most common immune-mediated events of any grade in the atezolizumab plus bevacizumab or active surveillance groups were hepatic adverse events (ie, hepatitis [diagnosis and laboratory abnormalities]) and hypothyroidism; most of these events were grade 1 or 2 (appendix pp 9–10). Most hepatic adverse events were alanine aminotransferase increased, aspartate aminotransferase increased, and blood bilirubin increased. Immune-mediated adverse events requiring systemic corticosteroids occurred in 28 patients (8%) in the atezolizumab plus bevacizumab group and three (1%) in the active surveillance group.

The most common adverse events of special interest with bevacizumab in the atezolizumab plus bevacizumab group and in the active surveillance group were proteinuria, hypertension, and bleeding or haemorrhage (appendix p 11). Most of these events were grade 1 or 2. The most commonly reported bleeding or haemorrhage events were minor bleeding (eg, grade 1–2 epistaxis, haematuria, and gingival bleeding).

Grade 5 events occurred in six patients (2%; COVID-19 [n=2]; pneumonia aspiration [n=1]; oesophageal varices haemorrhage [n=1], upper gastrointestinal haemorrhage [n=1], ischaemic stroke [n=1]) in the atezolizumab plus bevacizumab group, and one patient (<1%; oesophageal varices haemorrhage) in the active surveillance group. In the atezolizumab plus bevacizumab group, two of the six grade 5 events were considered related to treatment by investigator assessment (oesophageal varices haemorrhage and ischaemic stroke). One death due to oesophageal varices haemorrhage occurred in the active surveillance group.

Adverse events of any grade that led to discontinuation of both atezolizumab and bevacizumab occurred in 29 (9%) patients.

Discussion

Despite concerted efforts, effective adjuvant treatment for hepatocellular carcinoma has proven elusive.[12,27] To our knowledge, IMbrave050 is the first phase 3 study of adjuvant treatment for hepatocellular carcinoma to report positive results.

	Number of patients	Median recurrence-free survival, months		Unstratified hazard ratio (95% CI)
		Atezolizumab plus bevacizumab (n=334)	Active surveillance (n=334)	
Age, years				
<65	427	Not estimable	Not estimable	0·80 (0·58–1·08)
≥65	241	Not estimable	Not estimable	0·64 (0·41–1·00)
Sex				
Male	555	Not estimable	24·9	0·74 (0·56–0·98)
Female	113	Not estimable	Not estimable	0·73 (0·38–1·40)
Race				
Asian	545	Not estimable	Not estimable	0·75 (0·56–0·99)
White	78	Not estimable	23·0	0·59 (0·28–1·25)
Other	45	19·3	22·7	0·91 (0·36–2·29)
Geographical region				
Asia-Pacific excluding Japan	475	Not estimable	Not estimable	0·80 (0·59–1·08)
Rest of world	193	Not estimable	22·7	0·61 (0·38–0·97)
Eastern Cooperative Oncology Group performance status score				
0	527	Not estimable	Not estimable	0·65 (0·48–0·87)
1	141	19·4	23·0	1·13 (0·67–1·91)
Baseline programmed death-ligand 1 expression				
≥1%	294	Not estimable	Not estimable	0·82 (0·55–1·20)
<1%	270	22·1	16·8	0·62 (0·43–0·91)
Unknown	104	Not estimable	Not estimable	0·82 (0·39–1·71)
Number of of high-risk features				
1	311	Not estimable	Not estimable	0·74 (0·48–1·14)
≥2	274	16·8	13·9	0·77 (0·55–1·08)
Not applicable*	83	Not estimable	Not estimable	0·61 (0·26–1·41)
Barcelona Clinic Liver Cancer stage at study entry				
0/A	569	Not estimable	Not estimable	0·78 (0·59–1·04)
B	57	20·7	18·5	0·44 (0·18–1·08)
C	42	14·7	11·0	0·73 (0·31–1·73)
Hepatocellular carcinoma cause				
Hepatitis B	416	Not estimable	Not estimable	0·87 (0·63–1·20)
Hepatitis C	72	Not estimable	24·9	0·65 (0·30–1·40)
Non-viral	83	Not estimable	22·7	0·70 (0·34–1·42)
Unknown	97	Not estimable	16·7	0·45 (0·23–0·89)
Curative procedure				
Resection	585	Not estimable	Not estimable	0·75 (0·58–0·98)
Ablation	83	Not estimable	Not estimable	0·61 (0·26–1·41)
Number of tumours†				
1	526	Not estimable	Not estimable	0·77 (0·58–1·03)
>1	59	20·7	7·0	0·60 (0·28–1·27)
Tumour size, cm†				
>5	327	19·4	14·0	0·66 (0·48–0·91)
≤5	258	Not estimable	Not estimable	1·06 (0·65–1·74)
Microvascular invasion†				
Yes	354	22·1	Not estimable	0·79 (0·56–1·10)
No	231	Not estimable	24·9	0·69 (0·45–1·06)
Poor tumour differentiation†				
Yes	245	Not estimable	18·5	0·76 (0·51–1·12)
No	340	Not estimable	Not estimable	0·74 (0·52–1·07)
Transarterial chemoembolisation†				
Yes	66	14·9	Not estimable	1·21 (0·57–2·59)
No	519	Not estimable	Not estimable	0·71 (0·53–0·94)
All patients	**668**	**Not estimable**	**Not estimable**	**0·74 (0·57–0·95)**

