Tivantinib for second-line treatment of MET-high, advanced hepatocellular carcinoma (METIV-HCC): a final analysis of a phase 3, randomised, placebo-controlled study

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Summary

Background Tivantinib (ARQ 197), a selective, oral MET inhibitor, improved overall survival and progression-free survival compared with placebo in a randomised phase 2 study in patients with high MET expression (MET-high) hepatocellular carcinoma previously treated with sorafenib. The aim of this phase 3 study was to confirm the results of the phase 2 trial.

Methods We did a phase 3, randomised, double-blind, placebo-controlled study in 90 centres in Australia, the Americas, Europe, and New Zealand. Eligible patients were 18 years or older and had unresectable, histologically confirmed, hepatocellular carcinoma, an Eastern Cooperative Oncology Group performance status of 0–1, high MET expression (MET-high; staining intensity score ≥2 in ≥50% of tumour cells), Child-Pugh A cirrhosis, and radiographically-confirmed disease progression after receiving sorafenib-containing systemic therapy. We randomly assigned patients (2:1) in block sizes of three using a computer-generated randomisation sequence to receive oral tivantinib (120 mg twice daily) or placebo (twice daily); patients were stratified by vascular invasion, extrahepatic spread, and α-fetoprotein concentrations (≤200 ng/mL or >200 ng/mL). The primary endpoint was overall survival in the intention-to-treat population. Efficacy analyses were by intention to treat and safety analyses were done in all patients who received any amount of study drug. This study is registered with ClinicalTrials.gov, number NCT01755767.

Findings Between Dec 27, 2012, and Dec 10, 2015, 340 patients were randomly assigned to receive tivantinib (n=226) or placebo (n=114). At a median follow-up of 18·1 months (IQR 14·1–23·1), median overall survival was 8·4 months (95% CI 6·8–10·0) in the tivantinib group and 9·1 months (7·3–10·4) in the placebo group (hazard ratio 0·97; 95% CI 0·75–1·25; p=0·81). Grade 3 or worse treatment-emergent adverse events occurred in 125 (56%) of 225 patients in the tivantinib group and in 63 (55%) of 114 patients in the placebo group, with the most common being ascites (16 [7%] patients]), anaemia (11 [5%] patients), abdominal pain (nine [4%] patients), and neutropenia (nine [4%] patients) in the tivantinib group. 50 (22%) of 226 patients in the tivantinib group and 18 (16%) of 114 patients in the placebo group died within 30 days of the last dose of study medication, and general deterioration (eight [4%] patients) and hepatic failure (four [2%] patients) were the most common causes of death in the tivantinib group. Three (1%) of 225 patients in the tivantinib group died from a treatment-related adverse event (one sepsis, one anaemia and acute renal failure, and one acute coronary syndrome).

Interpretation Tivantinib did not improve overall survival compared with placebo in patients with MET-high advanced hepatocellular carcinoma previously treated with sorafenib. Although this METIV-HCC trial was negative, the study shows the feasibility of doing integral tissue biomarker studies in patients with advanced hepatocellular carcinoma. Additional randomised studies are needed to establish whether MET inhibition could be a potential therapy for some subsets of patients with advanced hepatocellular carcinoma.

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Introduction

Hepatocellular carcinoma is an aggressive cancer with poor prognosis. The overall median survival of patients with advanced hepatocellular carcinoma is 9 months and the estimated 5 year overall survival is about 10%.[1] To date, the only approved treatment options for patients with advanced hepatocellular carcinoma are the antiangiogenic drugs sorafenib and regorafenib and the immune checkpoint inhibitor nivolumab (approved in the USA only).[2] Sorafenib significantly improved median time to progression compared with placebo (5·5 months *vs* 2·8 months; p<0·001) and median overall survival

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Research in context

Evidence before this study

At the time this study was planned, we searched PubMed, ClinicalTrials.gov, and conference websites for articles published in English from June 1, 2009, to June 30, 2012, with the search terms "advanced HCC", "advanced hepatocellular carcinoma", "liver cancer", and "sorafenib". We did not identify any phase 3, second-line therapy trials in patients with advanced hepatocellular carcinoma that had positive results. Tivantinib (ARQ 197), a selective, oral MET inhibitor, improved overall survival and progression-free survival compared with placebo in a phase 2 study in patients with high MET expression (MET-high) hepatocellular carcinoma previously treated with sorafenib. Therefore, in view of the positive results of the phase 2 study, the absence of other approved therapies in this setting, and the known role of MET in hepatocellular carcinoma, we deemed the design of the current phase 3 study of tivantinib in patients with MET-high hepatocellular carcinoma appropriate.

Added value of the study

This phase 3, double-blind study showed that tivantinib 120 mg twice daily did not improve overall survival or progression-free survival compared with placebo in patients with MET-high advanced hepatocellular carcinoma who were previously treated with sorafenib-containing systemic therapy.

Implications of all the available evidence

Although the results of the METIV-HCC trial were negative, this study demonstrated the feasibility of doing integral tissue biomarker studies, which could be a requirement for enrolment in future trials to stratify patients with advanced hepatocellular carcinoma and, ultimately, improve clinical outcomes.

(10·7 months *vs* 7·9 months for placebo; p<0·001) in patients with unresectable disease previously untreated with systemic therapy.[1,3,4] The multitargeted tyrosine kinase inhibitor (TKI) lenvatinib has been shown to be non-inferior to sorafenib as a first-line therapy in patients with unresectable hepatocellular carcinoma (median overall survival 13·6 months for lenvatinib *vs* 12·3 months for sorafenib; hazard ratio [HR] 0·92; 95% CI 0·79–1·06).[5] Although regorafenib has been shown to improve overall survival compared with placebo in patients with advanced hepatocellular carcinoma previously treated with sorafenib (10·6 months *vs* 7·8 months for placebo; p<0·0001),[6] a need for additional effective second-line therapies remains.

