On-demand transarterial chemoembolisation combined with atezolizumab and bevacizumab in patients with untreated hepatocellular carcinoma (TALENTACE): a multicentre, randomised, open-label, phase 3 trial

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Summary

Background TACE is the standard treatment for intermediate-stage hepatocellular carcinoma but has limited survival benefits. TALENTACE evaluated adding atezolizumab and bevacizumab to on-demand TACE versus on-demand TACE alone in patients with systemically untreated, intermediate-to-high tumour burden unresectable hepatocellular carcinoma.

Methods In this randomised, open-label, phase 3 study at 40 centres in China and Japan, patients aged 18 years or older with confirmed, unresectable hepatocellular carcinoma and an anticipated life expectancy of 12 months or more were eligible for inclusion. Eligible patients were required to have an Eastern Cooperative Oncology Group performance status of 0–1, Child-Pugh class A liver function, no previous systemic therapy, and a sum of tumour maximum diameter (cm) and lesion number of six or more based on the six-and-twelve score. Patients were randomly assigned (1:1), using a permuted-block method implemented via an interactive voice and web response system, to on-demand TACE plus atezolizumab 1200 mg intravenously and bevacizumab 15 mg/kg intravenously once every 3 weeks (initiated 14 days to 8 weeks after TACE), or on-demand TACE alone, with TACE administered at the investigators' discretion. The randomisation sequence was generated by an independent biostatistician at the system vendor and was concealed from the sponsor study team and investigators until randomisation; allocation was stratified by baseline α-fetoprotein, prior locoregional therapy, and baseline Vp1/2 (and geographic region in earlier protocol versions). Primary endpoints were investigator-assessed TACE progression-free survival (TACE-PFS; time from randomisation to untreatable [unTACEable] progression, TACE failure or refractoriness, or death), and overall survival, both analysed in the intention-to-treat population. Overall survival was assessed under a prespecified adaptive (group sequential) design comprising two interim analyses and one final analysis. Safety was evaluated in the as-treated population, defined as all randomised patients who received any study treatment, analysed according to the treatment received. This study is registered with ClinicalTrials.gov (NCT04712643) and is ongoing.

Findings Between Feb 23, 2021, and August 11, 2023, 342 patients were randomly assigned to TACE plus atezolizumab and bevacizumab (n=171) or on-demand TACE alone (n=171). Median age was 61·0 years (range 21·0–90·0), 66 (19%) of 342 participants were female, 276 (81%) were male, 308 (90%) were Chinese, and 34 (10%) were Japanese. The mean size of the largest target lesion per RECIST 1.1 was 7·7 cm (SD 4·3) in both arms. In the TACE plus atezolizumab and bevacizumab group, 36 (21%) of 171 patients were Barcelona Clinic Liver Cancer stage A, 100 (58%) were stage B, and 35 (20%) were stage C; in the TACE alone group, 42 (25%) of 171 patients were Barcelona Clinic Liver Cancer stage A, 105 (61%) were stage B, and 24 (14%) were stage C. At data cutoff (Feb 28, 2025; median follow-up 26·25 months [IQR 21·16–33·74]), median TACE-PFS was 11·30 months (95% CI 7·52–15·01) with TACE plus atezolizumab and bevacizumab versus 7·03 months (95% CI 5·32–8·41) with TACE alone (hazard ratio [HR] 0·71 [95% CI 0·55–0·92]; two-sided stratified log-rank p=0·0089). Overall survival remains immature and was assessed at the first of the prespecified interim analyses; median overall survival was 34·53 months (99·62% CI 24·80–not evaluable) in the TACE plus atezolizumab and bevacizumab group compared with 35·38 months (99·62% CI 24·74–not evaluable) in the TACE alone group (HR 0·96 [99·62% CI 0·58–1·58]). The most common grade 3–4 adverse events in the TACE plus atezolizumab and bevacizumab group were decreased platelet count (23 [14%] of 166), hypertension (23 [14%]), and post-embolisation syndrome (21 [13%]); in the TACE alone group, the most common were post-embolisation syndrome (23 [13%] of 173), decreased platelet count (12 [7%]), and increased aspartate aminotransferase (12 [7%]). The most common serious adverse event was ascites (eight [5%]) in the TACE plus atezolizumab and bevacizumab group and post-embolisation syndrome (six [3%]) in the TACE alone group. Treatment-related deaths occurred in five patients in the TACE plus atezolizumab and bevacizumab group (gastrointestinal haemorrhage, liver abscess, haemolytic anaemia, hypertension, and unknown death) and three patients in the TACE alone group (post-procedural haemorrhage, ascites, and unknown death). No new safety signals were identified.

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Interpretation On-demand TACE plus atezolizumab and bevacizumab significantly improved TACE-PFS versus on-demand TACE alone. Overall survival follow-up is ongoing.

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Introduction

Transarterial chemoembolisation (TACE) is the standard of care for patients with intermediate-stage hepatocellular carcinoma.[1] In Asia, TACE has been used in a broader population defined by tumour burden and liver function rather than stage alone, extending beyond the intermediate stage to patients with unresectable, locally advanced disease.[2,3] However, median progression-free survival after TACE remains poor.[4,5] As this population is highly heterogeneous,[6] not all patients treated with TACE will benefit.[7] To simplify the identification of patients who are ideal candidates for TACE, the six-and-twelve score was developed, which categorises patients according to tumour burden and predicts prognosis.[8] The score is based on the sum of tumour maximum diameter (cm) and number of tumours and stratifies patients into one of three prognostic groups (score ≤6, >6 to ≤12, and >12), with TACE showing limited efficacy in patients with higher tumour burden.

Combination strategies have been explored to improve the therapeutic efficacy of TACE. TACE can lead to increased expression of vascular endothelial growth factor (VEGF) in hepatocellular carcinoma tumours.[9] Thus, combining TACE with anti-angiogenic therapy was expected to limit tumour neovascularisation and enhance anti-tumour effects. Several studies have evaluated the combination of TACE with multi-kinase inhibitors, however no significant improvement in clinical outcomes has been observed.[4,10–13]

The combination of anti-VEGF receptor agents with immune checkpoint inhibitors has shown improved tumour responses.[14] In the IMbrave150 trial, atezolizumab plus bevacizumab significantly improved survival compared with sorafenib, and it is now recommended as a first-line systemic treatment for unresectable hepatocellular carcinoma.[14,15] Meanwhile, TACE has been reported to increase intratumoral $CD8^+$ T-cell and tumour programmed death ligand 1 (PD-L1) expression,[16] providing a mechanistic rationale for combining TACE with immune checkpoint inhibitors and anti-VEGF agents. Thus, further investigation into this treatment strategy in patients with intermediate-to-advanced stage hepatocellular carcinoma, for whom treatment options remain limited, is warranted.

The TALENTACE study was designed to evaluate whether on-demand TACE plus atezolizumab and bevacizumab could improve clinical outcomes in patients with unresectable hepatocellular carcinoma with

Research in context

Evidence before this study

We searched PubMed from database inception to June 30, 2025, without language restrictions, using the terms ("hepatocellular carcinoma" OR "HCC") AND ("transarterial chemoembolisation" OR "TACE"), filtered by article type "Randomized Controlled Trial". The search yielded 220 articles. We manually screened these results to identify studies evaluating immune-based systemic therapy in combination with transarterial chemoembolisation (TACE) for patients with unresectable hepatocellular carcinoma. Two randomised phase 3 trials were identified: LEAP-012 (pembrolizumab plus lenvatinib and TACE) and EMERALD-1 (durvalumab plus bevacizumab and TACE). Both trials showed significant progression-free survival benefits with TACE combined with immunotherapy plus anti-VEGF receptor therapy. However, in EMERALD-1, bevacizumab was administered only after completion of TACE because of safety concerns, and in LEAP-012, patients with a high tumour burden were excluded. There remains an unmet medical need for the concurrent combination of on-demand TACE and immunotherapy plus anti-VEGF receptor therapy in patients with systemically untreated, intermediate-to-high tumour burden and unresectable hepatocellular carcinoma.

Added value of this study

To our knowledge, TALENTACE is the first randomised phase 3 study to evaluate on-demand TACE combined with atezolizumab plus bevacizumab in patients with systemically untreated, intermediate-to-high tumour burden unresectable hepatocellular carcinoma. This study showed a significant improvement in the primary endpoint of investigator-assessed TACE-related progression-free survival. The safety profile was consistent with the well-established profiles of the individual agents and the underlying disease.

Implications of all the available evidence

On-demand TACE combined with atezolizumab plus bevacizumab could be a potential treatment option for patients with systemically untreated, unresectable hepatocellular carcinoma with an intermediate-to-high tumour burden. However, longer follow-up to obtain mature overall survival is warranted to comprehensively assess the benefit-to-risk profile.

intermediate-to-high tumour burden, who had not received previous systemic therapy, in China and Japan.

