Liver resection after atezolizumab and bevacizumab versus maintenance therapy for locally advanced hepatocellular carcinoma (TALENTOP): a multicentre, open-label, randomised, phase 3 trial

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Summary

Background Resection might offer additional benefit in patients with advanced-stage hepatocellular carcinoma treated with systemic therapy. However, high-quality evidence supporting the procedure is absent. We aimed to establish whether resection can provide survival benefit in patients with advanced hepatocellular carcinoma who respond to systemic therapy.

Methods In this randomised, open-label, multicentre, phase 3 trial, we recruited treatment-naive patients with hepatocellular carcinoma, macrovascular invasion, and no extrahepatic metastasis from 24 hospitals in China. These patients were treated in the induction phase with three cycles of intravenous atezolizumab (1200 mg every 3 weeks) plus intravenous bevacizumab (15 mg/kg bodyweight every 3 weeks) and one cycle of atezolizumab monotherapy. Patients who completed the induction phase, had a partial response or stable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and were considered feasible for resection were randomly assigned (1:1) to undergo surgical resection followed by 12 months of atezolizumab plus bevacizumab initiated 4–6 weeks after surgery (ie, the surgery group), or to maintenance atezolizumab plus bevacizumab until loss of clinical benefit or intolerable toxicity (the maintenance therapy group). Randomisation was by computer-generated sequence with permuted blocks via a central interactive web response system, stratified by tumour response and Eastern Cooperative Oncology Group performance status. Treatment administered to patients was not masked. The primary endpoint was time to treatment failure, assessed by an independent review facility and analysed by intention to treat. Time to treatment failure was defined as the time from randomisation to the first documented treatment failure (ie, local recurrence or disease progression according to RECIST 1.1, emergence of extrahepatic spread, or death). This study is registered with ClinicalTrials.gov (NCT04649489) and is ongoing.

Findings Between April 4, 2021, and July 18, 2024, a total of 489 patients were enrolled in the induction phase. Of them, 201 were randomly assigned to the surgery group (n=101; 93 male, eight female) or the maintenance therapy group (n=100; 87 male, 13 female). After a median follow-up of 18·4 months, the median time to treatment failure was 20·4 months in the surgery group and 11·8 months in the maintenance therapy group (hazard ratio 0·60, 95% CI 0·39–0·91; p=0·015). Grade 3 or 4 treatment-related adverse events occurred in 32 (39%) of 83 patients in the surgery group and 21 (21%) of 100 in the maintenance therapy group, the most common of which were increased alanine aminotransferase (seven patients [8%] in the surgery group *vs* one [1%] in the maintenance therapy group), reduced platelet count (seven [8%] *vs* three [3%]), and proteinuria (three [4%] *vs* seven [7%]). Two treatment-related deaths occurred in the surgery group due to abnormal liver function (considered related to atezolizumab) and liver failure (considered related to atezolizumab, bevacizumab, or surgery).

Interpretation In patients with advanced hepatocellular carcinoma with macrovascular invasion after systemic therapy, time to treatment failure was longer in those who had liver resection than in those who received maintenance therapy.

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Introduction

Hepatocellular carcinoma is the main pathological type of liver cancer, which is the sixth most common cancer and the third leading cause of cancer mortality worldwide.[1] For patients with advanced stage hepatocellular carcinoma, systemic therapy is the

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Research in context

Evidence before this study

We searched PubMed from database inception to Feb 28, 2026, using the search terms "hepatocellular carcinoma", "HCC", "resection", "surgery", "PD-1 inhibitor", "PD-L1 inhibitor", "immune checkpoint inhibitors", "anti-angiogenic", "atezolizumab", and "bevacizumab", with no language restrictions, and identified no randomised controlled trials with published data similar to TALENTOP. Atezolizumab plus bevacizumab has been established as the first-line standard of care for unresectable hepatocellular carcinoma (HCC) based on the IMbrave150 trial. However, long-term survival outcomes remain unsatisfactory. Several retrospective studies have suggested that liver resection might provide additional curative opportunities and improve prognosis in patients with advanced HCC who respond to systemic therapy. The survival benefit of liver resection followed by systemic therapy compared with maintenance systemic therapy has not been prospectively evaluated, and direct head-to-head comparisons between these two treatment strategies are yet to be established.

Added value of this study

To our knowledge, TALENTOP is the first multicentre, randomised, phase 3 trial designed to assess whether liver resection can provide a time-to-treatment-failure benefit in patients with advanced HCC who respond to systemic therapy. This question represents a common clinical dilemma for surgeons and medical oncologists in the era of immunotherapy and is of paramount concern to patients and their families. The TALENTOP study showed that, compared with maintenance systemic therapy, liver resection provided a statistically significant and clinically meaningful benefit in time to treatment failure.

Implications of all the available evidence

The favourable risk–benefit profile for the TALENTOP regimen supports atezolizumab plus bevacizumab as an effective conversion therapy in patients with advanced HCC. Patients who have a partial response or stable disease after initial systemic therapy should undergo multidisciplinary team assessment for resectability and be considered for liver resection.

standard of care.[2] Patients who respond to systemic therapy typically continue the same regimen until disease progression or onset of intolerable adverse effects. In patients receiving atezolizumab plus bevacizumab treatment, one of the standard-of-care approaches for those with unresectable hepatocellular carcinoma,[3] the median duration of response was 18·1 months (95% CI 14·6–not evaluable).[4] Effective second-line options after progression remain scarce.[5,6] However, complete responses with systemic therapy alone are rare; most patients experience only temporary tumour control, with residual tumours remaining and no chance for a cure.[7,8]

Several studies have reported favourable outcomes following curative resection in selected patients whose tumours were down-staged or downsized after immunotherapy, providing preliminary evidence for conversion therapy followed by curative resection as a potential treatment strategy.[9–11] Surgical resection might provide longer recurrence-free survival for some patients, and conversion therapy has become a key focus in several guidelines, including the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines,[12] the Barcelona Clinic Liver Cancer (BCLC) strategy,[13] and the China Liver Cancer (CNLC) guideline;[5] however, due to the paucity of robust evidence, clinical decision making remains challenging. To investigate the clinical value of conversion resection for patients with locally advanced hepatocellular carcinoma after systemic therapy, we initiated the TALENTOP study. In this study, we aimed to assess the efficacy and safety of liver resection versus maintenance atezolizumab plus bevacizumab in locally advanced hepatocellular carcinoma after atezolizumab plus bevacizumab treatment.