MET is the receptor tyrosine kinase for the hepatocyte growth factor (HGF); binding of MET to HGF activates RAS-MAPK and PI3K-AKT signalling pathways involved in tumour development and metastasis.[7,8] Tivantinib (ARQ 197) is a selective, oral, small-molecule MET receptor TKI that preferentially inhibits growth and induces apoptosis in human tumour cell lines expressing MET.[9] Tivantinib has been shown to reduce MET activity and expression of downstream signalling pathways in tumour biopsy samples.[10] In a previous randomised phase 2 study[11] in patients with advanced hepatocellular carcinoma and Child-Pugh class A cirrhosis, second-line treatment with tivantinib (360 mg twice daily and then 240 mg twice daily) improved median time to progression compared with placebo in a subset of patients with high MET expression (MET-high) tumours (2·7 months for tivantinib combined *vs* 1·4 months for placebo; p=0·03). In these patients, tumour MET expression was an adverse prognostic factor, and MET was more frequently overexpressed in tumour tissue after sorafenib therapy.[12] MET-high tumours predicted poor median overall survival (3·8 months), and treatment with tivantinib improved this overall survival prediction (7·2 months), which was similar to that observed in patients with low MET expression (MET-low) treated with placebo (9·0 months).[11] These findings supported further investigation of tivantinib in patients with MET-high hepatocellular carcinoma. Moreover, higher amounts of circulating MET and HGF were negative prognostic factors in this study.[12] The poor prognosis associated with circulating MET was also confirmed in a post-hoc analysis of the phase 3 regorafenib clinical study.[13] Our current phase 3 study (METIV-HCC trial) evaluated the efficacy and safety of tivantinib as second-line therapy in patients with MET-high hepatocellular carcinoma. To our knowledge, METIV-HCC is the first phase 3 clinical study in patients with advanced hepatocellular carcinoma to stratify the patient population on the basis of biomarker analysis at screening, spanning the recommended phases of clinical development and being an example of a structured approach to the development of new therapeutics.[14]

Methods

Study design and participants

The METIV-HCC trial was a phase 3, double-blind, randomised, placebo-controlled, multicentre study done at 90 centres in Australia, the Americas, Europe, and New Zealand (appendix pp 18–20). Eligible patients were 18 years or older; and had unresectable, histologically confirmed, measurable, advanced hepatocellular carcinoma; MET-high tumours (staining intensity score ≥2 in ≥50% of tumour cells); Child-Pugh A cirrhosis; Eastern Cooperative Oncology Group performance status of 0–1; documented radiographic disease progression or intolerance to 4 weeks or longer of one sorafenib-containing regimen in the first-line setting; and adequate bone marrow, liver, and renal function (defined as platelet count ≥60×10⁹ per L, haemoglobin ≥9·0 g/dL, absolute neutrophil count ≥1·5×10⁹ per L, total bilirubin ≤2 mg/dL, alanine transaminase [ALT] and aspartate transaminase

[AST] ≤5×upper limit of normal [ULN], serum creatinine ≤1·5×ULN, albumin ≥2·8 g/dL, and international normalised ratio of 0·8 to the ULN or ≤3 for patients receiving anticoagulant therapy). Barcelona clinic liver cancer (BCLC) stage A patients were eligible if they had disease progression after sorafenib therapy or were not candidates for surgery, ablation, or transarterial chemoembolisation and, as a result, received sorafenib therapy and developed resistance or intolerance.

We excluded patients if they had a history of clinically relevant cardiovascular disease (New York Heart Association Class II to IV congestive heart failure within 6 months before study entry, active coronary artery disease, clinically significant bradycardia or another uncontrolled, cardiac arrhythmia [grade ≥3 per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03], uncontrolled hypertension, or a myocardial infarction within 6 months before study entry), a Child-Pugh B-C cirrhotic status, known HIV infection, or a history of liver transplantation.

The study was designed to include two dose groups of tivantinib and placebo (240 mg twice daily until unacceptable toxicity, or clinical or radiological disease progression, followed by 120 mg twice daily or equivalent placebo). However, after reviewing the pharmacokinetic results during the first safety analyses from patients treated with 240 mg twice daily followed by 120 mg twice daily, the frequency of grade 3 or worse neutropenia in the tivantinib group was high and the Data Monitoring Committee recommended stopping enrolment to the 240 mg tivantinib dose group and equivalent placebo group (protocol amendment on Aug 29, 2013).

This study was done in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and Good Clinical Practice standards. Institutional review board approval was obtained from all participating institutions. Patients provided written informed consent before any study-related procedures were done.

Randomisation and masking

Participants were randomly assigned (2:1) to receive tivantinib or placebo. The randomisation sequence was computer generated and implemented via an interactive voice-response system with block sizes of three. Treatment assignment was stratified on the basis of vascular invasion (present or absent), extrahepatic spread (including distant metastasis or involved [≥20 mm in the shortest diameter] regional or distant lymph nodes [present or absent]), and α-fetoprotein (AFP; >200 ng/mL or ≤200 ng/mL) concentrations. The number of stratification factors was limited to ensure an adequate number of patients in each treatment stratum for a meaningful analysis. Patients and study personnel were masked to treatment assignment. Masking was achieved with colour-matched and size-matched placebo tablets (both tivantinib and placebo were red-orange film-coated tablets) and central computer assignment of numerically coded treatment kits for each patient on the basis of their group assignment and the contents of each kit. No study site personnel had information about the nature of the kits at their site.

Procedures

Tumour MET expression was analysed by central pathology review (LabCorp, Burlington, NC, USA) by immuno histochemistry in archival or recent biopsy samples using the Ventana CONFIRM anti-total c-MET (SP44) rabbit monoclonal antibody (Ventana Medical Systems, Tucson, AZ, USA) before enrolment.[15] Staining intensity (0, 1, 2, or 3) and percentage of cells stained were independently scored. Samples that scored 2 or higher in 50% or more of tumour cells were considered as being MET-high.[16] We determined the H-score by multiplying the percentage of cells stained by the intensity of the stain.[17]

Eligible patients received oral tivantinib in the form of 120 mg tablets twice daily or oral placebo tablets (Daiichi Sankyo Europe GmbH, Pfaffenhofen, Germany) twice daily with meals, until unacceptable toxicity, or clinical or radiological disease progression. Sequential dose reductions (120 mg cohort was 120 mg once daily, 120 mg once every other day, or 120 mg once every 3 days; 240 mg cohort was 120 mg twice daily and then followed the reduction for 120 mg cohort) followed by dose interruption and treatment discontinuation were permitted at the discretion of the investigator in case of drug-related toxicity.