Methods

Study design and participants

TALENTACE is a phase 3, open-label, randomised study conducted in 40 medical centres and hospitals in China (n=30) and Japan (n=10). The study was conducted in accordance with the provisions of the Declaration of Helsinki. The institutional review board or ethical committee of each participating centre approved the study protocol and all related documentation (appendix p 2). All patients provided written informed consent before study participation. An independent committee regularly monitored safety at prespecified analyses, and an independent steering committee provided scientific oversight. The protocol and statistical analysis plan (SAP) for this study are available in the appendix (pp 16–194). This trial was prospectively registered at ClinicalTrials.gov (NCT04712643) and is ongoing.

Patients aged 18 years or older with unresectable hepatocellular carcinoma and an anticipated life expectancy of 12 months or more were eligible for inclusion. Biological sex and race were self-reported by patients at enrolment, with male and female as the available options for sex. Eligible patients had a confirmed diagnosis of hepatocellular carcinoma by histology or cytology, or by clinical features according to the American Association for the Study of Liver Diseases criteria (for patients with cirrhosis only); were suitable candidates for TACE (as determined by investigators at each site); had a combined maximum tumour diameter and tumour number of six or more, based on the six-and-twelve score; had received no previous systemic therapy for hepatocellular carcinoma; and had not undergone local therapy for target lesions. At least one measurable, untreated lesion was required according to the 2019 revised Response Evaluation Criteria in Cancer of the Liver (RECICL).[17] Patients were also required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, Child-Pugh class A liver function within 7 days before randomisation, and adequate haematological and organ function within 7 days before treatment initiation. The key exclusion criteria were the presence of Vp3 or Vp4 portal vein tumour thrombus,[2] hepatic vein tumour thrombus, or extrahepatic spread; a history of autoimmune disease; coinfection with both hepatitis B virus (HBV) and hepatitis C virus (HCV); and untreated or incompletely treated oesophageal or gastric varices (assessed with esophagogastroduodenoscopy and treated according to local clinical practice) with bleeding or high risk of bleeding. Full eligibility criteria are provided in the protocol, available in the appendix (pp 50–56).

Randomisation and masking

Eligible patients were randomly assigned (1:1) to on-demand TACE combined with atezolizumab and bevacizumab or to on-demand TACE alone, using a permuted-block method implemented via an interactive voice and web response system (IXRS; Almac Clinical Technologies, Souderton, PA, USA). Randomisation was stratified by baseline α-fetoprotein (<400 ng/mL *vs* ≥400 ng/mL), previous locoregional therapies excluding curative resection and ablation (yes *vs* no), presence of Vp1/2 at baseline (yes *vs* no; used in protocol version 5 and later versions), and geographical region (China *vs* Japan; used in protocol versions earlier than version 5). The randomisation sequence was generated by an independent biostatistician at the IXRS vendor and was concealed from the sponsor study team and investigators until the point of randomisation. The trial was open-label, and treatment administered to patients was unmasked.

Procedures

Patients in both treatment arms received first TACE (either conventional TACE or TACE using drug-eluting beads), followed by on-demand TACE at the investigator's discretion. On-demand TACE could also either be conventional TACE or using drug-eluting beads, and did not have to be the same as used during first TACE. Patients randomised to the TACE plus atezolizumab and bevacizumab group received atezolizumab 1200 mg intravenously and bevacizumab 15 mg/kg intravenously on day 1 of each 21-day cycle until loss of clinical benefit as evaluated by the investigator, unacceptable toxicity, or study withdrawal; no dose modifications were allowed for either agent. Atezolizumab and bevacizumab were administered at least 14 days and up to 8 weeks after TACE.

Both conventional TACE and drug-eluting-bead TACE were permitted according to institutional practice; each patient was required to receive the same type of chemoembolisation throughout the study wherever possible. Chemotherapeutic agents were restricted to anthracyclines sourced from routine hospital stock. The first TACE was required within 5 working days of randomisation. In the combination arm, subsequent procedures were performed at least 2 weeks after the last bevacizumab administration. On-demand TACE was repeated in both arms if the viable lesion area exceeded 50% of baseline due to insufficient necrosis, lesion expansion, or new lesions showing typical hepatocellular carcinoma hallmarks on multiphasic enhanced CT or dynamic contrast-enhanced MRI.

Baseline imaging was performed within the 28 days before randomisation. Tumour assessments were conducted every 6 weeks (±1 week) from the date of randomisation for 2 years, then every 12 weeks (±10 days) thereafter, using enhanced CT (with oral or intravenous contrast) or contrast-enhanced MRI of the chest, abdomen, and pelvis. Assessments were continued until disease progression, withdrawal of consent, death, or study discontinuation, whichever occurred first.

or

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See **Online** for appendix

Outcomes

The primary endpoints were investigator-assessed TACE progression-free survival (TACE-PFS) and overall survival. TACE-PFS was assessed by investigators according to RECICL[15] and defined as the time from randomisation to untreatable (unTACEable) progression or TACE failure or refractoriness,[18] or death from any cause, whichever occurred first. UnTACEable progression or TACE failure or refractoriness was defined as: (1) intrahepatic lesion progression (≥50% increase from baseline); (2) two or more consecutive insufficient responses of the treated tumour (viable lesion >50%) or two or more consecutive unnumbered increases in liver tumour number (even after changing the chemotherapeutic agents, reanalysis of the feeding artery, or both) as determined by the first CT or MRI assessment after adequate performance of selective TACE; (3) appearance of extrahepatic spread; (4) deterioration of macrovascular invasion (defined as tumour invasion in portal vein or hepatic vein and its branches); or (5) deterioration of liver function to Child-Pugh B8 or worse. Overall survival was defined as time from randomisation to death due to any cause.

The prespecified secondary endpoints were investigator-assessed progression-free survival per Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1); objective response rate (ORR, defined as the percentage of patients who have a complete or partial response) per RECICL and RECIST 1.1; duration of response (defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause, whichever occurred first) per RECICL and RECIST 1.1; time to unTACEable progression (defined as time from randomisation to Child-Pugh B8 or worse, intrahepatic tumour progression [≥50% increase from baseline] with new intrahepatic lesions not defined as tumour progression, deterioration of macrovascular invasion, or extrahepatic spread) per RECICL; time to progression (defined as the time from randomisation to unTACEable progression or TACE failure orrefractoriness); time to extrahepatic spread (defined as the time from randomisation to the first evidence of extrahepatic spread); and safety.

The secondary endpoints of time to deterioration (defined as the time from randomisation to first deterioration [decrease from baseline of 10 points], maintained for two consecutive assessments or one assessment followed by death from any cause within 3 weeks in the following European Organisation for Research and Treatment of Cancer QLQ-C30 subscales: physical functioning, role functioning, global health status, and quality of life) are not included in this study. A comprehensive analysis of all patient-reported outcomes will be reported in subsequent publications.

Safety assessment was conducted in the safety population (all randomly assigned patients who received any study treatment) and consisted of monitoring and recording of adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests deemed critical to the safety evaluation of the study, with adverse events and treatment-related adverse events graded per Common Terminology Criteria for Adverse Events (version 5.0).

Statistical analysis

The total sample size of approximately 342 patients was determined based on the number of TACE-PFS events. Approximately 237 events were required for 80% power at a two-sided α of 0·05 to detect a target hazard ratio (HR) of 0·695 (assumed median improvement from 11 months with TACE alone to 15·8 months with TACE plus atezolizumab and bevacizumab); the corresponding minimally detectable difference was an HR of 0·775. For overall survival, a three-look group sequential design (two interim analyses and one final analysis planned at approximately 144, 208, and 256 deaths, corresponding to planned information fractions of approximately 56%, 81%, and 100% of the 256-death target) was pre-specified with efficacy stopping boundaries determined by the Lan-DeMets approximation to the O'Brien-Fleming spending function (planned two-sided boundaries of α ≤0·0055, ≤0·024, and ≤0·042, respectively), providing 73·8% overall power across the three planned analyses to detect a target HR of 0·72 (expected median overall survival of 28 months with TACE alone and of 38·9 months with TACE plus atezolizumab and bevacizumab). Both target HRs were informed by the IMbrave150 trial.[14]

Sample size calculation assumed one-piece exponential distributions for both endpoints; a piecewise constant accrual rate over approximately 31·2 months (appendix pp 34–35); and dropout rates of 8% over 12 months for TACE-PFS and 5% over 24 months for overall survival, applied uniformly across both arms. Full design details are provided in the SAP (appendix pp 161–194).

Efficacy was assessed in all patients who had been randomly assigned to treatment (ie, intention-to-treat population). The treatment effect of interest for both co-primary endpoints was defined under a treatment policy estimand: intercurrent events, early treatment discontinuation, and receipt of non-protocol anti-cancer therapy, were not used to censor or exclude patients from analysis.

The two coprimary endpoints were tested sequentially to control the overall two-sided family-wise type I error at 0·05. TACE-PFS was tested first, and overall survival was formally tested only upon demonstration of statistical significance for TACE-PFS. No multiplicity adjustment was applied to secondary endpoints, and therefore their reported CIs are descriptive.