See Online for appendix 1

See Online for appendix 2

Methods

Study design

TALENTOP is a multicentre, open-label, randomised, phase 3 trial conducted across 24 hospitals in China. Participating sites had to be a tertiary hospital with (1) an established hepatobiliary surgical programme experienced in major liver resection for hepatocellular carcinoma; (2) capacity to deliver and monitor atezolizumab plus bevacizumab, including immune-related adverse events; and (3) a functioning multidisciplinary team for treating and monitoring patients with hepatocellular carcinoma. The trial protocol was approved by the institutional review board or ethics committee at each participating site (appendix 1 pp 2–3). Patients or members of the public were not involved in the design, conduct, reporting, or dissemination plans of this research. The study was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. A prespecified safety analysis was done in the first ten patients who had surgical resection, and an independent safety review committee reviewed urgent and critical safety events as well as overall safety data, confirming that the procedure was generally safe.[14] The protocol and statistical analysis plan for this study are available in appendix 2. Protocol deviations were documented, reviewed, and reported throughout the study and were defined as any change, divergence, or departure from the trial design or procedures specified in the protocol. Investigators were required to document and explain all protocol deviations. Deviations that might have affected patient safety or data integrity were promptly reported to the sponsor and the relevant institutional review board or ethics committee in accordance with local policies and procedures. The

sponsor reviewed all protocol deviations and determined their clinical significance. This trial is registered with ClinicalTrials.gov (NCT04649489) and is ongoing.

Patients

Eligible patients were aged 18 years or older, had histologically or radiologically confirmed hepatocellular carcinoma according to American Association for the Study of Liver Diseases criteria,[15] had not received previous anti-tumour therapy, had at least one measurable lesion with macrovascular invasion and no extrahepatic spread, had a future liver remnant ratio of at least 25%, had Child–Pugh class A liver function, and an Eastern Cooperative Oncology Group performance status of 0 or 1. Key exclusion criteria included known fibrolamellar, sarcomatoid, or mixed cholangiocarcinoma–hepatocellular carcinoma histology; severe, untreated oesophagogastric varices; clinically significant ascites; or a history of hepatic encephalopathy. Full eligibility criteria are provided in the trial protocol in appendix 2 (pp 88–92). Biological sex was self-reported by patients at enrolment, with male and female as the available options. Race and ethnicity were also self-reported by patients at enrolment. All patients provided written informed consent before enrolment.

Randomisation and masking

Eligible participants received an induction phase of intravenous atezolizumab (1200 mg every 3 weeks for three cycles) plus bevacizumab (15 mg/kg bodyweight every 3 weeks for three cycles), followed by one cycle of atezolizumab monotherapy (1200 mg). All treatments were administered by intravenous infusion on day 1 of each 21-day cycle. Patients who completed the induction phase and had a partial response or stable disease (according to Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1 criteria) and were considered feasible for liver resection by the investigators, were assessed for eligibility. Criteria for resection included technical feasibility of complete (R0) resection and adequate performance status, as well as an adequate future liver remnant ratio (≥40% of standard liver volume in patients with chronic liver disease, parenchymal injury, or cirrhosis, and ≥30% in those without hepatic fibrosis or cirrhosis).[5,16] Given the inherent subjectivity in determining resectability, a structured adjudication process was implemented. Resectability was independently assessed by the national principal investigator and by a site-level panel comprising the site principal investigator and the multidisciplinary tumour board at each participating centre. Tumour response (either partial or stable disease) was evaluated by an independent review facility (IRF). All site investigators received standardised training on these criteria, and the lead principal investigator conducted regular site visits to ensure protocol adherence and consistency across centres. Patients who met these criteria were randomly assigned in a 1:1 ratio to receive liver resection followed by 12 months of atezolizumab plus bevacizumab (initiated 4–6 weeks after surgery; the surgery group) or to continue atezolizumab plus bevacizumab until loss of clinical benefit or unacceptable toxicity (the maintenance therapy group). Randomisation was done with a computer-generated sequence with permuted blocks and was stratified according to tumour response (ie, a ≥10% reduction in the sum of diameters of target lesions from screening to pre-randomisation visit *vs* a <10% reduction) and Eastern Cooperative Oncology Group performance status (0 *vs* 1). The allocation sequence was generated by an independent statistician who took no further part in the trial and had no involvement in patient recruitment, treatment, outcome assessment, or data analysis. The sequence was loaded into a central interactive web response system, to which no investigator or site staff member had access. Patients were enrolled by the treating site investigators, who entered eligibility confirmation and stratification factors into the system, and the system then assigned each patient to a trial group. No member of the study team was involved in generating or holding the allocation sequence. The trial was open-label, and treatment administered to patients was unmasked.

Procedures

Tumours were assessed by contrast-enhanced CT or MRI according to RECIST version 1.1 and mRECIST after cycle 2 and on day 21 (±7 days) of cycle 4 of the induction phase (pre-randomisation baseline), and at regular intervals thereafter. After randomisation, patients assigned to liver resection were allowed an additional assessment before surgery as a preoperative confirmation, a further assessment in the preceding 7 days of the first postoperative dose, and assessments every 9 weeks (±7 days) thereafter. Patients assigned to continued drug therapy had a tumour assessment at week 6 (±7 days) after randomisation and every 9 weeks (±7 days) thereafter. All tumour assessments were completed within 7 days before dosing. All resections were done by surgeons qualified in liver resection, each holding the rank of Associate Chief Physician or above.

Safety was monitored systematically and prospectively throughout the study. Vital signs, clinical laboratory parameters, and the incidence and severity of adverse events were assessed at each study visit and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Postoperative complications within 30 days after surgery were classified according to the Clavien–Dindo system.[17]

Outcomes

The primary endpoint was time to treatment failure, as assessed by an IRF, defined as the time from randomisation to the first documented treatment failure (ie, local recurrence or disease progression according to RECIST 1.1, emergence of extrahepatic spread, or death)

in the intention-to-treat population. Secondary endpoints comprised overall survival (defined as the time from randomisation to death from any cause); overall survival rate at 12, 18, and 24 months; investigator-assessed time to treatment failure as per RECIST 1.1; IRF-assessed and investigator-assessed time to treatment failure as per modified RECIST criteria specific to hepatocellular carcinoma; IRF-assessed and investigator-assessed time to extrahepatic spread; and safety. Further details on study endpoints are provided in the trial protocol (appendix 2 pp 82–83).

Statistical analysis

We estimated that a sample size of 198 randomly assigned patients, targeting 166 IRF-assessed time-to-treatment-failure events, would provide 80% power to detect a hazard ratio (HR) of 0·63 for the surgery group versus the maintenance therapy group using a log-rank test at a two-sided significance level of 0·05. The dropout rate was assumed to be 5% for both arms over 12 months. The target HR of 0·63 was based on an expected median time to treatment failure of approximately 9·2 months in the surgery group, derived from post-resection recurrence-free survival data for patients with hepatocellular carcinoma and Vp1–Vp4 portal vein invasion,[18] and approximately 5·8 months in the maintenance therapy group, estimated from contemporary data on patients with macrovascular invasion without extrahepatic spread who had disease control beyond 3 months on first-line atezolizumab plus bevacizumab, adjusted for the 3-month induction period.