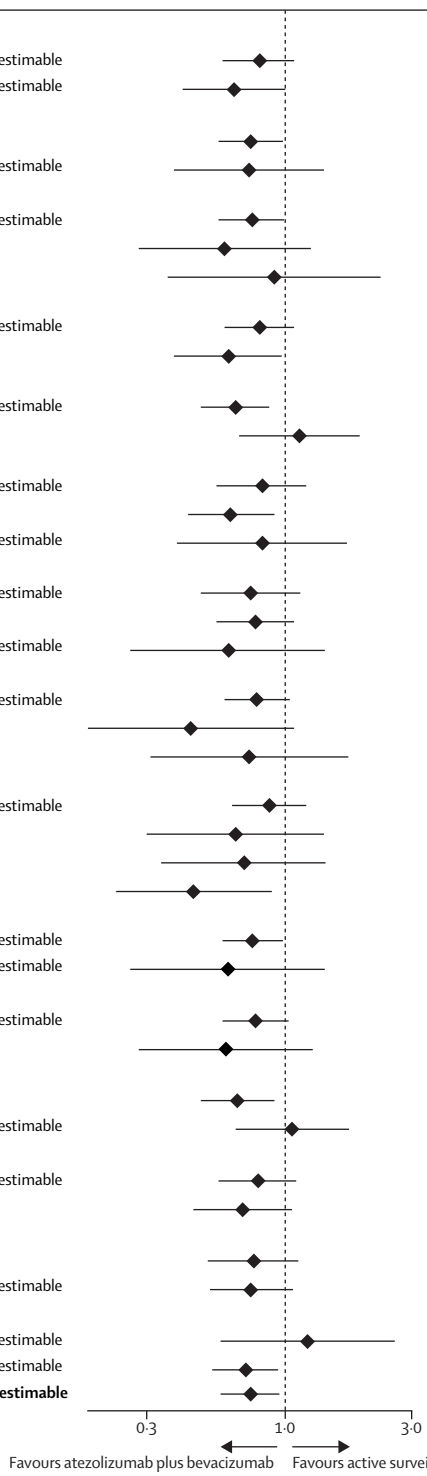

Figure 3: **Recurrence-free survival by subgroup**
Confidence intervals were not adjusted for multiplicity. Race was reported by the patients. Eastern Cooperative Oncology Group performance status scores range from 0 to 5, with higher scores indicating greater disability. *Patients who underwent ablation were categorised in the not applicable category. †In patients who underwent resection.