TACE-PFS was tested at a single final analysis using a stratified log-rank test at the full two-sided α of 0·05 (stratified by baseline α-fetoprotein; previous loco-regional therapy and baseline Vp1/2 were removed per the prespecified contingency rule for strata with fewer than ten events). HRs with 95% CIs were estimated from a stratified Cox proportional hazards model (Breslow method for ties); medians with 95% CIs were estimated by the Kaplan-Meier method (Brookmeyer-Crowley method for CI construction). The proportional hazards assumption was assessed using the Grambsch-Therneau test based on scaled Schoenfeld residuals.[19]

For overall survival, efficacy stopping boundaries at each prespecified analysis were recomputed from the actual number of events observed, rather than the planned information fraction, using the Lan-DeMets approximation to the O'Brien-Fleming spending function. By Feb 28, 2025, the primary TACE-PFS analysis data cutoff, the first overall survival interim analysis was triggered and therefore performed at 132 deaths (an actual information fraction of approximately 52%, compared with the planned approximately 56% at 144 deaths), yielding a multiplicity-adjusted two-sided α boundary of 0·0038; correspondingly, 99·62% CIs are reported for overall survival estimates. No formal futility stopping rule, binding or non-binding, was prespecified at any interim analysis; the interim analyses monitored overall survival for efficacy only, and the trial could not be stopped for futility.

For progression-free survival, patients who were event-free at the data cutoff (ie, alive without progression) were censored at the last evaluable hepatocellular carcinoma assessment; those with progression or death after two or more consecutive missed assessments were censored at the last assessment before the missed visits. For overall survival, patients alive at the data cutoff were censored at the last date known to be alive. Patients with no post-baseline radiographic assessment were censored at the date of randomisation.

Prespecified sensitivity and supplementary analyses for TACE-PFS (unstratified analysis, missed-assessment reclassification, restricted mean survival time, and hypothetical strategy for non-protocol anti-cancer therapy) are described in the SAP. Two additional post-hoc sensitivity analyses (Efron ties handling and interval-censored analysis)[20] were also conducted.

For the summary adverse event categories, proportion of deaths, and adverse events of special interest, between-group risk differences are presented with 95% CIs calculated using the Newcombe method based on Wilson score intervals. These intervals are descriptive; no multiplicity adjustment was applied and no formal hypothesis testing of safety endpoints was performed.

Statistical analyses were performed using SAS (version 9.4). The SAP (version 1.0, finalised March 12, 2021) was amended (version 2.0, finalised Jan 26, 2025 prior to database lock) to introduce the estimand framework; analytical methods, populations, and stopping boundaries were unchanged. An independent data monitoring committee regularly evaluated the benefit–risk balance during the study. Unblinded data displays for the independent data monitoring committee safety review were prepared by an independent data coordinating centre, independent of the trial conduct and of the sponsor, whereas the prespecified efficacy analyses (TACE-PFS and the group sequential overall-survival interim and final analyses) were performed by the sponsor's contract research organisation statistical function under a documented data access plan. The study team remained blinded throughout all preceding monitoring and was unblinded at the first overall survival interim analysis, conducted at the primary analysis data cutoff (Feb 28, 2025). The independent data monitoring committee's role was advisory and it did not report to the steering committee. The independent data monitoring committee conducted four prespecified safety reviews during the study and recommended continuation without modification at

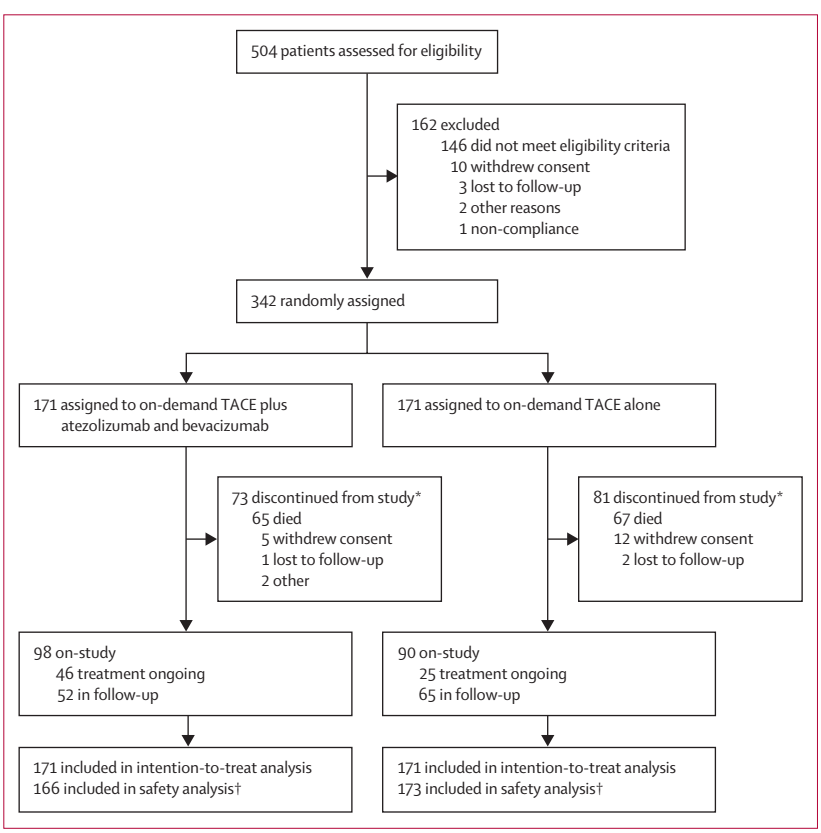


Figure 1: **Trial profile**
At data cutoff (Feb 28, 2025), we conducted the TACE-PFS prespecified final analysis and first prespecified interim analysis for overall survival (group sequential; 132 of 256 planned deaths [information fraction ≈52%]; efficacy boundary [two-sided α=0·0038] not crossed). The trial continued after this point to further assess overall survival. TACE=transarterial chemoembolisation. *By Feb 28, 2025. †In the TACE plus atezolizumab and bevacizumab group, one patient did not receive any treatment and four received TACE only, resulting in 166 patients included in the safety analysis. In the TACE group, two patients did not receive treatment, and together with the four patients who received TACE only in the TACE plus atezolizumab and bevacizumab group, a total of 173 patients were included in the safety analysis.

	TACE + atezolizumab + bevacizumab (n=171)	TACE alone (n=171)
Median age, years	62 (53–69)	60 (54–69)
<65 years	102 (60%)	97 (57%)
≥65 years	69 (40%)	74 (43%)
Sex		
Female	35 (20%)	31 (18%)
Male	136 (80%)	140 (82%)
BMI, kg/m²	23·4 (21·1–25·7)	23·4 (20·9–25·4)
Race		
Asian	171 (100%)	171 (100%)
Geographical region		
China	156 (91%)	152 (89%)
Japan	15 (9%)	19 (11%)
ECOG performance status		
0	139/170 (82%)	149 (87%)
1	31/170 (18%)	22 (13%)
Child-Pugh score		
5	139 (81%)	134 (78%)
6	32 (19%)	37 (22%)
Cause of HCC*		
HBV	143 (84%)	135 (79%)
HCV	8 (5%)	5 (3%)
History of HBV and HCV	4 (2%)	14 (8%)
Non-viral	16 (9%)	17 (10%)
α-fetoprotein		
<400 ng/mL	112 (65%)	110 (64%)
≥400 ng/mL	59 (35%)	61 (36%)
Vp1/2		
Yes	3 (2%)	4 (2%)
No	168 (98%)	167 (98%)
Barcelona Clinic Liver Cancer stage		
A	36 (21%)	42 (25%)
B	100 (58%)	105 (61%)
C	35 (20%)	24 (14%)
Albumin-bilirubin grade		
1	102 (60%)	103 (60%)
2	69 (40%)	68 (40%)
Liver cirrhosis at initial diagnosis		
Yes	141 (82%)	143 (84%)
No	26 (15%)	24 (14%)
Unknown	4 (2%)	4 (2%)
(Table 1 continues in next column)		

	TACE + atezolizumab + bevacizumab (n=171)	TACE alone (n=171)
(Continued from previous column)		
Size of the largest lesion per RECIST 1.1		
Mean, cm	7·7 (4·3)	7·7 (4·3)
Median, cm	6·9 (4·2–11·1)	6·8 (4·2–10·1)
Tumour burden score by six-and-twelve score‡		
≤6	1 (1%)	3 (2%)
>6 to ≤12	101 (59%)	107 (63%)
>12	69 (40%)	61 (36%)
Tumour burden score by up-to-7 criteria†		
Within up-to-7 criteria (≤7)	34 (20%)	38 (22%)
Beyond up-to-7 criteria (>7)	137 (80%)	133 (78%)
Previous locoregional therapy for non-target lesions		
Yes, TACE	9 (5%)	13 (8%)
Yes, other locoregional therapy	1 (1%)	2 (1%)
No	161 (94%)	156 (91%)
Concomitant HCC-directed medications	36 (21%)	43 (25%)
Concomitant non-HCC-directed medications	171 (100%)	168 (98%)

Data are median (IQR), n (%), n/N (%), or mean (SD). ECOG=Eastern Cooperative Oncology Group. HBV=hepatitis B virus. HCC=hepatocellular carcinoma. HCV=hepatitis C virus. RECIST=Response Evaluation Criteria in Solid Tumours·. TACE=transarterial chemoembolisation. *HBV cause was defined as a positive result for HBcAb, positive HBsAg, or HBV DNA (HBV DNA which is greater than the upper limit should be regarded as positive). HCV cause was defined as a positive result for HCV-Ab or HCV RNA (HCV RNA which is greater than the upper limit should be regarded as positive). A history of HBV or HCV infection was defined as previous infection with undetectable viral replication; patients with a history of HCV infection but who are negative for HCV RNA by PCR was considered non-infected with HCV, and patients with a history of HBV infection but who are negative for HBV DNA was considered non-infected with HBV. Non-viral was defined as neither HBV nor HCV aetiology. †Tumour burden score was defined as tumour number + longest tumour diameter (cm).