A group-sequential design was implemented for testing the IRF-assessed time to treatment failure, with one prespecified interim analysis and a planned final analysis. The overall two-sided type I error rate was controlled at 0·05, with stopping boundaries determined using the Lan–DeMets method to approximate the Pocock boundary,[19] with the α at each analysis determined by the actual information fraction. The interim analysis was prespecified to be triggered when at least 90 IRF-assessed time-to-treatment-failure events had occurred and at least 2 months had elapsed since completion of randomisation. As of Jan 27, 2025, a total of 96 IRF-assessed time-to-treatment-failure events had occurred and the prespecified two-sided α boundary was 0·0341. Had the boundary not been crossed at interim, the α for the final analysis would have been approximately 0·026 at full information.

The key secondary endpoint, overall survival, was to be tested hierarchically if the IRF-assessed time to treatment failure reached statistical significance, with the overall type I error rate controlled at 0·05 using the Lan–DeMets method to approximate the O'Brien–Fleming boundary. As the time-to-treatment-failure interim analysis met its primary efficacy endpoint, three overall survival analyses were prespecified: the first concurrent with the time-to-treatment-failure interim analysis; the second at the planned final time-to-treatment-failure analysis or upon reaching 90 overall survival events, whichever occurs later; and the final overall survival analysis thereafter.

Multiplicity control was prespecified only for IRF-assessed time to treatment failure and overall survival. All other secondary endpoints are reported descriptively, without formal hypothesis testing.

Time to treatment failure and overall survival analyses were done in all randomly assigned patients (ie, the intention-to-treat population). For time to treatment failure, patients without an event at the time of analysis were censored at the date of the last evaluable assessment; for overall survival, patients alive at analysis were censored at the last date known to be alive. Patients without post-baseline information were censored at the randomisation date. Missing datapoints were generally not imputed, except for the date of death; specific imputation rules are provided in the statistical analysis plan (appendix 2 pp 206–207). Analyses of R0 resection (defined as complete tumour removal with microscopically negative margins) and pathological complete response (the absence of viable tumour cells in the resected specimen) were conducted in the modified intention-to-treat population of the surgery group, defined as randomly assigned patients excluding those in the surgery group who did not undergo liver resection.

Time to treatment failure and overall survival were compared between treatment arms using a stratified log-rank test. Corresponding HRs and 95% CIs were estimated with a stratified Cox proportional-hazards model. Kaplan–Meier methods were used to estimate time to treatment failure and overall survival distributions. The proportional-hazards assumption was tested using Schoenfeld residuals (supremum test based on cumulative residuals); if violated, the restricted mean survival time method was used as a sensitivity analysis. To assess the homogeneity of the treatment effect on IRF-assessed time to treatment failure across important subgroups, prespecified subgroup analyses were done and presented as forest plots based on unstratified HRs. Prespecified subgroups are listed in appendix 2 (p 11).

Safety analyses included all patients who received at least one dose of study treatment after randomisation.

Role of the funding source

Shanghai Roche Pharmaceuticals funded the study and provided the study drugs. This was an investigator-initiated trial. All funders of the study had no role in study design, data collection, data analysis, interpretation of data, or writing of the report.

Results

Between April 4, 2021, and July 18, 2024, a total of 627 patients across 24 sites in China were screened, and 489 patients entered the induction phase. After

completion of induction therapy, 201 patients (41%) were randomly assigned to receive liver resection followed by atezolizumab plus bevacizumab (ie, the surgery group, n=101) or maintenance atezolizumab plus bevacizumab (the maintenance therapy group, n=100). These patients constituted the intention-to-treat population (figure 1). The remaining patients were not randomly assigned, primarily because of disease progression (n=183) or because the investigator assessed that discontinuation of treatment was most appropriate for the patient (n=60), protocol deviation (n=15), adverse events (n=13), withdrawal of consent (n=11), death (n=4), loss to follow-up (n=1), and other reasons (n=1). Baseline demographic and disease characteristics of the randomly assigned patients were well balanced across the treatment arms (table 1). In the surgery group, 83 patients (82%) underwent liver resection followed by atezolizumab plus bevacizumab. In the maintenance therapy group, all 100 patients (100%) received atezolizumab plus bevacizumab. These patients comprised the safety population.

As of the clinical data cutoff (Jan 27, 2025), the overall median duration of follow-up was 18·4 months (IQR 16·2–19·7). The median follow-up was 17·2 months (12·4–24·6) in the surgery group and 19·1 months (12·0–26·2) in the maintenance therapy group. Local recurrence or progression, extrahepatic spread, or death from any cause occurred in 37 (37%) patients in the surgery group and 59 (59%) patients in the maintenance therapy group. The primary endpoint of this study was met, as IRF-assessed time to treatment failure was significantly improved in the surgery group versus the maintenance therapy group (median time to treatment failure 20·4 months [95% CI 10·2–not evaluable] in the surgery group *vs* 11·8 months [9·5–13·8] in the maintenance therapy group; stratified HR 0·60, 0·39–0·91; p=0·015, prespecified two-sided α boundary was 0·0341; figure 2A, appendix 1 p 4). The proportional hazards assumption was not violated (Schoenfeld residuals test, p=0·184). The IRF-assessed time-to-treatment-failure benefit of liver resection plus atezolizumab and bevacizumab over atezolizumab and bevacizumab alone was generally consistent across prespecified clinically relevant subgroups (figure 2B), including patients with or without tumour shrinkage greater than 10% (appendix 1 p 7). 18 patients randomly assigned to the surgery group did not undergo liver resection, and the results of the supplementary analysis based on the modified intention-to-treat population were consistent with those of the primary analysis (stratified HR for IRF-assessed time to treatment failure 0·52, 95% CI 0·34–0·80; appendix 1 p 8).

The median investigator-assessed time to treatment failure per RECIST 1.1 was 18·0 months (95% CI 11·50–28·29) in the surgery group and 11·8 months (7·69–14·52) in the maintenance therapy group (stratified HR 0·60, 95% CI 0·39–0·90; appendix 1 p 8). Moreover,