	Atezolizumab plus bevacizumab (n=332)			Active surveillance (n=330)		
	Any grade	Grade 3 or 4	Grade 5	Any grade	Grade 3 or 4	Grade 5
Any adverse event	326 (98%)	136 (41%)	6 (2%)	205 (62%)	44 (13%)	1 (<1%)
Related adverse event	293 (88%)	116 (35%)	2 (<1%)	NA	NA	NA
Serious adverse event	80 (24%)	53 (16%)	6 (2%)	34 (10%)	26 (8%)	1 (<1%)
Related serious adverse event	44 (13%)	32 (10%)	2 (<1%)	NA	NA	NA
Adverse event leading to withdrawal from both atezolizumab and bevacizumab	29 (9%)	23 (7%)	0	NA	NA	NA
Adverse event leading to withdrawal from atezolizumab	31 (9%)	24 (7%)	0	NA	NA	NA
Adverse event leading to withdrawal from bevacizumab	62 (19%)	38 (11%)	0	NA	NA	NA
Adverse events (of any grade) with an incidence rate of at least 10% in either treatment group by preferred term						
Proteinuria	154 (46%)	29 (9%)	0	12 (4%)	0	0
Hypertension	127 (38%)	61 (18%)	0	10 (3%)	3 (1%)	0
Platelet count decreased	66 (20%)	15 (5%)	0	22 (7%)	4 (1%)	0
Aspartate aminotransferase increased	52 (16%)	3 (1%)	0	18 (5%)	2 (1%)	0
Alanine aminotransferase increased	47 (14%)	2 (1%)	0	18 (5%)	3 (1%)	0
Hypothyroidism	47 (14%)	0	0	1 (<1%)	0	0
Arthralgia	40 (12%)	1 (<1%)	0	8 (2%)	1 (<1%)	0
Pruritus	40 (12%)	1 (<1%)	0	3 (1%)	0	0
Rash	40 (12%)	0	0	1 (<1%)	0	0
Blood bilirubin increased	34 (10%)	1 (<1%)	0	23 (7%)	1 (<1%)	0
Pyrexia	34 (10%)	0	0	7 (2%)	0	0

Data are n (%). NA=not available.

Table 2: **Safety summary for the safety-evaluable population**

At the prespecified interim analysis, results from the IMbrave050 study showed that adjuvant treatment with atezolizumab plus bevacizumab conferred a statistically significant and clinically meaningful improvement in RFS, compared with active surveillance, in patients with hepatocellular carcinoma who had undergone curative-intent liver resection or ablation and had a high risk of disease recurrence.

The RFS Kaplan-Meier curves separated early and remained clearly separated up to the median follow-up of 17·4 months, after which the curves began to come together. The numbers at risk beyond the median follow-up are small, with an appreciable amount of censoring in both groups. Thus, the Kaplan-Meier estimates in the tails of the curve were not stable, and longer follow-up is needed. Early separation could indicate that atezolizumab plus bevacizumab is targeting early recurrence events associated with micrometastases. Further follow-up will be required to determine the effect of atezolizumab plus bevacizumab on late recurrence events (after 24 months) that are more associated with the underlying disease. Longer follow-up will also be needed to see whether the wide early separation of the RFS curves with later convergence will be maintained. The RFS benefit with atezolizumab plus bevacizumab was generally consistent across key clinical subgroups. However, in some subgroups the number of events was small and should be interpreted with caution. The benefit of atezolizumab plus bevacizumab appeared to be enhanced, relative to the overall population, in patients who had tumours larger than 5 cm, had more than one tumour, or underwent ablation. Conversely, less benefit was observed in subgroups with an Eastern Cooperative Oncology Group performance status score of 1, tumour size 5 cm or smaller, and adjuvant transarterial chemoembolisation. Further descriptive analyses with more mature data are planned in the subsequent analyses. Observations from subgroup analyses are hypothesis generating.