Tumour response, using RECIST criteria, was assessed by CT or MRI every 8 weeks. Radiographic disease progression was confirmed by repeat CT and MRI scans 4 weeks after radiographic progression was first suspected. Safety was regularly assessed by physical examination and monitoring of vital signs, electrocardiograms, adverse events (according to NCI CTCAE per protocol version 4.03), and changes in laboratory biomarker concentrations in laboratory analyses.

Quality of life (QOL) was evaluated using the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) and EuroQOL five dimensions (EQ-5D) questionnaires at day 1 of each cycle and at the end of treatment. Questionnaires were given to patients before meeting with the physician or when having any other assessments (appendix pp 23–25).

Outcomes

The primary endpoint was overall survival in the intention-to-treat population. Overall survival was defined as the time from randomisation to the date of death from any cause. Secondary endpoints were safety and progression-free survival by central, independent radiology review. Progression-free survival was defined as the time from randomisation to the date of first objective documentation of disease progression per

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See Online for appendix

Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1), or death resulting from any cause, whichever occurred first. Prespecified exploratory endpoints included objective response evaluation (complete response and partial response), proportion of patients with disease control (complete response, partial response, and stable disease), time to progression (time from randomisation to the date of the first objective documentation of disease progression per RECIST), type of disease progression, population pharmacokinetic parameters, biomarkers, patient-reported outcomes (FACT-Hep-based FACT-Hepatobiliary Symptom Index-3 [FHSI-3] Pain Score [pain, pain in back, pain or discomfort in stomach], FHSI-8 score, Emotional Well Being [EWB] score, and FACT-Hep total score), and time to hospital admission (all cause and hepatocellular carcinoma-related). Pharmacokinetic, biomarker, and QoL data will be fully analysed and reported in a separate publication.

Statistical analysis

Efficacy analyses were by intention to treat (all patients who were randomly assigned to the 120 mg treatment group) and safety analyses were done in all patients who received any amount of study drug (however, because of the protocol amendment, only patients assigned to receive 120 mg were considered). The final overall survival analysis required 257 events to ensure 90% power to detect a difference in overall survival by stratified log-rank test at a one-sided type I error of $\alpha=0{\cdot}025$ and an HR of 0·65 (or 54% improvement in median overall survival from 5 months in the placebo group to 7·7 months in the tivantinib group). Assuming 10% dropout, we required about 303 patients for enrolment. An interim efficacy analysis was planned by protocol when at least 60% of total overall survival events (about 154 events) were documented, to stop the trial early if superior efficacy was proved. The final overall survival analysis required a one-sided, nominal p value of 0·0238 or lower for the study to show superior

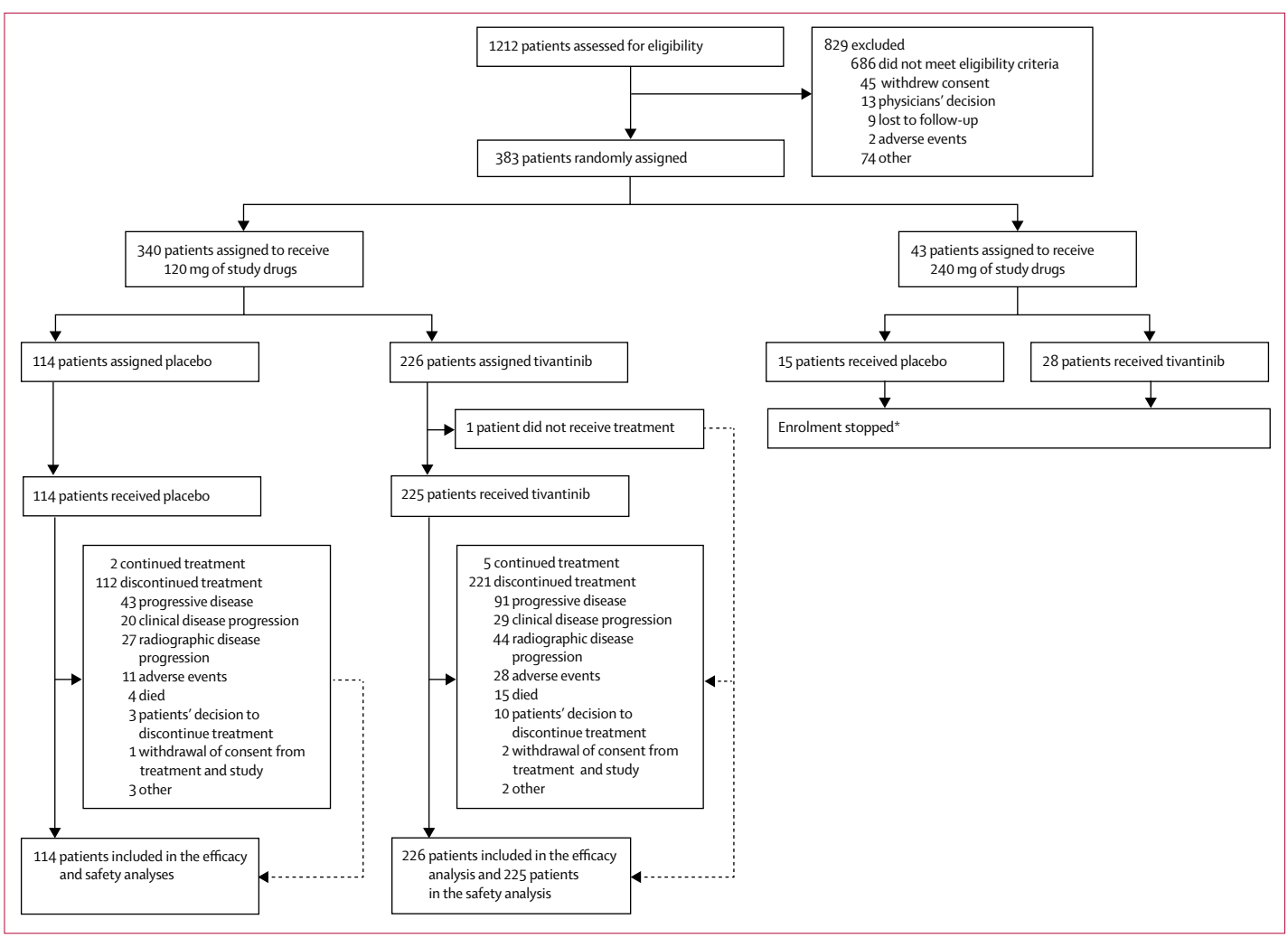

Figure 1: **Trial profile**

*As per the Data Monitoring Committee recommendation, these cohorts stopped enrolment because of toxicity and were not included in the analyses (protocol amendment on Aug 29, 2013).

efficacy. Overall survival, progression-free survival, and time to progression were estimated by the Kaplan-Meier method. We compared treatment groups using a stratified Cox proportional hazards regression model, with treatment group as the only factor to obtain point estimates of HRs and two-sided 95% CIs.