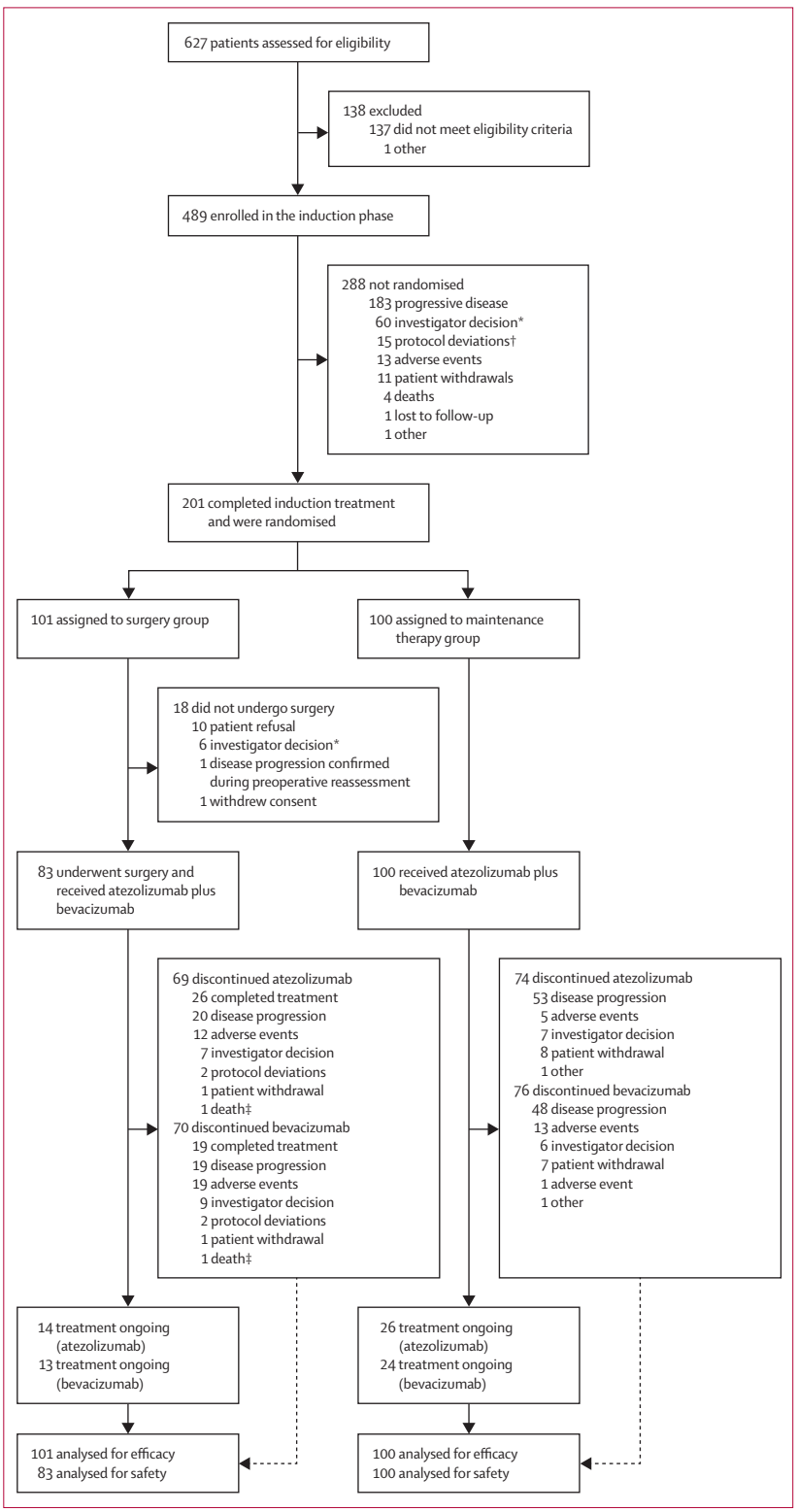


Figure 1: **Trial profile**
*Treatment was discontinued as this was considered most appropriate for the patient by the investigator. †Protocol deviations included three patients who did not meet the eligibility criteria and 12 patients who did not adhere to the study protocol requirements. ‡These deaths refer to the same patient, who died of COVID-19 infection unrelated to the study treatment.

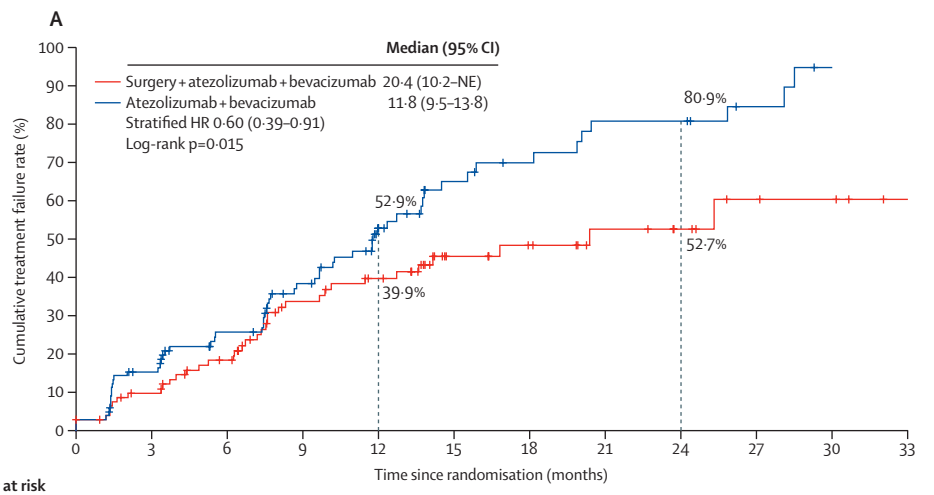
	Surgery group (N=101)	Maintenance therapy group (N=100)
Median age, years	58 (52–65)	56 (48–65)
Sex		
Male	93 (92%)	87 (87%)
Female	8 (8%)	13 (13%)
Ethnicity		
Han Chinese	96 (95%)	98 (98%)
Other	5 (5%)	2 (2%)
Aetiology		
Hepatitis B virus	91 (90%)	91 (91%)
Hepatitis C virus	3 (3%)	2 (2%)
Other	9 (9%)	9 (9%)
Portal vein classification		
Vp0	6 (6%)	7 (7%)
Vp1	5 (5%)	9 (9%)
Vp2	27 (27%)	29 (29%)
Vp3	46 (46%)	44 (44%)
Vp4	17 (17%)	11 (11%)
Hepatic vein tumour thrombosis		
Yes	17 (17%)	16 (16%)
No	84 (83%)	84 (84%)
Inferior vena cava tumour thrombus		
Yes	3 (3%)	1 (1%)
No	98 (97%)	99 (99%)
ECOG performance status score at induction phase		
0	84 (83%)	87 (87%)
1	17 (17%)	13 (13%)
ECOG performance status score at randomisation phase		
0	88 (87%)	86 (86%)
1	13 (13%)	14 (14%)
Albumin–bilirubin grade at induction phase		
1	67 (66%)	80 (80%)
2	34 (34%)	20 (20%)
3	0	0
Albumin–bilirubin grade at randomisation phase		
1	75 (74%)	81 (81%)
2	25 (25%)	19 (19%)
3	1 (1%)	0
(Continued from previous column)		
Median target lesion diameter, mm	56 (36–86)	57 (39–84)
Number of lesions (target and non-target)		
1	6 (6%)	4 (4%)
2–3	84 (83%)	82 (82%)
>3	11 (11%)	14 (14%)
AFP at induction phase		
<400 ng/mL	50 (50%)	49 (49%)
≥400 ng/mL	51 (51%)	51 (51%)
AFP at randomisation phase		
<400 ng/mL	77 (76%)	75 (75%)
≥400 ng/mL	24 (24%)	25 (25%)
Tumour treatment response		
Target lesion shrinkage ≥10%	72 (71%)	71 (71%)
No shrinkage or shrinkage <10%	29 (29%)	29 (29%)
Tumour response at randomisation phase as assessed by an IRF per RECIST version 1.1		
Complete response	0	0
Partial response	45 (45%)	42 (42%)
Stable disease	56 (55%)	57 (57%)
Progressive disease	0	1* (1%)

Data are median (IQR) or n (%). AFP=α-fetoprotein. ECOG=Eastern Cooperative Oncology Group. IRF=independent review facility. RECIST=Response Evaluation Criteria in Solid Tumors. *One patient in the maintenance therapy group was retrospectively reclassified as having progressive disease at the pre-randomisation assessment. After completion of induction phase treatment, no new lesions were identified by either the investigator or the IRF during tumour assessment, and the patient therefore proceeded to randomisation per protocol. Disease progression due to a newly detected lesion was identified after five treatment cycles. Retrospective review by both the investigator and IRF subsequently identified a previously unrecognised new lesion on the pre-randomisation imaging scans; the pre-randomisation tumour response was therefore revised to progressive disease.