Identification of patients at high risk of relapse is critical for the design of adjuvant studies because postoperative therapy might be particularly beneficial in this subgroup. A principle criticism of the STORM trial was that it enrolled a patient population at relatively low risk of recurrence (92% with a single tumour; median tumour size, 3·5 cm; 32% with microvascular invasion).[12,28] In our study, we sought to include patients at high risk of recurrence, defined according to tumour-related and clinicopathological factors.[5,29] The median tumour size in our study is similar to that reported in global retrospective studies of resected hepatocellular carcinoma; more than half of patients who underwent resection had a tumour larger than 5 cm, and the proportion of patients with microvascular invasion and poor tumour differentiation is higher than that in previous adjuvant studies and retrospective studies, reflecting a population at high risk of early recurrence.[5,29,30] In the context of ablation, tumours larger than 2 cm are associated with a higher rate of tumour recurrence than are those smaller than 2 cm.[31,32] In our study, the median tumour size was 2·5 cm for patients who underwent ablation, reflecting a population at high risk of recurrence. However, the size of the ablation subgroup is small, and the confidence interval for RFS crosses one, precluding definitive interpretation. Additional studies of post-ablation adjuvant therapy are warranted.

The very early separation of the RFS and time-to-recurrence Kaplan-Meier curves might reflect the enrolment of a population at high risk of recurrence. In the active surveillance group, several patients had recurrence within 3–6 months following curative treatment. This observation is consistent with retrospective studies that have reported that approximately a third of patients have recurrence within 6–8 months after resection.[33,34] Most postoperative recurrences were intrahepatic in both groups, which is consistent with retrospective data series in comparable

patient populations.[10] With longer follow-up, additional data will allow for a more detailed analysis of the patterns and characteristics of recurrence, including localised versus multifocal intrahepatic recurrence, and time to extrahepatic recurrence will be undertaken and presented in future publications.

The OS analysis was immature at the data cutoff and included only 47 deaths (7% event-to-patient ratio), which was far fewer than the protocol assumption of 107 deaths. With so few events, meaningful interpretation of OS is not possible. Our trial is ongoing, and further analysis of OS will be conducted in the next prespecified OS interim analysis. Importantly, per protocol we allowed crossover to atezolizumab plus bevacizumab for patients randomly allocated to the active surveillance group upon independent review facility confirmation of recurrence, which will probably confound OS. At the data cutoff, 61% of patients with centrally confirmed recurrence crossed over to receive atezolizumab and bevacizumab.

The protocol-defined 17-cycle period of atezolizumab and bevacizumab treatment is consistent with other ongoing adjuvant immunotherapy trials for hepatocellular carcinoma,[35,36] and most patients in our study were able to receive the planned 17 cycles. The spectrum, incidence, and severity of adverse events observed with adjuvant atezolizumab plus bevacizumab were generally consistent with the known safety profile of each agent and with the underlying disease. The adverse event profile of adjuvant atezolizumab plus bevacizumab was similar to that reported in patients with advanced hepatocellular carcinoma in IMbrave150.[17] Although the percentage of patients who had grade 3 or 4 adverse events was higher in the atezolizumab plus bevacizumab group than in the active surveillance group (41% *vs* 13%), the most common grade 3 or 4 adverse events with a 2% or greater difference between both groups were hypertension, proteinuria, and decreased platelet count, all of which are known adverse drug reactions associated with bevacizumab. Furthermore, the incidence of grade 3 or 4 adverse events observed in the hepatocellular carcinoma adjuvant setting (ie, this study) is lower in comparison with the incidence of these events in the unresectable hepatocellular setting (ie, IMbrave150; 41% *vs* 57%, respectively) even though the median duration of atezolizumab plus bevacizumab treatment was much longer in the adjuvant setting (atezolizumab, 11·1 months *vs* 7·4 months, respectively; bevacizumab, 11·0 months *vs* 6·9 months, respectively).[17] Immune-mediated adverse events and toxicities associated with vascular endothelial growth factor inhibition occurred more frequently in treated patients, which was expected as these are known risks with atezolizumab combined with bevacizumab. Notably, the incidence of proteinuria and hypothyroidism (predominantly grades 1 or 2) was higher in IMbrave050 than in IMbrave150, which might reflect a longer duration of treatment in the adjuvant setting.[17] Bleeding is a known adverse reaction to bevacizumab and, as expected, bleeding events were more common in patients treated with atezolizumab plus bevacizumab; these bleeding events primarily included grade 1 or 2 epistaxis, haematuria, and gingival bleeding. Oesophageal varices haemorrhage is a common and potentially life-threatening complication in patients with cirrhosis and hepatocellular carcinoma. As in IMbrave150,[17] patients in our trial were evaluated for the presence of varices before enrolment, and varices of any size were assessed and treated per local standards of care. The incidence of all-grade oesophageal varices haemorrhage was slightly lower in our study than in IMbrave150 (2%).[17] Overall, although more toxicity was observed in the atezolizumab plus bevacizumab group than in the active surveillance group, it was generally tolerable, and median duration of treatment with atezolizumab was 11·1 months and that with bevacizumab was 11·0 months. However, the risk of treatment-related toxicity should be weighed against the degree of treatment benefit, which in this case is a 28% reduction in the risk of recurrence or death. In this context, the initial overall benefit to risk ratio appears to be favourable; however, longer follow-up of RFS and OS (as well as toxicity) is needed to more fully characterise this assessment.