We did statistical analyses using SAS (version 9.1) software. A Data Monitoring Committee oversaw the study. This study is registered with ClinicalTrials.gov, number NCT01755767.

Role of the funding source

The funders contributed to the study design and collection of data along with the investigators, and data analysis and interpretation were done by a contract research organisation. The funder provided editorial support. All authors had unrestricted access to the final study data upon request, and were responsible for the decision to submit for publication.

Results

Between Dec 27, 2012, and Dec 10, 2015, 1212 patients were assessed for eligibility, including 589 (49%) patients with MET-high tumours, and 383 (32%) patients were randomly assigned (figure 1). Initially, 43 (11%) of 383 patients were randomly assigned to receive 240 mg twice daily of tivantinib (n=28) or placebo (n=15; figure 1). However, enrolment to this dose cohort was stopped as per a recommendation from the Data Monitoring Committee because of toxicity (grade 3 or worse neutropenia in 13 [46%] of 28 patients in the tivantinib group). We noted that tivantinib exposure was higher in the 240 mg twice daily tablet cohort of this trial (mean area under the curve [AUC] 31939 ng×h/mL; 90% CI 27730–36147) than the the 120 mg twice daily tablet cohort (26106 ng×h/mL; 24790–27422).

340 patients were randomly assigned to the 120 mg dose cohorts (226 to the tivantinib group and 114 to the placebo group; figure 1). The median time between obtaining patient consent and being randomly assigned was 43 days (range 11–406) because of the time required to obtain tumour tissue to confirm the MET-high status, do other screening procedures, and because patients could consent for this study while still receiving first-line therapy.

Baseline demographics and disease characteristics were balanced between groups (table 1). The median duration of previous sorafenib therapy was 6·3 months (IQR 0·4–46·5) in the tivantinib group and 5·8 months (0·7–65·0) in the placebo group, and most patients in both groups (275 [81%] of 340 patients) had discontinued sorafenib because of radiographically confirmed disease progression.

The interim analysis done by Feb 26, 2016 (179 events), found no difference in relative risk between the two groups so the trial continued.

At the time of data cutoff (Jan 6, 2017), with a median follow-up time of 18·1 months (IQR 14·1–23·1) for the 120 mg dose cohorts, 46 (20%) of 226 patients were alive in the tivantinib group and 20 (18%) of 114 patients were alive in the placebo group. Median overall survival was similar in the tivantinib (8·4 months; 95% CI 6·8–10·0) and placebo (9·1 months; 7·3–10·4) groups (HR 0·97; 95% CI 0·75–1·25; p=0·81; figure 2A). Similarly, median progression-free survival was 2·1 months (95% CI 1·9–3·0) in the tivantinib group and 2·0 months (1·9–3·6) in the placebo group (0·96; 95% CI 0·75–1·22; p=0·72; figure 2B). Median time to progression was 2·4 months (95% CI 1·9–3·6) in the tivantinib group versus 3·0 months (1·9–3·7) in the placebo group (0·96; 95% CI 0·74–1·25; p=0·76), and the proportion of patients with disease control was 112 (50%) of 226 patients in the

	Tivantinib group (n=226)	Placebo group (n=114)
Age (years)	66 (19–87)	65 (26–84)
Sex		
Male	199 (88%)	107 (94%)
Female	27 (12%)	7 (6%)
Ethnic origin*		
White	162 (72%)	86 (75%)
Black	11 (5%)	1 (1%)
Asian	8 (4%)	7 (6%)
American Indian or Alaska Native	2 (1%)	0
Other	40 (18%)	19 (17%)
ECOG PS		
PS 0	141 (62%)	66 (58%)
PS 1	85 (38%)	48 (42%)
BCLC stage		
A	15 (7%)	7 (6%)
B	27 (12%)	17 (15%)
C	184 (81%)	90 (79%)
Extrahepatic spread†	130 (58%)	67 (59%)
Vascular invasion†	79 (35%)	38 (33%)
Extrahepatic spread or vascular invasion	160 (71%)	81 (71%)
AFP >200 ng/mL†	97 (43%)	48 (42%)
AFP (ng/mL)	149 (2–347837)	509 (2–440008)
Hepatitis B virus positive	40 (18%)	21 (18%)
Hepatitis C virus positive	73 (32%)	33 (29%)
Child-Pugh A	215 (95%)	108 (95%)
Previous sorafenib for <60 days	25 (11%)	11 (10%)
Time on sorafenib (months)	6·3 (0·4–46·5)	5·8 (0·7–65·0)
Time from last sorafenib dose (months)	2·2 (0·4–32·4)	2·2 (0·5–43·0)
Reason for sorafenib discontinuation		
Intolerance	38 (17%)	24 (21%)
Radiographic progression	186 (82%)	89 (78%)
Increased size of existing lesions	148 (65%)	64 (56%)
New intrahepatic lesions	66 (29%)	42 (37%)
New distant metastasis	28 (12%)	20 (18%)
New vascular invasion	12 (5%)	3 (3%)

Data are median (range) or n (%). ECOG PS=Eastern Cooperative Oncology Group performance status. BCLC=Barcelona Clinic Liver Cancer. AFP=α-fetoprotein. *Not all patients provided information (n=3 tivantinib and n=1 placebo). †Stratification factor.