Table 1: **Baseline characteristics of randomly assigned patients**

both IRF-assessed time to treatment failure (20·4 months [10·15–not evaluable] in the surgery group *vs* 11·8 months [9·67–13·83] in the maintenance therapy group; stratified HR 0·59, 0·39–0·89]) and investigator-assessed time to treatment failure (18·5 months [12·75–28·29] *vs* 11·8 months [7·69–14·52], stratified HR 0·57, 0·37–0·86) per modified RECIST criteria showed an advantage for the surgery group over the maintenance therapy group (appendix 1 p 9).

A total of 15 patients (15%) in the surgery group and 23 (23%) in the maintenance therapy group had died at the time of data cutoff. Overall survival at 12, 18, and 24 months was 86%, 86%, and 83% in the surgery group, and 91%, 78%, and 67% in the maintenance therapy group, respectively. Overall survival data were immature and follow-up is ongoing; however, non-significant results in favour of the surgery group were observed (HR 0·67, 95% CI 0·35–1·29; figure 3). The proportional hazards assumption was violated (Schoenfeld residuals test, p=0·0097), consistent with crossing of the Kaplan–Meier curves. Prespecified sensitivity analyses based on restricted mean survival time were truncated at 39·8 months and yielded estimates of 33·4 months in the surgery group and 30·5 months in the maintenance therapy group (difference 2·9 months, 95% CI –1·4 to 7·1), consistent with the Cox-based analysis. The number of time-to-extrahepatic-spread events was low at this cutoff point. Investigator-assessed median time to extrahepatic spread was not reached in either arm (surgery group: not estimable [95% CI not estimable] *vs* maintenance therapy group: not estimable [32·0–not estimable]; HR 0·60, 0·25–1·41).



Number at risk (censored)												
Surgery + atezolizumab + bevacizumab	101 (0)	77 (15)	64 (21)	44 (30)	37 (33)	21 (46)	17 (49)	11 (54)	8 (57)	4 (60)	3 (61)	0 (64)
Atezolizumab + bevacizumab	100 (0)	78 (7)	61 (15)	46 (20)	28 (28)	15 (35)	11 (37)	7 (37)	7 (37)	3 (40)	0 (41)	.. (..)

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	Surgery + atezolizumab + bevacizumab		Atezolizumab + bevacizumab		HR (95% CI)
	n/N	Median (95% CI)	n/N	Median (95% CI)	
All patients	37/101	20·4 (10·2–NE)	59/100	11·8 (9·5–13·8)	0·59 (0·39–0·89)
Tumour response					
Tumour reduction (≥10%)	21/72	25·3 (16·8–NE)	38/71	13·8 (9·7–18·2)	0·54 (0·32–0·93)
No reduction	16/29	9·7 (6·3–14·2)	21/29	11·0 (2·1–12·4)	0·64 (0·33–1·23)
ECOG Performance Status score at randomisation					
0	33/88	20·4 (9·9–NE)	51/86	11·8 (8·8–14·5)	0·61 (0·39–0·95)
1	4/13	NE (1·2–NE)	8/14	11·8 (1·5–20·4)	0·52 (0·15–1·81)
Age group					
<45 years	2/8	NE (0·0–NE)	11/13	5·5 (1·4–8·7)	0·21 (0·05–0·95)
45–65 years	28/64	14·2 (8·3–NE)	33/59	12·7 (10·2–15·9)	0·76 (0·46–1·27)
≥65 years	7/29	NE (7·6–NE)	15/28	11·8 (7·4–28·5)	0·50 (0·20–1·23)
Sex					
Male	33/93	20·4 (10·2–NE)	52/87	12·0 (9·7–14·5)	0·61 (0·39–0·94)
Female	4/8	14·2 (1·6–NE)	7/13	7·4 (1·5–NE)	0·49 (0·12–1·95)
Vp classification at enrolment					
Vp0	2/6	NE (3·4–NE)	4/7	7·6 (1·5–NE)	0·41 (0·07–2·26)
Vp1	0/5	NE (NE–NE)	2/9	NE (3·5–NE)	0·00 (0·00–NE)
Vp2	9/27	25·3 (6·7–NE)	15/29	9·7 (7·4–25·9)	0·64 (0·28–1·49)
Vp3	16/46	20·4 (12·7–NE)	31/44	12·4 (8·8–14·5)	0·46 (0·25–0·84)
Vp4	10/17	8·0 (1·5–NE)	7/11	7·8 (1·4–15·5)	0·83 (0·31–2·19)
ALBI score at randomisation					
Grade 1 score ≤–2·60	29/75	16·8 (10·2–NE)	51/81	11·8 (7·8–13·8)	0·60 (0·38–0·95)
Grade 2 ≤–2·60<score≤–1·39	7/25	NE (7·6–NE)	8/19	11·8 (9·5–20·4)	0·58 (0·21–1·62)
Grade 3 –1·39<score	1/1	4·4 (NE–NE)	0/0	NC	NC
AFP at randomisation					
≥400 ng/mL	13/24	7·6 (4·0–11·5)	19/25	7·5 (1·5–11·8)	0·77 (0·38–1·57)
<400 ng/mL	24/77	25·3 (14·2–NE)	40/75	13·8 (10·3–18·2)	0·52 (0·31–0·87)

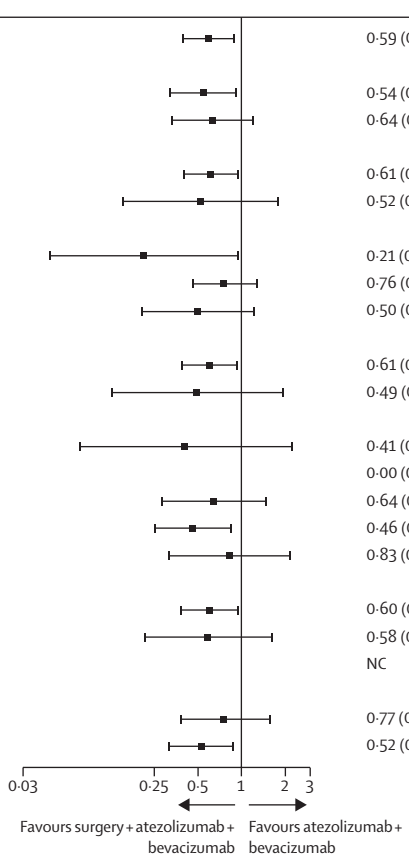

Figure 2: **Time to treatment failure in randomly assigned patients, according to independent review facility assessment per Response Evaluation Criteria in Solid Tumors 1.1**

(A) Kaplan–Meier estimates of time to treatment failure. (B) Time to treatment failure in key subgroups. AFP=α-fetoprotein. ALBI=albumin–bilirubin. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. NC=not calculable. NE=not estimable.