Table 1: **Baseline characteristics**

each (appendix p 5). A separate, independent steering committee of oncology experts provided scientific and medical advice and reviewed efficacy results only after completion of the primary analysis.

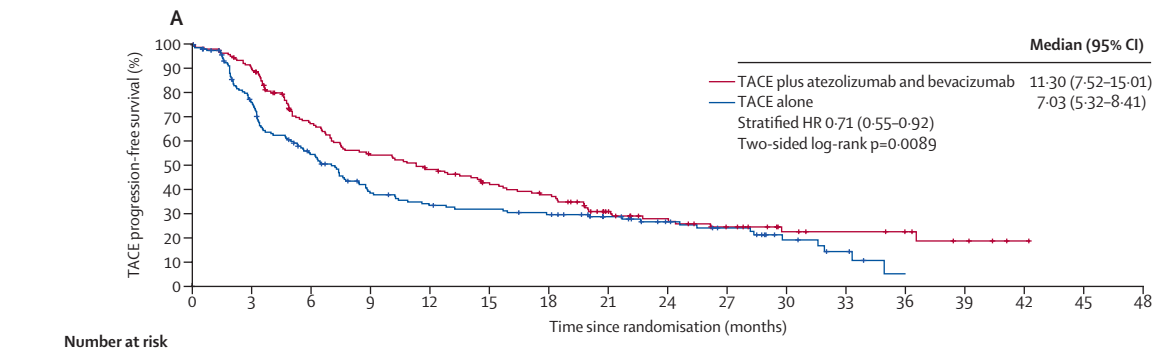
Role of the funding source

Shanghai Roche Pharmaceuticals 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, and assisted in drafting the manuscript.

Results

Between Feb 23, 2021, and August 11, 2023, 504 patients were assessed for eligibility and 342 were enrolled and randomly assigned to either the TACE plus atezolizumab and bevacizumab group (n=171) or the TACE alone group (n=171; figure 1). All 342 patients were included in the intention-to-treat efficacy analysis; three patients received no treatment, meaning 339 treated patients were included in the safety analysis (figure 1). Median age was 61·0 years (range 21·0–90·0), 66 (19%) of 342 patients were female, 276 (81%) were male, 308 (90%) were Chinese, and 34 (10%) were Japanese. 130 (38%) patients had a tumour burden score greater than 12, and 208 (61%) had a score between 6 and 12 (table 1).

As of data cutoff (Feb 28, 2025), median follow-up was 26·25 months (IQR 21·16–33·74). TACE-PFS events occurred in 114 patients in the TACE plus atezolizumab



Number at risk (censored)															
TACE plus atezolizumab and bevacizumab	171 (0)	150 (4)	104 (14)	83 (15)	73 (16)	60 (21)	52 (22)	33 (32)	26 (36)	19 (40)	11 (47)	9 (49)	7 (51)	4 (53)	1 (56)
TACE	171 (0)	119 (14)	81 (19)	54 (23)	46 (24)	43 (25)	39 (26)	30 (34)	22 (40)	17 (43)	9 (48)	5 (50)	0 (52)		

B

	TACE plus atezolizumab and bevacizumab		TACE alone		HR (95% CI)
	n/N	Median (95% CI)	n/N	Median (95% CI)	
Sex					
Male	93/136	11·73 (7·59–15·87)	96/140	6·44 (5·29–8·41)	0·76 (0·57–1·01)
Female	21/35	10·12 (4·86–NE)	23/31	7·43 (3·52–17·87)	0·66 (0·36–1·20)
Age (years)					
<65	75/102	8·77 (6·47–13·47)	71/97	5·59 (3·68–7·26)	0·80 (0·58–1·11)
≥65	39/69	15·67 (7·69–36·53)	48/74	10·38 (6·44–21·68)	0·64 (0·42–0·98)
ECOG performance status					
0	95/139	11·30 (7·59–15·47)	100/149	7·39 (5·59–8·80)	0·78 (0·59–1·03)
1	18/31	11·73 (4·86–NE)	19/22	4·02 (1·91–20·07)	0·50 (0·26–0·96)
Child-Pugh score					
5	88/139	14·62 (10·64–18·40)	90/134	7·43 (5·62–10·25)	0·71 (0·53–0·95)
6	26/32	4·86 (3·35–6·74)	29/37	4·67 (2·86–7·39)	0·95 (0·56–1·61)
Aetiology of HCC					
HBV	94/143	11·30 (7·13–15·87)	96/135	7·03 (4·80–8·41)	0·71 (0·53–0·95)
HCV	7/8	5·95 (0·59–18·46)	3/5	7·66 (1·61–NE)	1·77 (0·45–6·96)
History of HBV and HCV	2/4	NE (8·77–NE)	9/14	5·88 (1·87–NE)	0·44 (0·09–2·06)
Non-viral	11/16	15·24 (6·51–24·38)	11/17	11·93 (3·68–21·68)	0·80 (0·35–1·85)
α-fetoprotein					
<400 ng/mL	69/112	15·01 (8·41–18·46)	75/110	7·66 (6·21–11·93)	0·76 (0·55–1·06)
≥400 ng/mL	45/59	7·13 (5·85–11·73)	44/61	4·67 (3·15–6·44)	0·63 (0·41–0·95)
Prior locoregional therapy for non-target lesions					
Yes, TACE	6/9	8·97 (3·19–NE)	10/13	5·34 (1·77–10·25)	0·56 (0·20–1·54)
Yes, other locoregional therapy	1/1	22·74 (NE–NE)	1/2	3·45 (NE–NE)	0·00 (0·00–NE)
No	107/161	11·30 (7·46–15·01)	108/156	7·26 (5·45–8·80)	0·76 (0·58–0·99)
Vp1/2					
Yes	2/3	7·00 (0·13–NE)	4/4	2·74 (1·54–NE)	0·46 (0·05–4·33)
No	112/168	11·73 (7·59–15·47)	115/167	7·26 (5·59–8·74)	0·74 (0·57–0·96)
Country					
China	105/156	10·64 (7·13–14·62)	104/152	6·34 (4·80–8·38)	0·74 (0·57–0·98)
Japan	9/15	24·02 (6·51–NE)	15/19	11·40 (5·32–21·68)	0·59 (0·26–1·35)
Barcelona Clinic Liver Cancer stage					
A	24/36	12·71 (6·21–19·78)	25/42	5·95 (3·32–29·77)	0·88 (0·50–1·57)
B	70/100	10·22 (7·13–15·01)	73/105	7·59 (6·31–9·13)	0·80 (0·58–1·12)
C	20/35	12·88 (5·22–NE)	21/24	3·63 (2·20–8·38)	0·47 (0·26–0·87)
Albumin-bilirubin grade					
1	61/102	15·87 (10·09–21·09)	70/103	7·39 (5·45–9·13)	0·62 (0·44–0·88)
2	53/69	6·93 (5·03–11·30)	49/68	6·31 (3·45–7·66)	0·96 (0·65–1·42)
Tumor burden score by six-and-twelve score					
≤6	1/1	36·53 (NE–NE)	2/3	8·84 (2·63–NE)	0·00 (0·00–NE)
>6 to ≤12	62/101	14·52 (10·64–18·46)	71/107	7·43 (5·95–12·81)	0·71 (0·51–1·01)
>12	51/69	6·47 (4·96–11·73)	46/61	3·32 (2·96–7·72)	0·71 (0·48–1·06)
Tumour burden score by up-to-7 criteria					
Within up-to-7 criteria (≤7)	22/34	14·52 (10·81–36·53)	18/38	21·68 (7·66–NE)	0·94 (0·50–1·76)
Beyond up-to-7 criteria (>7)	92/137	8·97 (6·74–15·01)	101/133	6·18 (4·07–7·39)	0·70 (0·52–0·92)
Overall	**114/171**	**11·30 (7·52–15·01)**	**119/171**	**7·03 (5·32–8·41)**	**0·73 (0·56–0·95)**

Figure 2: **TACE-PFS overall (A) and in key subgroups (B) of the intention-to-treat population**
ECOG=Eastern Cooperative Oncology Group. HBV=hepatitis B virus. HCC=hepatocellular carcinoma. HCV=hepatitis C virus. NE=not estimable. TACE-PFS=transarterial chemoembolisation progression-free survival.