In prespecified exploratory analyses of patient-reported outcomes, patients did not experience any clinically meaningful deterioration at any time during the treatment period.[37] Health-related quality-of-life and functioning scores between the atezolizumab plus bevacizumab and the active surveillance group were similar throughout treatment, as evidenced by overlapping 95% CIs for the majority of datapoints.[37]

To our knowledge, IMbrave050 is the first phase 3 study to report positive results in the adjuvant hepatocellular carcinoma setting. Other ongoing global randomised phase 3 studies evaluating either anti-programmed death-1 (PD-1) or PD-L1 monotherapy, or dual PD-L1 and vascular endothelial growth factor blockade could further elucidate the role of checkpoint inhibitor-based adjuvant therapy for hepatocellular carcinoma, including delineating the relative benefits of single-agent PD-1 or PD-L1 blockade versus combination treatment. Building on the positive outcome of IMbrave050, the role of immunotherapy in the neoadjuvant (preoperative treatment) or perioperative (neoadjuvant followed by adjuvant therapy) treatment setting remains to be evaluated. A series of small phase 2 studies have reported preliminary evidence of efficacy, safety, and favourable modulation of antitumour immunity with neoadjuvant PD-1-based or PD-L1-based regimens.[38–40] Additional randomised studies in hepatocellular carcinoma are warranted.

Strengths of our study include the use of the recommended primary endpoint and stratification factors suggested for adjuvant studies in hepatocellular carcinoma.[41] In addition, our study used standardised and internationally recognised criteria for intrahepatic and extrahepatic hepatocellular carcinoma recurrence.[16,26] The

study also has some limitations. The open-label design was used to spare patients in the control group from two placebo infusions and unwarranted corticosteroids or other immunosuppressants to manage toxicities with a suspected immune cause. To minimise potential bias associated with the open-label design, a masked independent review of imaging for RFS was selected as the primary endpoint. Notably, independent review and investigator assessment of RFS benefit with atezolizumab plus bevacizumab had similar results. This interim analysis is limited by the relatively short follow-up duration; however, 33% of patients in the atezolizumab plus bevacizumab group and 40% in the active surveillance group had already had disease recurrence or had died. Our study enrolled patients at high risk of recurrence; therefore, the benefit with adjuvant atezolizumab plus bevacizumab in patients with lower risk or very high risk is unknown. Most patients were recruited from the Asia-Pacific region, primarily China, compared with the USA and Europe. Nonetheless, based on tumour burden and staging, the patients enrolled reflect real-world data on surgical resection for hepatocellular carcinoma globally, and are aligned with major treatment guidelines for resection or ablation in both western and Asian countries.[42–44] Consistent with other recent global hepatocellular carcinoma trials, enrolment of patients from under-represented minority groups was poor.

In conclusion, adjuvant atezolizumab plus bevacizumab was associated with a statistically significant improved RFS compared with active surveillance for patients at high risk of recurrence following resection or local ablation. These positive findings, coupled with a safety profile that was consistent with previous studies and had no new safety signals, suggest that the combination of atezolizumab plus bevacizumab offers a promising adjuvant treatment option. These results might affect recommendations for clinical practice, and could lead to new considerations in clinical indications for surgical resection.