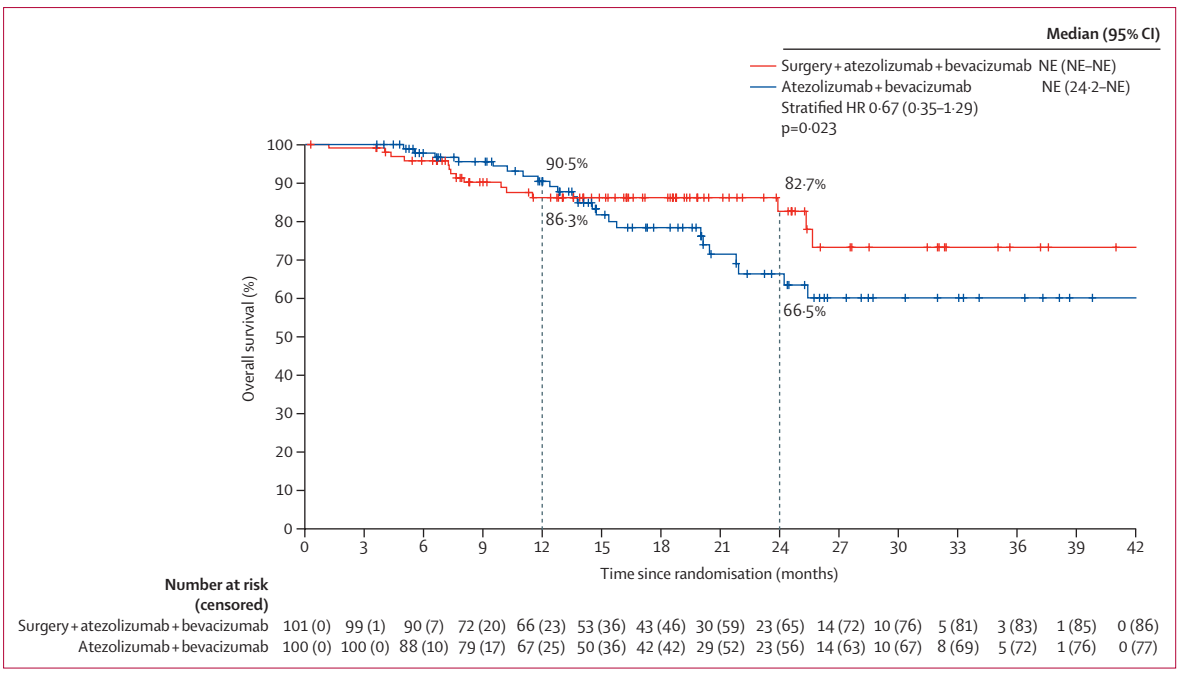

Figure 3: **Kaplan–Meier analysis of overall survival in randomly assigned patients**
HR=hazard ratio. NE=not estimable.

	Surgery group (N=83)	Maintenance therapy group (N=100)
Median treatment duration, cycles		
Atezolizumab	11·5 (5·0–17·0)	11·0 (5·0–17·5)
Bevacizumab	9·0 (4·0–16·0)	9·0 (5·0–17·0)
Patients with any adverse event	73 (88%)	93 (93%)
Treatment-related adverse event	66 (80%)	78 (78%)
Adverse events related to surgery	29 (35%)	..
Adverse events related to atezolizumab or bevacizumab	64 (77%)	78 (78%)
Grade 3 or 4 adverse event	41 (49%)	25 (25%)
Treatment-related grade 3 or 4 adverse event	32 (39%)	21 (21%)
Adverse events related to surgery	17 (21%)	..
Adverse events related to atezolizumab or bevacizumab	21 (25%)	21 (21%)
Serious adverse event	26 (31%)	17 (17%)
Treatment-related serious adverse event	19 (23%)	7 (7%)
Adverse events related to surgery	10 (12%)	0
Adverse events related to atezolizumab or bevacizumab	15 (18%)	7 (7%)
Deaths	3 (4%)	2 (2%)
Treatment-related deaths	2* (2%)	0
Patients discontinued any treatment due to adverse events	21 (25%)	25 (25%)
Patients discontinued and recovered after adverse events	21 (25%)	22 (22%)

Data are median (IQR) or n (%). The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. *Two treatment-related deaths occurred: abnormal liver function (n=1; suspected related to atezolizumab) and liver failure (n=1; considered related to atezolizumab, bevacizumab, or surgery).

Table 2: **Summary of adverse events in randomly assigned patients**

Of the 83 patients who underwent liver resection in the surgery group, the R0 resection rate was 93% (77 of 83) and the pathological complete response rate was 28% (23 of 83). Open surgery was done in 82% of patients (68 of 83) and laparoscopic surgery in 18% (15 of 83). The median operating time was 211 min (IQR 160–265), and the median postoperative hospital stay was 10 days (IQR 8–13).

Adverse events of any cause were reported in 88% of patients in the surgery group and 93% in the maintenance therapy group (table 2). Grade 3 or 4 treatment-related adverse events (TRAEs) occurred in 39% of patients in the surgery group and 21% in the maintenance therapy group. The most common grade 3 or 4 TRAEs were increased alanine aminotransferase (8% in the surgery group *vs* 1% in the maintenance therapy group), reduced platelet count (8% *vs* 3%), and proteinuria (4% *vs* 7%; table 3). TRAEs of at least grade 3 that were related to atezolizumab and bevacizumab occurred in 28% of patients in the surgery group and 21% in the maintenance therapy group. Serious TRAEs occurred in 23% of patients in the surgery group and 7% in the maintenance therapy group (table 2). Two treatment-related deaths in the surgery group were reported: one due to liver function abnormality, considered related to atezolizumab; and one due to liver failure, considered related to atezolizumab, bevacizumab, or surgery. Adverse events of any grade led to treatment discontinuation in 25% of patients in both arms. Of the patients who temporarily interrupted treatment due to adverse events, therapy was