Table 1: **Baseline characteristics of patients included in the 120 mg dose cohorts**

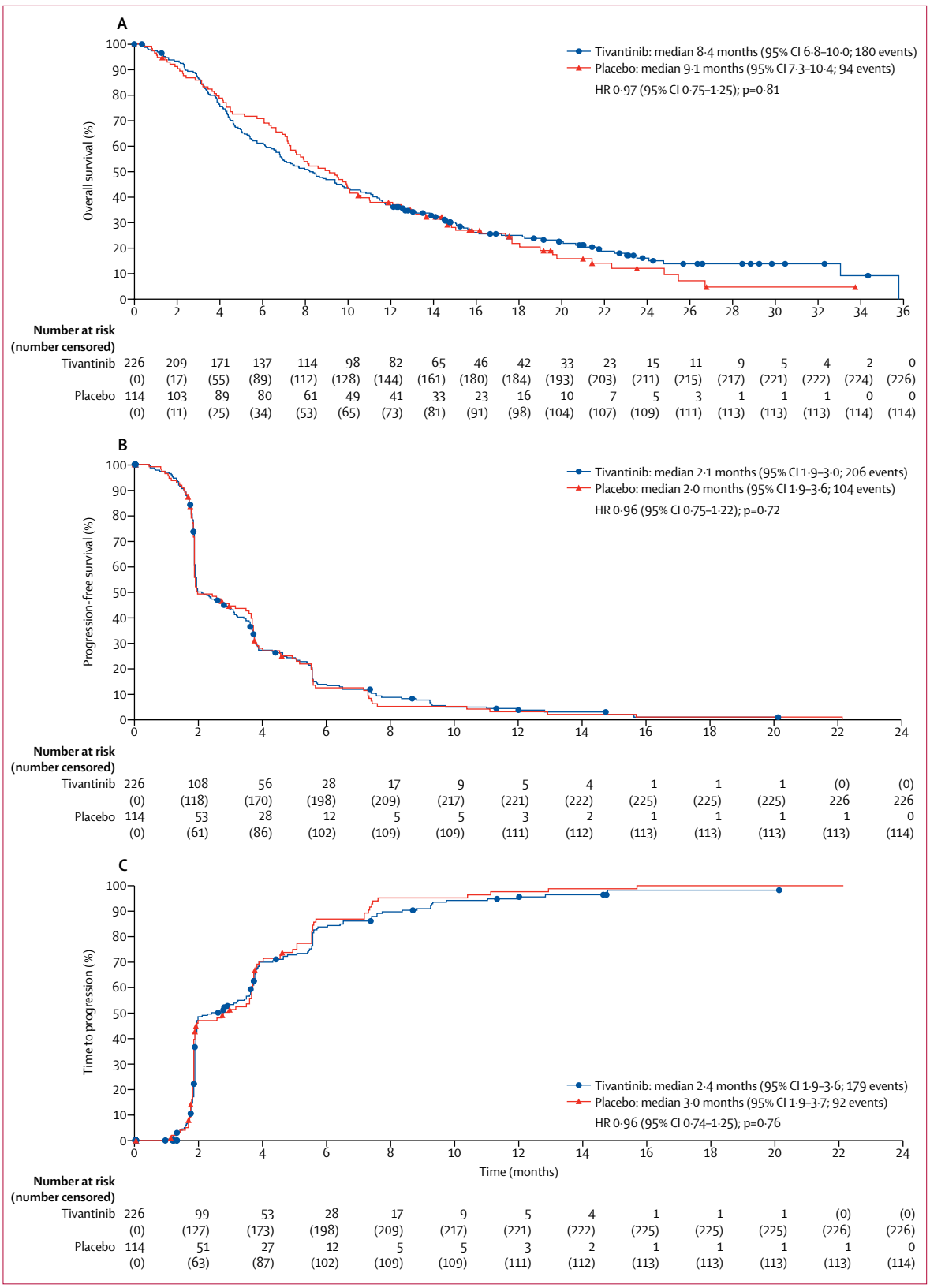

Figure 2: **Kaplan-Meier estimate of overall survival (A), progression-free survival (B), and time to progression (C) in the intention-to-treat population**
HR=hazard ratio.

tivantinib compared with 57 (50%) of 114 patients in the placebo group (figure 2C). There were no complete or partial responses in either treatment group at this stage.

Before enrolment was stopped, in the 240 mg dose cohorts, median overall survival was 5·2 months (95% CI 3·6–7·1) tivantinib versus 5·8 months (3·3–9·6) in the placebo group (HR 1·2; 95% CI 0·64–2·33; p=0·54), and progression-free survival was 2·1 months (1·4–2·7) in the tivantinib group versus 2·1 months (1·3–3·8) in the placebo group (HR 1·2; 95% CI 0·39–3·65; p=0·75). However, survival estimates in these dose cohorts might have been affected by the high frequency of treatment discontinuations due to adverse events (six [21%] of 28 patients in the tivantinib group *vs* none for placebo).

Over half of the 1125 tumour samples that we tested expressed high amounts of MET protein at baseline (table 2). The median H-score in the MET-high cohort was similar regardless of whether the tumour biopsy was taken before or after sorafenib therapy (table 2). Overall, 51 (61%) of 84 patients who were MET-low before sorafenib therapy and had another biopsy after treatment with sorafenib and before enrolment in the METIV-HCC trial converted to MET-high (figure 3). The median H-score increase was 100 (10–285) in patients who converted to MET-high status after treatment with sorafenib. A correlation was observed between MET-high status and previous sorafenib treatment (p<0·0001). However, no correlation was observed between MET status and duration of sorafenib therapy, response to sorafenib therapy, or other factors related to previous therapies (data not shown).

No difference between treatment groups with respect to overall survival was observed in subgroup analyses defined by prespecified stratification factors, including vascular invasion, extrahepatic spread, or AFP concentrations higher than 200 ng/mL (figure 4). Likewise, no overall survival differences were observed between treatment groups based on geographical region, Eastern Cooperative Oncology Group performance status, hepatitis status, reason for sorafenib discontinuation (disease progression or poor tolerability), previous systemic treatment duration, AST and ALT at baseline, platelets at baseline, best response to previous sorafenib therapy, age, ethnicity, sex, and CYP3A4 inhibitor use (figure 4). Similarly, based on an unplanned, post-hoc analysis, median overall survival was comparable in both treatment groups regardless of whether biopsies were done before (8·9 months [range 6·8–11·7] for tivantinib *vs* 11·0 months [5·2–14·7] for placebo) or after sorafenib treatment (7·7 months [6·1–10·6] *vs* 9·1 months [7·3–10·1], respectively). Patients who developed new extrahepatic metastases during previous sorafenib therapy had a worse prognosis in the tivantinib and placebo groups (median overall survival of 6·9 months [95% CI 5·5–9·5] and 8·2 months [6·6–12·1], respectively) compared with the overall patient population. Baseline AFP concentrations (with median value of 200 ng/mL or 600 ng/mL as cutoffs) were also prognostic for overall survival (appendix p 2). Patients with baseline AFP concentrations lower than the median survived 12·1 months (95% CI 9·5–14·3), whereas patients with baseline concentrations higher than the median survived 6·4 months (4·6–7·3; p<0·0001; regardless of treatment; appendix p 2).