and bevacizumab group (six deaths and 108 progressions) and in 119 patients in TACE arm (six deaths and 113 progressions; appendix p 6); the remaining patients were censored, predominantly due to administrative censoring at the data cutoff. Median TACE-PFS was significantly improved in the TACE plus atezolizumab and bevacizumab group compared with TACE alone group (median 11·30 months [95% CI 7·52–15·01] *vs* 7·03 months [5·32–8·41]; HR 0·71 [95% CI 0·55–0·92], two-sided stratified log-rank p=0·0089; figure 2A). Progression of intrahepatic lesions was reported in 10 (6%) of 171 patients in the TACE plus atezolizumab and bevacizumab group and 21 (12%) of 171 patients in the TACE alone group (appendix p 6). TACE failure or refractoriness was reported in 46 (27%) of 171 patients in the TACE plus atezolizumab and bevacizumab group and 62 (36%) patients in the TACE alone group (appendix p 6). The proportional hazards assumption was not formally rejected for TACE-PFS (Grambsch-Therneau test, p=0·083). Prespecified and post-hoc sensitivity analyses consistently supported the robustness of the primary TACE-PFS finding (HR range 0·71–0·73 across analyses; appendix p 4). Median progression-free survival per RECIST 1.1 was 10·32 months (95% CI 8·51–11·93) with TACE plus atezolizumab and bevacizumab versus 6·37 months (5·32–7·46) with TACE alone (HR 0·64 [95% CI 0·50–0·82]; appendix p 14). TACE-PFS and progression-free survival per RECIST across key clinical subgroups assessed by investigators is shown in figure 2B and the appendix (p 15).

At the first prespecified interim analysis for overall survival (data cutoff Feb 28, 2025), median overall survival was 34·53 months (99·62% CI 24·80–not evaluable) in the TACE plus atezolizumab and bevacizumab group compared with 35·38 months (24·74–not evaluable) in the TACE alone group (HR 0·96 [0·58–1·58]; figure 3) and 132 deaths observed. Of the 132 deaths, 65 (49%) occurred in the TACE plus atezolizumab and bevacizumab group and 67 (51%) in the TACE alone group. The overall survival data did not cross the prespecified efficacy boundary, and the study continues to accrue events toward the next planned analyses per the group sequential design. Other efficacy outcomes are presented in the appendix (p 7).

In the TACE plus atezolizumab and bevacizumab group, the respective median duration of treatment was 13·11 months (IQR 5·06–20·17) for atezolizumab and 11·56 months (IQR 3·75–18·66) for bevacizumab (safety population). The median time from first TACE to first dose of atezolizumab plus bevacizumab was 23·00 days (IQR 20·00–29·00), with a mean of 29 days (SD 24); 149 (90%) of 166 patients initiated atezolizumab plus bevacizumab within 42 days of first TACE. The median number of TACE sessions was 2 (IQR 1–4) in the TACE plus atezolizumab and bevacizumab group and 3 (1–4) in the TACE alone group, with a median interval between procedures of 95·80 days (IQR 71·00–152·30) in the TACE plus atezolizumab and bevacizumab group and 88·30 days (IQR 61·00–142·80) in the TACE alone group. In the intention-to-treat population, 170 patients in the TACE plus atezolizumab and bevacizumab group and 169 in the TACE alone group received TACE. In the TACE plus atezolizumab and bevacizumab group, conventional TACE was used in six (4%) of 170 patients, drug-eluting-bead TACE was used in 128 (75%), and both methods were used in 36 (21%). In the TACE alone group, conventional TACE was used in seven (4%) of 169 patients, drug-eluting-bead TACE was used in 121 (72%), and both methods were used in 41 (24%).

Subsequent anti-cancer therapy is summarised in the appendix (p 8). In the TACE plus atezolizumab and bevacizumab group, 54 (32%) of 171 received at least one subsequent systemic anti-cancer therapy, 36 (21%) received at least one locoregional therapy, and ten (6%) underwent at least one surgery. In the TACE alone group, 82 (48%) of 171 patients received at least one subsequent

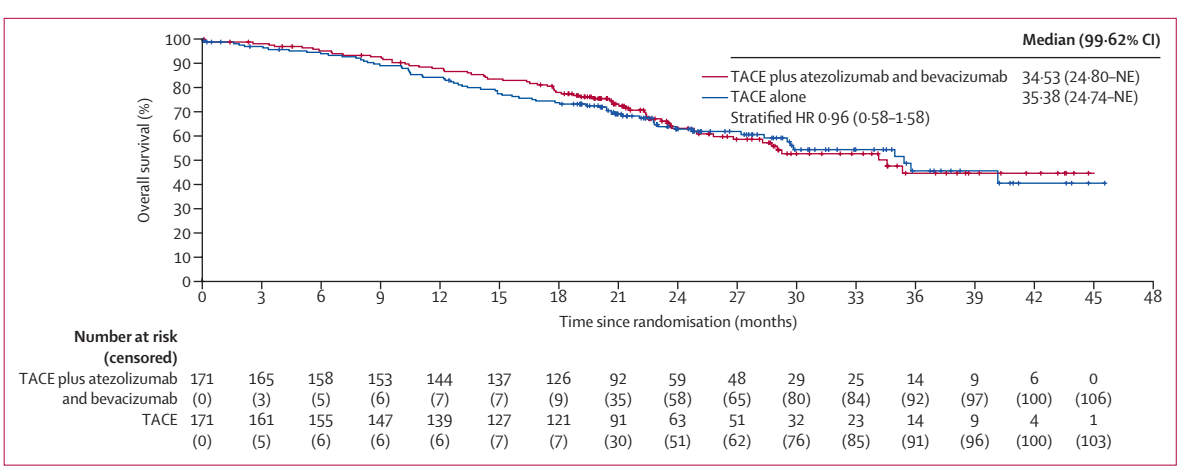


Figure 3: **Overall survival in the intention-to-treat population**
TACE=transarterial chemoembolisation.

systemic anti-cancer therapy, 60 (35%) received at least one locoregional therapy, and 15 (9%) underwent at least one surgery. Overall, subsequent treatments were more frequently administered in the TACE alone group than in the TACE plus atezolizumab and bevacizumab group; there was an approximately two-fold higher use of subsequent immunotherapy and higher use of targeted therapy in the TACE alone group compared with the TACE plus atezolizumab and bevacizumab group (appendix p 8). For both treatment groups, targeted therapy was the most common systemic therapy, followed by immunotherapy; conventional TACE was the most common locoregional therapy.

At least one adverse event was reported in all 166 (100%) patients in the TACE plus atezolizumab and bevacizumab group and 172 (99%) of 173 in the TACE alone group (table 2). Adverse events occurring in 10% or more of patients in either group with a 5% or greater between-group difference are presented by grade in table 3. Grade 3–4 adverse events were reported in 113 (68%) of 166 patients in the TACE plus atezolizumab and bevacizumab group and 88 (51%) of 173 in the TACE alone group; grade 5 events (ie, deaths) occurred in seven (4%) and five (3%) people, respectively. The most common grade 3–4 adverse events in the TACE plus atezolizumab and bevacizumab group were decreased platelet count (23 [14%] of 166), hypertension (23 [14%]), and post-embolisation syndrome (21 [13%]); in the TACE alone group, the most common were post-embolisation syndrome (23 [13%] of 173), decreased platelet count (12 [7%]), and increased aspartate aminotransferase (12 [7%]). Treatment-related grade 3 and 4 adverse events were reported in 101 (61%) of 166 patients in the TACE plus atezolizumab and bevacizumab group and 70 (40%) of 173 patients in the TACE alone group. TACE-related grade 3–4 adverse events were reported in 69 (42%) of 166 patients in the TACE plus atezolizumab and bevacizumab group and 70 (40%) patients in the TACE alone group. In the TACE plus atezolizumab and bevacizumab group, atezolizumab-related and bevacizumab-related grade 3–4 adverse events were reported in 46 (28%) and 64 (39%) patients, respectively. The adverse events of special interest, based on the prespecified identified risks for atezolizumab and for bevacizumab, are summarised with between-group risk differences and 95% CIs in the appendix (pp 9–10).