	Surgery group (N=83)				Maintenance therapy group (N=100)			
	Any grade	Grade 1–2	Grade 3–4	Death	Any grade	Grade 1–2	Grade 3–4	Death
Any treatment-related adverse events	66 (80%)	32 (39%)	32 (39%)	2 (2%)	78 (78%)	57 (57%)	21 (21%)	0
Proteinuria	31 (37%)	28 (34%)	3 (4%)	0	40 (40%)	33 (33%)	7 (7%)	0
Platelet count decreased	21 (25%)	14 (17%)	7 (8%)	0	19 (19%)	16 (16%)	3 (3%)	0
Alanine aminotransferase increased	15 (18%)	8 (10%)	7 (8%)	0	10 (10%)	9 (9%)	1 (1%)	0
White blood cell count decreased	13 (16%)	11 (13%)	2 (2%)	0	13 (13%)	12 (12%)	1 (1%)	0
Aspartate aminotransferase increased	13 (16%)	7 (8%)	6 (7%)	0	12 (12%)	12 (12%)	0	0
Blood bilirubin increased	13 (16%)	12 (15%)	1 (1%)	0	11 (11%)	10 (10%)	1 (1%)	0
Anaemia	10 (12%)	9 (11%)	1 (1%)	0	5 (5%)	4 (4%)	1 (1%)	0
Neutrophil count decreased	10 (12%)	8 (10%)	2 (2%)	0	4 (4%)	4 (4%)	0	0
Blood corticotropin increased	9 (11%)	9 (11%)	0	0	14 (14%)	14 (14%)	0	0
Hypothyroidism	9 (11%)	9 (11%)	0	0	10 (10%)	10 (10%)	0	0
Hypertension	8 (10%)	4 (5%)	4 (5%)	0	12 (12%)	10 (10%)	2 (2%)	0
Hypoalbuminaemia	8 (10%)	8 (10%)	0	0	0	0	0	0
Adrenal insufficiency	6 (7%)	6 (7%)	0	0	5 (5%)	4 (4%)	1 (1%)	0
Hypokalaemia	6 (7%)	4 (5%)	2 (2%)	0	0	0	0	0
Blood creatinine increased	5 (6%)	5 (6%)	0	0	3 (3%)	3 (3%)	0	0
Lymphocyte count decreased	5 (6%)	3 (4%)	2 (2%)	0	3 (3%)	3 (3%)	0	0
Pruritus	5 (6%)	5 (6%)	0	0	3 (3%)	3 (3%)	0	0
Pleural effusion	5 (6%)	4 (5%)	1 (1%)	0	0	0	0	0

Table 3: **Treatment-related adverse events occurring in more than 5% of randomly assigned patients in either arm (safety analysis set)**

subsequently resumed in 25% of those in the surgery group and 22% in the maintenance therapy group.

In the surgery group, surgery-related adverse events occurred in 35% of patients, of which 22% were at least grade 3. Details of surgery-related adverse events are provided in appendix 1 (p 5). Serious surgery-related adverse events were reported in 12% of patients; the most common was postoperative wound infection (2%). According to the Clavien–Dindo classification, grade 3 or higher surgical complications occurred in 16% (13 of 83) of patients. The median intraoperative blood loss was 300 mL (IQR 150–500), and 22% of the patients received intraoperative blood transfusion.

Discussion

To our knowledge, TALENTOP is the first study to show that the addition of liver resection to systemic therapy with atezolizumab plus bevacizumab results in a statistically significant improvement in IRF-assessed time to treatment failure, compared with maintenance atezolizumab plus bevacizumab treatment, in patients with locally advanced hepatocellular carcinoma who have partial response or stable disease and are feasible for resection after initial systemic therapy. This strategy had a manageable safety profile.

Several studies[9–11,20] have suggested that surgical resection might offer additional curative opportunities and improve outcomes in patients with advanced hepatocellular carcinoma who respond to systemic therapy. However, the benefit of surgery, as compared with maintenance systemic therapy, has not been prospectively evaluated, and head-to-head comparisons of these two treatment approaches remain challenging. To establish an objective and practical efficacy endpoint for comparing these strategies, time to treatment failure was adopted as a composite endpoint that integrates clinically relevant failure patterns, allowing a fair comparison between treatment approaches with different methodological endpoints. Methodologically, recurrence-free survival in the surgery group and progression-free survival in the maintenance therapy group were aligned under the framework of time to treatment failure, providing a unified measure of the durability of oncological benefit achieved with surgical versus continuous systemic treatment. Prolongation of time to treatment failure corresponds to a longer duration before failure of first-line therapy, which is particularly meaningful for patients with hepatocellular carcinoma given the dearth of effective second-line treatments after immunotherapy-based combination therapy.[16] In this study, the beneficial effect of surgery on time to treatment failure was stable and consistent with that for overall survival. Although data remain immature, non-significant results in favour of the surgery group were observed for both time to extrahepatic spread and overall survival, in line with findings for time to treatment failure. The IRF-assessed time-to-treatment-failure benefit with the addition of liver resection to systemic therapy with atezolizumab plus bevacizumab was generally consistent across key clinical subgroups, including patients with or without tumour shrinkage greater than 10%. Several mechanisms might account for this observation. First, this effect might be related to the substantial

intratumoural heterogeneity of hepatocellular carcinoma,[21] a recognised driver of therapeutic resistance that is even more commonly observed in metastatic disease.[22] Surgical resection might eliminate or reduce the burden of treatment-resistant cellular populations, thereby prolonging disease control and potentially translating into a survival benefit. Second, tumour response to atezolizumab plus bevacizumab during the induction phase suggests that postoperative continuation of the same regimen has an anti-tumour effect on residual tumour cells, providing a rationale for maintaining systemic therapy after resection. Moreover, the neoadjuvant setting offers a unique opportunity to capture dynamic tumour and immune changes induced by immune checkpoint inhibition, which is particularly relevant in hepatocellular carcinoma, where no robust predictive biomarker has been established.[23]

International and Chinese guidelines have increasingly endorsed conversion strategies that expand the surgical candidacy for initially unresectable hepatocellular carcinoma. In the 2026 BCLC strategy, patients who initially exceed surgical criteria but respond to locoregional or systemic treatments and fulfil downstaging criteria can be reconsidered by a multidisciplinary team for resection or transplantation.[13] The 2025 EASL Clinical Practice Guidelines provide a strong recommendation (level of evidence: 2) for liver resection or transplantation in patients whose tumours shrink or are down-staged after locoregional treatment, and a weak recommendation (level of evidence: 3) for those responding to systemic treatment, preferably within prospective studies.[12] The 2024 CNLC guideline defines conversion therapy as an approach for patients initially unsuitable for resection who might become eligible following locoregional or systemic antitumour therapy (level of evidence: 4; recommendation C), while recognising that further evidence from randomised controlled trials is necessary to substantiate this approach.[5] These evolving recommendations reflect a shift towards dynamic, response-adapted subsequent therapy in surgical decision making for hepatocellular carcinoma. The TALENTOP study adopted this approach, which is consistent with the strategy used in the trial by Mazzaferro and colleagues[24] and in the ongoing IMPACT study.[25] In our study, surgical candidacy for conversion therapy was determined not only by tumour response (including partial response or stable disease), but also by overall oncological benefit, technical feasibility of R0 resection, and the patient's willingness to undergo surgery. The results suggest that patients who proceeded to resection had better clinical outcomes than those who remained on systemic therapy, enabling some patients with advanced hepatocellular carcinoma to attain long-term disease-free survival. Although overall survival data are not yet mature, results consistently favoured the surgery group.