Contributors

All authors met the International Committee of Medical Journal Editors criteria for authorship, were involved in critical review of the manuscript, and approved the final version for submission. SPH and PKHC wrote the first draft of the report. QL conducted the statistical analyses. QL and PKHC have directly accessed and verified the underlying data reported here. All steering committee members contributed equally to the study.

Declaration of interests

A-LC reports honoraria from BMS, Eisai, Ipsen, and Ono Pharmaceutical; consulting or advisory roles with Bayer Schering Pharma, BMS, Eisai, Exelixis, Ipsen, IQVIA, Merck Serono, Novartis, Nucleix, Omega Therapeutics, Ono Pharmaceutical, and Roche/Genentech; and participation on data monitoring or advisory boards for Abbisko Therapeutics. AOK reports honoraria from AstraZeneca, Bayer, BMS, Eisai, Exelixis, Merck, and Roche/Genentech; and travel expenses from Roche/Genentech. MK reports honoraria from Bayer, Chugai, Eisai, Eli Lilly, and Takeda; and grants or contracts from AbbVie, Chugai, EA Pharma, Eisai, GE Healthcare, Otsuka, and Taiho. HCL reports grants or contracts from AstraZeneca, MSD, and Roche. JH reports a leadership role in AstraZeneca; honoraria from Oncolys; consulting or advisory roles with AbbVie Korea; grants or contracts from Roche; and speaker's bureau from AstraZeneca, Gilead, Roche, and Yuhan Korea. WYT reports consulting or advisory roles with Eisai Korea, Roche Korea, and Sysmex Korea; and speaker's bureau from Bayer Korea, Gilead Korea, Samil Pharm, and Yuhan. TU reports grants or contracts from Roche and travel expenses from Gilead. EC, NM, JHS, YW, SPH, and QL report employment at Genentech and stock in Roche. CW reports employment at, and stock in, Roche. PKHC reports being Chief Medical Officer for AVATAMED; stock in AVATAMED; honoraria from AstraZeneca, Bayer, Perspectum, Roche, Sirtex, and Worrell; consulting fees from Asia-Pacific Association for the Study of the Liver, Asia-Pacific Primary Liver Cancer Expert Meeting, Bayer Liver Forum, Eastern and Western Association for Liver Tumors, Hong Kong Liver Cancer and Gastrointestinal Cancer Foundation, IQVIA, JSH International Liver Conference, Korean Radioembolization Association, Korean Radioembolization Association Webinar, Liver Cancer Collaborative Annual Scientific and Clinical Meeting, Malaysian Hepato-pancreato-biliary Congress, Malaysian Society of Interventional Radiology, Perspectum, Philippine Society of Nuclear Medicine, Roche, Singapore Hepatology Conference, State Key Laboratory of Liver Research, Taiwan Society of Interventional Radiology, and Tsinghua Medical Forum; consulting or advisory roles with AUM Biosciences, BeiGene, Omega Therapeutics, Roche, and Sirtex; grants or contracts from A*Star, AMiLi, MiRXES, National Medical Research Council, Perspectum, Roche, SingHealth Duke-NUS Programme Grant Award, SingHealth Duke-NUS Global Health Institute Pilot Research Grant, Stratificare and Sirtex; speaker's bureau from AstraZeneca, Bayer, Omega Therapeutics, Roche, and Worrell; support for attending meetings or travel expenses from Roche Diagnostics Asia Pacific and Roche Singapore; patent publication number 10202007868Q; participation in a Data Safety Monitoring Board or Advisory Board for AUM Biosciences, Genentech, IMCB, Perspectum, and Singapore-Samsung Medical Centre (SG-SMC) Joint Lab; and receipt of equipment, materials, drugs, assistance with medical writing, gifts, or other services from Roche and Sirtex. All other authors declare no competing interests.

Data sharing

Qualified researchers can request access to individual patient-level data through the clinical study data request platform https://vivli.org/. Further details on Roche's criteria for eligible studies are available at https://vivli.org/members/ourmembers/. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

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