Median time on treatment was generally similar in the tivantinib (3·3 months; IQR 2·1–6·4) and placebo (3·7 months; 2·0–7·0) groups. The most common reasons for discontinuation of 120 mg twice daily were radiographic disease progression, clinical progression, and adverse events (figure 1). Treatment-related adverse events that resulted in treatment discontinuation are shown in the appendix (p 1). At the data cutoff date (Jan 6, 2017), only five (2%) of 226 patients were continuing treatment in the tivantinib group and two (2%) of 114 patients were continuing treatment in the placebo group. A similar

	Tumour MET expression		MET-high tumour samples	
	High expression	Low expression	Biopsy before sorafenib treatment	Biopsy after sorafenib treatment
Overall	591/1125 (53%)	534/1125 (47%)	197/591 (33%)	394/591 (67%)
Biopsied before sorafenib treatment	197/558 (35%)	361/558 (65%)	..	..
Biopsied after sorafenib treatment	394/567 (69%)	173/567 (31%)	..	..
H-score	170 (120–300)	90 (0–180)	170 (130–290)	170 (120–300)

Data are n/N (%) or median (range). MET expression was assessed by immunohistochemistry. H-score was calculated by multiplying the percentage of cells stained by the intensity of the stain. MET-high=staining intensity score of 2 or higher in 50% or more of tumour cells.

Table 2: **Baseline tumour MET expression in all samples assessed for eligibility**

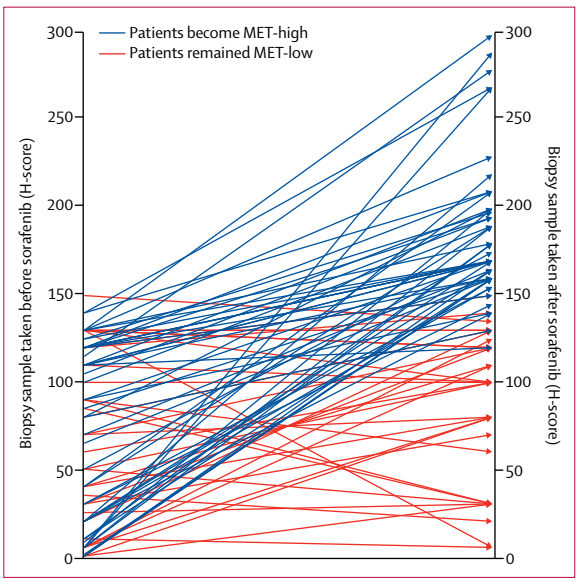

Figure 3: **Tumour MET expression before and after sorafenib therapy**
MET expression in tumour tissues was assessed by immunohistochemistry. MET-high=staining intensity score of 2 or higher in 50% or more of tumour cells. MET-low=staining intensity score of 1 or lower in any percentage of tumour cells, or 2 or higher in less than 50% of tumour cells. H-score was calculated by multiplying the percentage of cells stained by the intensity of the stain.

percentage of patients in each treatment group (61 [27%] patients for tivantinib and 38 [33%] patients for placebo) received systemic therapies after the study that included sorafenib, regorafenib, cabozantinib or crizotinib, nivolumab, hormonal therapy, or chemotherapy.

Most patients in the safety populations for the tivantinib (214 [95%] of 225 patients) and placebo (108 [95%] of 114 patients) groups had at least one treatment-emergent adverse event (appendix pp 3–13). Grade 3 or worse treatment-emergent adverse events occurred in

	Events/patients		HR (95% CI)	p value	$p_{interaction}$
	Tivantinib	Placebo			
Vascular invasion					0·4220
Yes	70/79	35/38	1·19 (0·79–1·79)	0·403	..
No	110/147	59/76	0·89 (0·65–1·22)	0·477	..
Extrahepatic spread*					0·2621
Yes	108/130	53/67	1·09 (0·78–1·52)	0·605	..
No	72/96	41/47	0·80 (0·54–1·18)	0·260	..
α-fetoprotein concentration*					0·4600
>200 ng/mL	85/98	44/48	0·83 (0·58–1·20)	0·329	..
≤200 ng/mL	95/128	50/66	1·00 (0·71–1·41)	0·989	..
Exposure (AUC)†‡					..
<26 000	87/107	94/114	0·97 (0·73–1·30)	0·846	..
≥26 000–35 000	48/61	94/114	0·87 (0·61–1·23)	0·430	..
≥35 000	27/37	94/114	0·68 (0·44–1·05)	0·085	..
Hepatitis					..
HBV positive	31/40	20/21	0·78 (0·44–1·37)	0·385	0·2848
HCV positive (HBV negative)	60/73	28/33	0·84 (0·53–1·33)	0·457	0·4045
HBV and HCV negative	89/113	46/60	1·08 (0·76–1·55)	0·663	..
Sorafenib discontinuation reason					..
Progressive disease	150/187	76/89	0·88 (0·67–1·16)	0·370	0·4111
Intolerance	29/38	18/24	1·18 (0·66–2·13)	0·574	..
CYP2C10 inhibitor use					0·0150
Yes	41/51	19/19	0·51 (0·29–0·89)	0·018	..
No	139/175	75/95	1·07 (0·81–1·42)	0·644	..
Key enrolment region§					..
North America	30/35	12/14	1·04 (0·53–2·05)	0·908	0·8272
European Union	140/180	76/94	0·95 (0·72–1·26)	0·742	..
ECOG PS					0·8576
0	107/141	53/66	0·99 (0·71–1·38)	0·955	..
1	71/83	40/47	0·97 (0·65–1·43)	0·872	..
Previous systematic treatment duration					0·4538
≤60 days	21/25	10/11	0·68 (0·32–1·47)	0·327	..
>60 days	159/201	84/103	0·98 (0·75–1·27)	0·857	..
AST and ALT at baseline					..
<ULN	20/36	17/25	1·06 (0·55–2·03)	0·868	0·5454¶
ULN to 3× ULN	123/151	58/69	0·86 (0·62–1·17)	0·336	0·8013¶
>3× ULN	37/39	19/20	0·84 (0·48–1·48)	0·547	..
Platelets at baseline					0·5404
<100 10^9/L	28/37	23/26	0·84 (0·48–1·46)	0·528	..
≥100 10^9/L	152/188	70/87	1·00 (0·75–1·33)	1·000	..
Best response to previous sorafenib therapy					0·8109
Progressive disease	75/88	40/44	0·99 (0·67–1·46)	0·528	..
Other	98/128	48/63	0·94 (0·66–1·33)	0·728	..
Age group					0·6158
<65 years	87/98	46/50	0·88 (0·62–1·27)	0·504	..
≥65 years	93/128	48/64	1·00 (0·71–1·43)	0·989	..
Ethnic origin					..
White	125/162	71/86	0·87 (0·65–1·17)	0·363	..
Black	11/11	0/1	>999 (0·00–—)	0·996	0·9700‖
Asian	4/8	7/7	0·61 (0·18–2·59)	0·425	0·4518‖
American Indian or Alaska Native**	2/2	—	..	..	..
Other	35/40	15/19	1·39 (0·75–2·59)	0·297	0·2863‖
Sex					0·2787
Female	21/27	6/7	0·57 (0·23–1·45)	0·239	..
Male	159/199	88/107	0·99 (0·76–1·28)	0·919	..
CYP3A4 inhibitor use					0·9901
Yes	14/17	14/16	1·14 (0·53–2·43)	0·742	..
No	166/209	80/98	0·96 (0·74–1·26)	0·774	..
Overall ITT population	**180/226**	**94/114**	**0·96 (0·74–1·23)**	**0·721**	