Serious adverse events occurred in 67 (40%) of 166 patients in the TACE plus atezolizumab and bevacizumab group and 41 (24%) of 173 patients in the TACE alone group. The most common serious adverse event was ascites (eight [5%]) in the TACE plus atezolizumab and bevacizumab group and post-embolisation syndrome (six [3%]) in the TACE alone group. Adverse events leading to withdrawal of any study treatment were reported in 35 (21%) in the TACE plus atezolizumab and bevacizumab group and four (2%) in the TACE alone group. In the TACE plus atezolizumab and bevacizumab group, 97 (58%) of 166 patients had adverse events leading to the interruption of study treatment, and four (2%) of 173 patients in the TACE

	TACE + atezolizumab + bevacizumab (n=166)	TACE alone (n=173)	Risk difference (95% CI)*
Patients with at least one adverse event	166 (100%)	172 (99%)	0·6% (–1·7 to 3·2)
Adverse event related to any treatment	166 (100%)	169 (98%)	2·3% (–0·4 to 5·8)
TACE-related	157 (95%)	169 (98%)	–3·1% (–7·9 to 1·2)
Atezolizumab or bevacizumab-related	144 (87%)	NA	NA
Grade 3–4 adverse event	113 (68%)	88 (51%)	17·2% (6·8 to 27·1)
Treatment-related grade 3–4 adverse event	101 (61%)	70 (40%)	20·4% (9·7 to 30·4)
TACE-related grade 3–4 adverse event	69 (42%)	70 (40%)	1·1% (–9·3 to 11·5)
Atezolizumab-related grade 3–4 adverse event	46 (28%)	NA	NA
Bevacizumab-related grade 3–4 adverse event	64 (39%)	NA	NA
Atezolizumab or bevacizumab-related grade 3–4 adverse event	69 (42%)	NA	NA
Grade 5 adverse event	7 (4%)	5 (3%)	1·3% (–3·0 to 5·9)
Treatment-related grade 5 adverse event	5 (3%)†	3 (2%)‡	1·3% (–2·4 to 5·3)
Atezolizumab or bevacizumab-related grade 5 adverse event	4 (2%)	NA	NA
Patients who died (any cause)§	62 (37%)	70 (40%)	–3·1% (–13·3 to 7·2)
Serious adverse event	67 (40%)	41 (24%)	16·7% (6·7 to 26·2)
Treatment-related serious adverse event	43 (26%)	24 (14%)	12·0% (3·5 to 20·4)
Adverse event leading to withdrawal from any study treatment	35 (21%)	4 (2%)	18·8% (12·3 to 25·7)
Adverse event leading to withdrawal from TACE	8 (5%)	4 (2%)	2·5% (–1·7 to 7·1)
Adverse event leading to withdrawal from atezolizumab	16 (10%)	NA	NA
Adverse event leading to withdrawal from bevacizumab	33 (20%)	NA	NA
Adverse event leading to any study treatment interruption or TACE delay¶	97 (58%)	4 (2%)	56·1% (47·8 to 63·5)
Adverse event leading to TACE delay	6 (4%)	4 (2%)	1·3% (–2·7 to 5·6)
Adverse event leading to dose interruption of atezolizumab	79 (48%)	NA	NA
Adverse event leading to dose interruption of bevacizumab	91 (55%)	NA	NA

Data are n (%). Adverse events were coded using the Medical Dictionary for Regulatory Activities (version 27.1) and graded using the Common Terminology Criteria for Adverse Events (version 5.0). TACE=transarterial chemoembolisation. *Risk difference (TACE+atezolizumab+bevacizumab minus TACE) in percentage points, with 95% CIs calculated using the Newcombe method based on Wilson score intervals. Risk differences are descriptive and were not adjusted for multiplicity. Risk differences are not applicable (NA) for rows specific to a single arm (atezolizumab-related or bevacizumab-related events), for which there is no comparator in the TACE group. †The causes of death for five patients in TACE+atezolizumab+bevacizumab group were gastrointestinal haemorrhage, liver abscess, haemolytic anaemia, hypertension, and unknown death. ‡The causes of death for three patients in the TACE group were post-procedural haemorrhage, ascites, and unknown death. §All all-cause deaths in the safety population at the data cutoff (Feb 28, 2025), predominantly due to disease progression and distinct from the grade 5 (fatal) adverse events. All-cause death in the intention-to-treat is reported separately in the appendix (p 11); the difference reflects the different analysis populations (the safety population reassigns patients who received only TACE in the combination group to the TACE only group). ¶In the TACE+atezolizumab+bevacizumab group, this category comprises interruption or delay of any study treatment (atezolizumab, bevacizumab, or TACE); in the TACE group it comprises TACE delays only, as no systemic study treatment was administered. The between-arm difference therefore predominantly reflects the additional systemic treatment in the combination group and does not indicate a difference in TACE tolerability; adverse event-related TACE delay occurred in six (4%) of 166 patients and four (2%) of 173 patients in each group.

Table 2: **Summary of adverse events in the safety population**

	TACE + atezolizumab + bevacizumab (n=166)				TACE alone (n=173)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any adverse events	69 (42%)	90 (54%)	5 (3%)	1 (1%)	95 (55%)	54 (31%)	4 (2%)	1 (1%)
Post-embolisation syndrome	50 (30%)	20 (12%)	1 (1%)	0	64 (37%)	22 (13%)	1 (1%)	0
Platelet count decreased	48 (29%)	22 (13%)	1 (1%)	0	40 (23%)	11 (6%)	1 (1%)	0
Aspartate aminotransferase increased	47 (28%)	14 (8%)	0	0	39 (23%)	11 (6%)	1 (1%)	0
Hypoalbuminaemia	64 (39%)	1 (1%)	0	0	40 (23%)	1 (1%)	0	0
Proteinuria	64 (39%)	19 (11%)	0	0	18 (10%)	2 (1%)	0	0
Anaemia	42 (25%)	12 (7%)	2 (1%)	0	31 (18%)	7 (4%)	0	0
Weight decreased	57 (34%)	2 (1%)	0	0	23 (13%)	0	0	0
Hypokalaemia	30 (18%)	9 (5%)	1 (1%)	0	21 (12%)	10 (6%)	1 (1%)	0
Hypertension	29 (17%)	23 (14%)	0	1 (1%)	6 (3%)	8 (5%)	0	0
White blood cell count decreased	29 (17%)	5 (3%)	0	0	21 (12%)	2 (1%)	0	0
Abdominal pain upper	30 (18%)	2 (1%)	0	0	24 (14%)	0	0	0
Diarrhoea	31 (19%)	1 (1%)	0	0	15 (9%)	0	0	0
Oedema peripheral	28 (17%)	1 (1%)	0	0	7 (4%)	0	0	0
Hypothyroidism	26 (16%)	0	0	0	6 (3%)	0	0	0
Rash	26 (16%)	0	0	0	4 (2%)	0	0	0
Blood lactate dehydrogenase increased	25 (15%)	1 (1%)	0	0	18 (10%)	0	0	0
Urinary tract infection	25 (15%)	1 (1%)	0	0	9 (5%)	0	0	0
COVID-19	24 (14%)	0	0	0	16 (9%)	0	0	0
Hypoproteinaemia	24 (14%)	1 (1%)	1 (1%)	0	10 (6%)	0	0	0
Cough	23 (14%)	0	0	0	15 (9%)	0	0	0
Epistaxis	22 (13%)	0	0	0	2 (1%)	0	0	0
Arthralgia	21 (13%)	0	0	0	11 (6%)	0	0	0
Pruritus	21 (13%)	1 (1%)	0	0	6 (3%)	0	0	0
Weight increased	18 (11%)	1 (1%)	0	0	5 (3%)	0	0	0
Neutrophil count decreased	17 (10%)	3 (2%)	0	0	7 (4%)	1 (1%)	0	0
Ascites	17 (10%)	7 (4%)	0	0	3 (2%)	0	0	1 (1%)

Data are n (%). The any adverse event row includes only patients experiencing at least one of the preferred terms displayed in this table. All subsequent rows report the number of events; hence, the total number of events can exceed the total number of patients.

Table 3: **Adverse events occurring in 10% of patients or more in any treatment arm and with a 5% difference or more between arms in the safety population**

alone group had adverse events leading to the delay of any study treatment. For both categories, the TACE-specific components were comparable between groups (withdrawal from TACE eight [5%] of 166 *vs* four [2%] of 173; TACE delay six [4%] of 166 *vs* four [2%] of 173); the higher overall rates in the TACE plus atezolizumab and bevacizumab group were driven by the systemic agents. Five treatment-related deaths occurred in the TACE plus atezolizumab and bevacizumab group (gastrointestinal haemorrhage, liver abscess, haemolytic anaemia, hypertension, and death of unknown cause) and three occurred in the TACE alone group (post-procedural haemorrhage, ascites, and death of unknown cause). All-cause deaths are summarised in the appendix (p 11).

Discussion

TALENTACE is the first phase 3 trial to show the efficacy and safety of on-demand TACE combined with atezolizumab and bevacizumab in patients with systemically untreated, unresectable hepatocellular carcinoma with an intermediate-to-high tumour burden. At this first interim analysis, there was a significant improvement in TACE-PFS with TACE plus atezolizumab and bevacizumab compared with TACE alone (median 11·30 months [95% CI 7·52–15·01] *vs* 7·03 months [5·32–8·41]; HR 0·71 [95% CI 0·55–0·92]; p=0·0089). The observed HR closely matches the target HR of 0·695 used in the sample size calculation, with the target HR contained within the observed 95% CI. The observed median improvement of 4·27 months is also consistent with the assumed 4·8-month median improvement.