There were no new safety signals related to atezolizumab or bevacizumab, and treatment-related toxicities were manageable. However, the incidence of adverse events of grade 3 or higher was greater in the surgery group (53%) than in the maintenance therapy group (27%), which could be attributed to surgery-related complications, with events of grade 3 or higher occurring in 22% of patients. The early crossing of the overall survival Kaplan–Meier curves was likely attributable to the high degree of data immaturity and could reflect acute risks associated with the surgical strategy, including one perioperative death within 30 days and a higher incidence of serious TRAEs (23% in the surgery group *vs* 7% in the maintenance therapy group). A retrospective study[26] has also reported that resection following systemic therapy is associated with increased risk of treatment-related adverse events, due to the large volume of liver resection required, or treatment-related hepatic toxicity. Therefore, multidisciplinary team evaluation and careful patient selection are crucial during conversion therapy to ensure perioperative safety.

Although the TALENTOP study was conducted in a population predominantly affected by hepatitis B virus, this reflects the global epidemiology of hepatocellular carcinoma. A systematic review estimated that hepatitis B virus accounts for 52% of all hepatocellular carcinoma cases worldwide,[27] and hepatitis B virus-related hepatocellular carcinoma comprised 48% of the IMbrave150 trial population.[3] Furthermore, atezolizumab plus bevacizumab has shown consistent efficacy across aetiological subgroups—including hepatitis B virus, hepatitis C virus, and non-viral populations—in IMbrave150,[28] suggesting that the tumour response enabling subsequent surgical conversion is not restricted to a single aetiology. Surgical candidacy is determined by aetiology-independent criteria, including liver function reserve (Child–Pugh class A), future liver remnant volume, and multidisciplinary assessment, which are applied uniformly across international guidelines.[5,14] Moreover, in patients with hepatocellular carcinoma undergoing hepatic resection, viral hepatitis status (ie, hepatitis B virus only, hepatitis C virus only, hepatitis B and C virus co-infection, or no viral hepatitis) was not associated with 30-day post-hepatectomy complications, major complications, or post-hepatectomy liver failure.[29] Taken together, these findings suggest that the conversion-to-resection strategy evaluated in this study is, in principle, applicable to patients with hepatocellular carcinoma regardless of underlying aetiology, provided that standard oncological and surgical criteria are met.

The study has several limitations. First, all patients were enrolled in China. Patients in this study were younger than those in IMbrave150 (median age 56 *vs* 64 years[3]), and most had macrovascular invasion without extrahepatic metastasis. The generalisability of the conversion strategy to broader, older populations with

a greater comorbidity burden warrants prospective validation. Second, preoperative systemic therapy was administered for a fixed duration of four cycles, precluding exploration of optimal resection timing. Real-world evidence suggests that a response depth of 40–50% could represent the optimal window for resection.[30] Future studies incorporating response-adapted treatment durations could help define the optimal surgical window. Third, the overall survival data are still maturing, and whether the improvement in time to treatment failure observed in this study will translate into a survival benefit warrants confirmation with longer follow-up. The final overall survival analysis will be reported in a subsequent publication. Finally, patient-reported outcomes, including quality of life, were not assessed in this study, which restricts our ability to fully evaluate the overall benefit of the intervention from the patient perspective.

In conclusion, the TALENTOP study showed that liver resection followed by maintenance therapy with atezolizumab plus bevacizumab resulted in a statistically significant and clinically meaningful benefit in time to treatment failure compared with sustained atezolizumab plus bevacizumab. Patients who have a partial response or stable disease after initial systemic therapy should undergo multidisciplinary team assessment for resectability and be considered for liver resection.

Contributors

JF, H-CS, and X-DZ conceptualised the study. H-CS, X-DZ, FS, T-QS, X-LB, Y-YZ, M-SC, Z-YH, J-QC, JG, MK, D-YL, B-CX, X-CL, T-FW, TP, Y-DW, L-XL, CH, Y-HS, X-WH, KW, QG, and JZ were involved in data collection. H-CS, X-DZ, and JF were involved in data analysis and data interpretation. H-CS and X-DZ drafted the manuscript. All authors critically reviewed the manuscript, had full access to all the data in the study, and had final responsibility for the decision to submit for publication. JF, H-CS, X-DZ, and FS directly accessed and verified the underlying data reported in the manuscript.

Declaration of interests

H-CS has received speaker fees from AstraZeneca, BeiGene, Eisai, Hengrui, Innovent, Merck Sharp & Dohme, Qilu Pharmaceutica, Roche, and Zelgen; and received research grants from Sino Biopharmaceutical, Eisai, Innovent, Roche, and Merck Sharp & Dohme. X-DZ has received speaker fees from AstraZeneca, BeiGene, Eisai, Hengrui, Innovent, Merck Sharp & Dohme, and Roche. JZ has received consulting fees from AstraZeneca; has received honoraria from the Asia-Pacific Primary Liver Cancer Expert Association (APPLE) and the Asian-Pacific Association for the Study of the Liver (APASL); has received travel support from the Chinese Medical Association, Beijing Dadi Medical Charity Foundation, China Zhongguancun Precision Medicine Science and Technology Foundation, Beijing Health Alliance Charitable Foundation, Beijing Medical Award Foundation, Chronic Disease Prevention and Treatment of Traditional Chinese Medicine Promotion Association, and Beijing Life Oasis Public Service Center; has served on data safety monitoring or advisory boards for AstraZeneca, Medlmmune, and Merck Sharp & Dohme; and holds leadership or fiduciary positions in boards, societies, committees, or advocacy organisations, including the Chinese Society of Oncology, the Chinese Medical Association, APPLE, the Chinese College of Surgeons, Experts Committee on Liver Cancer, Chinese Society of Clinical Oncology (CSCO), and APASL. JF has received consulting fees from AstraZeneca; has received honoraria from APPLE, the Chinese Society of Clinical Oncology, and the Chinese Anti-Cancer Association; has received travel support from CSCO, the Chinese Anti-Cancer Association, China Zhongguancun Precision Medicine Science and Technology Foundation, and Beijing Health Alliance Charitable Foundation; has served on data safety monitoring or advisory boards for AstraZeneca; and holds leadership or fiduciary positions in boards, societies, committees, or advocacy organisations, including Chinese Medical Association, the Chinese Medical Doctor Association, Chinese Society of Clinical Oncology, and the Chinese Anti-Cancer Association. All other authors declare no competing interests.

Data sharing

De-identified individual participant data underlying the results reported in this Article will be made available to qualified researchers upon reasonable request. The study protocol and statistical analysis plan are provided in appendix 2. Data requests should be submitted to the corresponding author (JF). Data will be shared for non-commercial academic research purposes only. Access will be granted following approval of a research proposal.

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