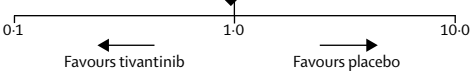

Figure 4: **Overall survival by baseline prognostic factors**

HR=hazard ratio. ITT=intention-to-treat. AUC=area under the curve. HBV=hepatitis B virus. HCV=hepatitis C virus. ECOG PS=Eastern Cooperative Oncology Group performance status. AST=aspartate transaminase. ALT=alanine transaminase. ULN=upper limit of normal. *Stratification factors. †Population pharmacokinetics. ‡Post-hoc analysis; all others were preplanned analyses. §17 patients were from Latin America, Australia, and New Zealand. ¶Reference was >3 × ULN subgroup. ||Reference was white subgroup. **Only two patients in the tivantinib group were American Indian or Alaska Native so interaction analysis was not done for this subgroup.

	Tivantinib group (n=225)				Placebo group (n=114)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Abdominal pain	60 (27%)	9 (4%)	0	0	39 (34%)	4 (4%)	1 (1%)	0
Fatigue	55 (24%)	3 (1%)	0	0	26 (23%)	5 (4%)	0	0
Oedema peripheral	53 (24%)	1 (<1%)	0	0	19 (17%)	0	0	0
Nausea	49 (22%)	1 (<1%)	0	0	12 (11%)	1 (1%)	0	0
Diarrhoea	46 (20%)	3 (1%)	1 (<1%)	0	15 (13%)	2 (2%)	0	0
Asthenia	41 (18%)	6 (3%)	0	1 (<1%)	23 (20%)	2 (2%)	0	0
Decreased appetite	34 (15%)	2 (1%)	0	0	18 (16%)	3 (3%)	0	0
Anaemia	31 (14%)	10 (4%)	0	1 (<1%)	10 (9%)	7 (6%)	0	0
Ascites	30 (13%)	16 (7%)	0	0	15 (13%)	8 (7%)	0	1 (1%)
Pruritus	21 (9%)	3 (1%)	0	0	21 (18%)	0	0	0
Other treatment-emergent adverse events of relevance*								
Bradycardia	30 (13%)	1 (<1%)	0	0	0	0	0	0
Neutropenia	19 (8%)	7 (3%)	2 (1%)	0	4 (4%)	1 (1%)	0	0

Data are n (%) for the events reported in 15% of patients or more. The complete list of adverse events is shown in the appendix (pp 14–17). *Not just reported in 15% of patients or more.

Table 3: **Most frequently reported treatment-emergent adverse events in the safety population**

125 (56%) patients in the tivantinib group and in 63 (55%) patients in the placebo group. The most common grade 3 or worse treatment-emergent adverse events in the tivantinib group were ascites, anaemia, abdominal pain, and neutropenia (table 3). Neutropenia and bradycardia were more common in the tivantinib group than the placebo group (table 3). Deaths during treatment were also more common among patients in the tivantinib group (47 [21%] of 225 patients) than in the placebo group (12 [11%] of 114 patients; appendix pp 3–13); three (1%) of 225 patients in the tivantinib group died from a treatment-related adverse event (one sepsis, one anaemia and acute renal failure, and one acute coronary syndrome; appendix p 17). In the intention-to-treat population, 50 (22%) of 226 patients in the tivantinib group and 18 (16%) of 114 patients in the placebo group died within 30 days of the last dose of study medication. The most common causes of death in the tivantinib group were general deterioration (eight [4%] patients) and hepatic failure (four [2%] patients; appendix p 15). Ten of these patients had disease progression before they died of general deterioration or hepatic failure. The number and reason for all deaths in each treatment group, regardless of whether treatment-related, are reported in the appendix (pp 14–17). 103 (46%) of 225 patients in the tivantinib group and 51 (45%) of 114 patients in the placebo group had serious adverse events (appendix pp 21–22). The most common serious adverse event in patients treated with tivantinib was general deterioration (11 [5%] patients). Four serious adverse events caused by bleeding were reported after biopsy (out of all biopsy samples done before randomisation). The percentage of patients who discontinued treatment (28 [12%] of 225 patients for tivantinib *vs* 11 [10%] of 114 patients for placebo; p=0·478) or had a dose interruption (34 [15%] *vs* 13 [11%], respectively; p=0·408) or dose reduction (77 [34%] *vs* 35 [31%], respectively; p=0·515) because of adverse events did not differ between groups. Most treatment-emergent adverse events leading to study discontinuation were related to gastrointestinal disorders (nine [4%] of 225 patients for tivantinib *vs* none for placebo in the safety population) and general disorders and administration site conditions (eight [4%] *vs* one [1%], respectively).