TACE-PFS was selected as a co-primary endpoint for TALENTACE because it captures the multidimensional effect of TACE combined with systemic therapy, integrating the assessment of viable tumour areas, TACE failure or refractoriness[18] according to RECICL,[17] and liver function. Although intrahepatic new lesions constitute progression per RECIST 1.1 or modified RECIST, this does not necessarily signify TACE treatment failure, as further sessions can still provide benefit.[9] In trials

evaluating TACE in combination with systemic therapy, the use of a TACE PFS-based endpoint additionally allows patients to continue both on-demand TACE and the concomitant systemic therapy until clinically meaningful treatment failure, rather than discontinuing therapy at the time of RECIST or modified RECIST-defined progression.[9,21–23] A positive association between TACE-PFS and overall survival has previously been reported in patients with hepatocellular carcinoma treated with TACE.[24]

The progression-free survival benefit observed with on-demand TACE plus atezolizumab and bevacizumab using RECIST 1.1 (HR 0·64 [95% CI 0·50–0·82]) is consistent with the treatment effects reported in EMERALD-1 (HR 0·77 for TACE plus durvalumab and bevacizumab *vs* TACE plus placebo),[25] LEAP-012 (HR 0·66 for TACE plus lenvatinib and pembrolizumab *vs* TACE plus dual placebo),[26] and CARES-005 (HR 0·55 for camrelizumab plus rivoceranib plus TACE *vs* TACE alone),[22] confirming the benefit of combining immune checkpoint inhibitors and anti-angiogenic agents with TACE across different regimens. Mechanistically, TACE induces immunogenic cell death and the release of tumour-associated antigens, activating tumour-specific immune responses. However, the resultant ischaemia and hypoxia upregulate VEGF expression and foster an immunosuppressive microenvironment characterised by increased regulatory T cells, myeloid-derived suppressor cells, and PD-L1 expression.[27] Bevacizumab counteracts these changes by inhibiting angiogenesis, reducing immunosuppressive cell populations, and enhancing $CD8^+$ T-cell and natural killer cell infiltration. Atezolizumab blocks the PD-1/PD-L1 pathway upregulated by TACE-induced hypoxia, restoring T-cell-mediated cytotoxicity. This tripartite synergy, locoregional antigen release, reversal of VEGF-mediated immunosuppression, and immune checkpoint blockade, provides the mechanistic foundation for the combination strategy evaluated herein.[14]

Although the relative treatment effects are consistent across trials, cross-trial comparison of median progression-free survival should be interpreted with caution given substantial differences in patient selection. TALENTACE required a six-and-twelve score of 6 or greater,[8] resulting in 79% of patients (270 of 342) having tumour burden beyond the up-to-7 criteria, compared with 52% in EMERALD-1[25] and 53% in LEAP-012.[26] The shorter median progression-free survival in the TACE alone group of TALENTACE (6·37 months) compared with EMERALD-1 (8·2 months) and LEAP-012 (10·0 months) is consistent with this higher baseline tumour burden and vascular invasion rate. China and Japan have a high incidence of hepatocellular carcinoma, particularly HBV-related hepatocellular carcinoma in China.[28] In the subgroup analysis, longer TACE-PFS was observed in patients from Japan than in those from China, both in the TACE plus atezolizumab and bevacizumab group (24·02 *vs* 10·64 months) and in the TACE alone group (11·40 *vs* 6·34 months). These differences might be explained by variations in baseline characteristics. In Japan, the incidence of HCV-related hepatocellular carcinoma has declined while non-viral hepatocellular carcinoma has increased,[29] yet liver cirrhosis remains closely associated with hepatocellular carcinoma;[29] in China, HBV is the predominant cause of hepatocellular carcinoma and cirrhosis is less prevalent. Despite these regional differences, TALENTACE showed consistent improvements in TACE-PFS and in progression-free survival per RECIST 1.1 with TACE plus atezolizumab and bevacizumab compared with TACE alone. Similarly, CARES-005, in which 80% of patients had HBV-related hepatocellular carcinoma, showed a consistent benefit in progression-free survival per RECICL[17] with TACE plus camrelizumab and rivoceranib compared with TACE alone. Both trials enrolled patients predominantly with HBV-related hepatocellular carcinoma, the leading cause of hepatocellular carcinoma globally.[27] Real-world studies have shown that disease aetiology does not affect outcomes in patients treated with atezolizumab plus bevacizumab.[30,31] Mechanistically, TACE-induced tumour hypoxia and subsequent upregulation of VEGF is an aetiology-independent pathophysiological process, providing a biological rationale for the combination approach irrespective of underlying liver disease.[22]

The present overall survival analysis represents the first prespecified interim analysis, with 132 deaths observed (information fraction approximately 52%). The observed HR was 0·96 (99·62% CI 0·58–1·58), and the observed CI includes the target HR of 0·72, indicating that the overall survival data remain statistically compatible with the treatment effect anticipated at the design stage, while also being compatible with no treatment effect. The overall survival data did not cross the prespecified efficacy boundary, and overall survival data remain insufficiently mature to draw definitive conclusions. Two further analyses are prespecified at approximately 208 and 256 deaths. Interpretation of this early overall survival signal is further complicated by an imbalance in subsequent anti-cancer therapies. A higher proportion of patients in the TACE alone group received subsequent systemic therapy compared with the TACE plus atezolizumab and bevacizumab group (48% *vs* 32%), including approximately two-fold higher use of subsequent immunotherapy (30% *vs* 15%) and higher use of targeted therapy (43% *vs* 25%). This pattern reflects the established sequential treatment paradigm in which patients progressing after TACE are transitioned to active systemic therapies, including atezolizumab plus bevacizumab as a standard of care for advanced hepatocellular carcinoma. Such crossover might attenuate observed overall survival differences at this early timepoint, and continued follow-up will provide a more definitive assessment of the overall survival benefit of upfront combination therapy.

The safety profile of on-demand TACE plus atezolizumab and bevacizumab was consistent with the well-established profiles of the individual agents and underlying disease. No new safety signals were identified. Treatment-related adverse events at grade 3 or above occurred in 101 (61%) of 166 patients in the TACE plus atezolizumab and bevacizumab group versus 70 (40%) of 173 in the TACE alone group. When compared with IMbrave150,[14] the rates of adverse events related to atezolizumab or bevacizumab were similar (87% in TALENTACE [table 2] *vs* 86% in IMbrave150), as were grade 3–4 events (42% *vs* 43%) and grade 5 events (2% *vs* 2%). However, the overall incidence of treatment-related adverse events was higher in TALENTACE than in IMbrave150 (100% *vs* 86%), a difference that is probably attributable to the addition of TACE, the longer treatment duration in TALENTACE (median 13·1 months for atezolizumab and 11·6 months for bevacizumab, compared with 8·4 and 7·0 months in IMbrave150), and a higher baseline tumour burden. Across the four trials combining immune checkpoint inhibitors and anti-angiogenic agents with TACE (appendix p 12), tyrosine kinase inhibitor-based regimens showed numerically higher rates of grade 3 or above treatment-related adverse events (LEAP-012 71%;[26] CARES-005 74%[22]) than bevacizumab-based regimens (TALENTACE 61%; EMERALD-1 27%[25]), a pattern consistent with the safety differences observed between tyrosine kinase inhibitor-based and bevacizumab-based combinations in the systemic therapy setting.[14–15] Within the bevacizumab-based regimens, the lower rate in EMERALD-1 probably reflects its treatment sequencing design, in which TACE and durvalumab were administered together during the first 16 weeks without bevacizumab, and bevacizumab was added only after TACE completion, so that patients never received concurrent triple-agent exposure.[23] In TALENTACE, all three agents were administered concurrently from cycle 1.

This study has several limitations. First, overall survival data were immature at the time of this interim analysis, with the observed HR not crossing the prespecified α boundary. The study continues to accrue events toward the final analysis, and results will be reported once the prespecified number of events has been reached. Second, the open-label design without blinded independent central review might introduce assessment bias; however, a double-blind placebo-controlled design was not feasible given the recognisable adverse event profiles of atezolizumab and bevacizumab, and the ethical and practical burden of prolonged placebo infusions in the control arm. Third, tumour response and TACE-PFS were assessed by site investigators without blinded independent central review. To mitigate potential bias, imaging assessments were standardised across all centres using the RECICL criteria[17] with a unified tumour assessment manual, and continued RECICL-based assessment was mandated beyond RECIST 1.1 progression. The concordance between investigator-assessed TACE-PFS (HR 0·71) and RECIST 1.1 progression-free survival (HR 0·64) supports the reliability of these assessments. Finally, all patients were Asian, and 276 (81%) of 342 were male, consistent with the epidemiology of hepatocellular carcinoma in this region.[32] Although the treatment effect appeared consistent across biological sexes in exploratory subgroup analyses, the small number of female patients limits conclusions in this subgroup. The generalisability of these findings to female and non-Asian populations remains to be confirmed.

In conclusion, on-demand TACE plus atezolizumab and bevacizumab led to a significant improvement in investigator-assessed TACE-PFS compared with on-demand TACE alone in patients with systemically untreated unresectable hepatocellular carcinoma with an intermediate-to-high tumour burden. Continued follow-up, including the final overall survival analysis, will help to define the role of this combination strategy in the treatment of this population.

Contributors

MK, SO, RL, MU, GH, and JD were involved in the study design. MK, SO, RL, SG, KW, MZ, HH, ZLiu, KL, JL, ZLin, YZ, TP, JS, MU, JZ, GH, and JD conducted patient recruitment, data collection and data interpretation. YS performed the statistical analysis. YS, LT, and LB accessed and verified the data. All authors had access to all data reported in the manuscript. All authors participated in the review and editing of the manuscript, agreed to be accountable for all aspects of the work, and accepted responsibility for the decision to submit for publication. All authors approved the final version of the manuscript for submission.

Declaration of interests

MK has received grants from Otsuka Pharmaceutical and Chugai Pharmaceutical; consulting fees from Chugai Pharmaceutical, Roche, AstraZeneca, and Eisai; and honoraria from Chugai Pharmaceutical, Eisai, and AstraZeneca. SO has received grants from Chugai, Daiichi Sankyo, and AstraZeneca; consulting fees from Chugai, Bristol Myers Squibb, Merck Sharpe & Dohme, and Ono; and honoraria from Chugai, AstraZeneca, Eisai, BMS, Takeda, AbbVie, Ono, and Gilead Sciences. MU has received grants from Taiho Pharmaceutical, AstraZeneca, MSD, Nihon Servier, Ono Pharmaceutical, Incyte Biosciences Japan GK, Chugai Pharmaceutical, Boehringer Ingelheim, Eisai, Novartis Pharma, Astellas Pharma, J-Pharma, Delta Fly Pharma, Novocure, Chiome Bioscience, Amgen, Jazz Pharmaceuticals, Revolution Medicines, and BMS; and honoraria from Taiho Pharmaceutical, AstraZeneca, Yakult Honsha, MSD, Nihon Servier, Ono Pharmaceutical, Incyte Biosciences Japan GK, Chugai Pharmaceutical, Boehringer Ingelheim, J-Pharma, Daiichi Sankyo, Eisai, Takeda Pharmaceutical, Novartis Pharma, ASKA Pharmaceutical, J-Pharma, Viatris, Amgen, Revolution Medicines, and Novovure. GH has received grants from Roche and Sirtex; and honoraria from Roche, Bayer, AstraZeneca, Boston Scientific, Gore, MSD, and Eisai. LT and YS are employees of Shanghai Roche Pharmaceuticals. LB was a former employee of Shanghai Roche Pharmaceuticals. All other authors declare no competing interests.

Data sharing

For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see https://go.roche.com/data_sharing. For eligible studies, qualified researchers may request access to individual patient-level clinical data via Vivli (https://vivli.org/ourmember/roche/). Anonymised records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient reidentification.

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References

1 Singal AG, Llovet JM, Yarchoan M, et al. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology* 2023; **78:** 1922–65.

2 Kudo M, Izumi N, Kokudo N, et al. Management of hepatocellular carcinoma in Japan: consensus-based clinical practice guidelines proposed by the Japan Society of Hepatology (JSH) 2010 updated version. *Dig Dis* 2011; **29:** 339–64.

3 Zhou J, Sun H, Wang Z, et al. China liver cancer guidelines for the diagnosis and treatment of hepatocellular carcinoma (2024 edition). *Liver Cancer* 2025; **14:** 779–835.

4 Meyer T, Fox R, Ma YT, et al. Sorafenib in combination with transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma (TACE 2): a randomised placebo-controlled, double-blind, phase 3 trial. *Lancet Gastroenterol Hepatol* 2017; **2:** 565–75.

5 Llovet JM, Villanueva A, Marrero JA, et al. Trial design and endpoints in hepatocellular carcinoma: AASLD Consensus Conference. *Hepatology* 2021; **73** (suppl 1)**:** 158–91.

6 Kudo M, Han KH, Ye SL, et al. A changing paradigm for the treatment of intermediate-stage hepatocellular carcinoma: Asia-Pacific primary liver cancer expert consensus statements. *Liver Cancer* 2020; **9:** 245–60.

7 Yamakado K, Kudo M. Treatment strategies of intermediate-stage hepatocellular carcinomas in Japan (Barcelona Clinic Liver Cancer stage B). *Oncology* 2014; **87** (suppl 1)**:** 78–81.

8 Wang Q, Xia D, Bai W, et al. Development of a prognostic score for recommended TACE candidates with hepatocellular carcinoma: a multicentre observational study. *J Hepatol* 2019; **70:** 893–903.

9 Kudo M, Ueshima K, Ikeda M, et al. Randomised, multicentre prospective trial of transarterial chemoembolisation (TACE) plus sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial. *Gut* 2020; **69:** 1492–501.

10 Kudo M, Han G, Finn RS, et al. Brivanib as adjuvant therapy to transarterial chemoembolization in patients with hepatocellular carcinoma: a randomized phase III trial. *Hepatology* 2014; **60:** 1697–707.

11 Kudo M, Cheng AL, Park JW, et al. Orantinib versus placebo combined with transcatheter arterial chemoembolisation in patients with unresectable hepatocellular carcinoma (ORIENTAL): a randomised, double-blind, placebo-controlled, multicentre, phase 3 study. *Lancet Gastroenterol Hepatol* 2018; **3:** 37–46.

12 Kudo M, Imanaka K, Chida N, et al. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. *Eur J Cancer* 2011; **47:** 2117–27.

13 Lencioni R, Llovet JM, Han G, et al. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: the SPACE trial. *J Hepatol* 2016; **64:** 1090–98.

14 Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med* 2020; **382:** 1894–905.

15 Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs sorafenib for unresectable hepatocellular carcinoma. *J Hepatol* 2022; **76:** 862–73.

16 Duffy AG, Ulahannan SV, Makorova-Rusher O, et al. Tremelimumab in combination with ablation in patients with advanced hepatocellular carcinoma. *J Hepatol* 2017; **66:** 545–51.

17 Kudo M, Ikeda M, Ueshima K, et al. Response Evaluation Criteria in Cancer of the Liver version 5 (RECICL 2019 revised version). *Hepatol Res* 2019; **49:** 981–89.

18 Kudo M, Matsui O, Izumi N, et al. Transarterial chemoembolization failure/refractoriness: JSH-LCSGJ criteria 2014 update. *Oncology* 2014; **87** (suppl 1)**:** 22–31.

19 Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika* 1994; **81:** 515–26.

20 Sun J. A non-parametric test for interval-censored failure time data with application to AIDS studies. *Stat Med* 1996; **15:** 1387–95.

21 Kudo M, Ueshima K, Saeki I, et al. A phase 2, prospective, multicenter, single-arm trial of transarterial chemoembolization therapy in combination strategy with lenvatinib in patients with unresectable intermediate-stage hepatocellular carcinoma: TACTICS-L trial. *Liver Cancer* 2023; **13:** 99–112.

22 Zhu HD, Fan WJ, Zhao C, et al. Transarterial chemoembolization combined with camrelizumab and rivoceranib for unresectable hepatocellular carcinoma (CHANCE2005/CARES-005): a randomized phase II trial. *J Clin Oncol* 2026; **44:** 959–69.

23 Kudo M. Sequential ICI plus anti-VEGF/TKI with on-demand TACE beyond RECIST progression improves pathological response, resectability, and survival in unresectable HCC. *Liver Cancer* 2026; **15:** 169–77.

24 Arizumi T, Minami T, Chishina H, et al. Time to transcatheter arterial chemoembolization refractoriness in patients with hepatocellular carcinoma in kinki criteria stages B1 and B2. *Dig Dis* 2017; **35:** 589–97.

25 Sangro B, Kudo M, Erinjeri JP, et al. Durvalumab with or without bevacizumab with transarterial chemoembolisation in hepatocellular carcinoma (EMERALD-1): a multiregional, randomised, double-blind, placebo-controlled, phase 3 study. *Lancet* 2025; **405:** 216–32.

26 Kudo M, Ren Z, Guo Y, et al. Transarterial chemoembolisation combined with lenvatinib plus pembrolizumab versus dual placebo for unresectable, non-metastatic hepatocellular carcinoma (LEAP-012): a multicentre, randomised, double-blind, phase 3 study. *Lancet* 2025; **405:** 203–15.

27 Zhong BY, Fan W, Guan JJ, et al. Combination locoregional and systemic therapies in hepatocellular carcinoma. *Lancet Gastroenterol Hepatol* 2025; **10:** 369–86.

28 Cao M, Wei F, Georges D, Alberts CJ, Clifford GM, de Martel C. Hepatocellular carcinoma attributable to hepatitis B, hepatitis C and other risk factors at global, regional and national levels: an updated systematic review and meta-analysis. *Gut* 2026; published online May 14. https://doi.org/10.1136/gutjnl-2025-337838.

29 Kudo M. Surveillance, diagnosis, and treatment outcome of hepatocellular carcinoma in Japan: 2023 update. *Liver Cancer* 2023; **12:** 95–102.

30 Rossari F, Tada T, Suda G, et al. Disease etiology impact on outcomes of hepatocellular carcinoma patients treated with atezolizumab plus bevacizumab: a real-world, multicenter study. *Liver Cancer* 2024; **13:** 522–36.

31 Brown TJ, Mamtani R, Gimotty PA, Karasic TB, Yang YX. Outcomes of hepatocellular carcinoma by etiology with first-line atezolizumab and bevacizumab: a real-world analysis. *J Cancer Res Clin Oncol* 2023; **149:** 2345–54.

32 Rumgay H, Arnold M, Ferlay J, et al. Global burden of primary liver cancer in 2020 and predictions to 2040. *J Hepatol* 2022; **77:** 1598–606.