Health-related QOL and hospital admissions were similar in the tivantinib and placebo groups (full analyses will be reported in a separate publication). Median time to deterioration in the FACT-Hep total score was 12·7 weeks (95% CI 11·9–16·6) in the tivantinib group and 12·4 weeks (8·3–24·1) in the placebo group (p=0·7638). The two treatment groups did not differ for FACT-Hep EWB (median 32·3 weeks; 95% CI 16·6–not determined for tivantinib *vs* 20·1 weeks; 12·3–not determined for placebo; p=0·4982), FHSI-3 pain score (20·1 weeks; 16·1–24·3 *vs* 16·1 weeks; 12·1–26·3; p=0·5789), or FHSI-8 score (20·7 weeks; 16·3–32·1 *vs* 28·1 weeks; 20·1–52·1; p=0·8944). Median change from baseline was similar in the tivantinib and placebo groups (last observation on treatment) for the EQ-5D health status-based utility index (0·7 [range –0·5 to 1·0] *vs* 0·8 [–0·3 to 1·0]) and EQ-5D VAS (70 [2 to 100] *vs* 70 [0 to 100]). The percentage of all-cause (97 [43%] of 226 patients for tivantinib *vs* 46 [40%] of 114 patients for placebo; p=0·5099) and hepatocellular carcinoma-related (40 [18%] *vs* 15 [13%]; p=0·2568) hospital admissions was also similar in the tivantinib and placebo groups.

Discussion

The METIV-HCC study showed that tivantinib 120 mg twice daily did not improve overall survival compared with placebo in patients with MET-high hepatocellular

carcinoma who had progressed on or were intolerant to sorafenib. Progression-free survival was also similar in patients who received tivantinib or placebo. Subgroup analyses of overall survival did not identify any patient subgroups likely to benefit from tivantinib treatment.

The previous phase 2 study[11] of tivantinib in this setting used a capsule formulation of tivantinib, whereas patients enrolled in the METIV-HCC trial received a tablet formulation. The formulation of tivantinib was changed because large-scale production was faster and less expensive with the tablet than the capsule formulation. Although tivantinib exposure was higher in the 240 mg twice daily tablet cohort of this trial, the 120 mg twice daily tablet cohort had exposure similar to that previously observed in the 240 mg twice daily capsule cohort of the phase 2 study (mean AUC 26 000 ng×h/mL).

Notably, although the tivantinib 240 mg twice daily dose was poorly tolerated in the tablet formulation, treatment-emergent adverse events were manageable at 120 mg and mean exposure was similar at the 120 mg twice daily dose (tablets) to that observed in the phase 2 study[11] in patients treated with 240 mg twice daily (capsules). Our unpowered, post-hoc analyses indicated that patients who did not develop new extrahepatic metastases during previous sorafenib therapy and patients with lower median AFP concentrations at baseline had improved overall survival. These findings are consistent with previous reports[13,18,19] showing that progression after sorafenib treatment and higher AFP concentrations at baseline are prognostic factors for poor overall survival.

Unfortunately, the results of the METIV-HCC trial did not confirm the hypothesis generated by the phase 2 study.[11] Both studies had similar proportions of patients with MET-high and MET-low tumours before and after sorafenib therapy, as well as similar median H-scores. However, the studies differed in terms of (i) the smaller patient population in the phase 2 study (which could have introduced bias); (ii) the tivantinib formulation (capsule in the phase 2 study and tablet in the phase 3 study), which could have caused some differences in drug absorption or elimination; (iii) laboratories that evaluated MET expression; (iv) the number of biopsies obtained before and after sorafenib therapy regardless of MET status (about two-thirds before and a third after sorafenib therapy in the phase 2 study *vs* half before and half after sorafenib therapy in the phase 3 study); (v) the number of patients with MET-high tumours identified before and after sorafenib treatment (roughly two-thirds before and a third after sorafenib therapy in the phase 2 study *vs* a third before and two-thirds after sorafenib therapy in the phase 3 study); (vi) exclusion of patients with pleural effusion in the phase 3 study; and, perhaps most importantly, (vii) the protocol-specified requirement for biopsy results to be available before enrolment in the phase 3 study, which might have selected patients who were able to maintain a good performance status during the time needed to organise, do a biopsy, and obtain biopsy results (median of 43 days; range 11–406). As a result, some patients with MET-high advanced hepatocellular carcinoma who had rapid disease progression might have been excluded from the METIV-HCC study, and only patients with less-aggressive disease might have been included. Finally, given reports suggesting that tivantinib also has antimitotic activity, cell proliferation markers, in addition to MET overexpression, could be predictors of tivantinib efficacy in advanced hepatocellular carcinoma.[20,21] However, conflicting data have been reported regarding the antimitotic effects of tivantinib,[22] and most patients treated with tivantinib in clinical trials do not have side-effects typical of antimitotic drugs. For example, no signs of neurotoxicity were reported in more than 1000 patients treated with tivantinib. Therefore, an antimitotic effect is probably not the primary mechanism of action of tivantinib.

Notably, median overall survival among patients with MET-high tumours in the placebo group of the METIV-HCC trial was longer (median 9·1 months; 95% CI 7·3–10·4) than was predicted on the basis of the observation in the phase 2 study, in which the median overall survival in the placebo group was 3·8 months (2·1–6·8).[11] This observation from the phase 2 study suggests that overall survival might be shorter in patients with MET-high tumours compared with the median overall survival reported in placebo-controlled studies of second-line therapies in biologically unselected patients with advanced hepatocellular carcinoma (roughly 8 months),[6,23–26] which could reflect the confirmed negative prognostic value of high amounts of tumour and circulating MET expression.[12,13,27] The reasons for the different results between the phase 2 and phase 3 studies is not clear; however, as mentioned, the requirement for biopsy results before study enrolment might have selected patients with an improved prognosis.

Considering the differences between the phase 2 and phase 3 studies and the other factors discussed, several potential explanations exist for the negative results of this phase 3 trial. MET expression might not be relevant as a mechanism of resistance to sorafenib or a true oncogenic driver in advanced hepatocellular carcinoma, or perhaps tivantinib might not be an effective MET inhibitor. It is also plausible that MET expression might be relevant after progression on anti-vascular endothelial growth factor (anti-VEGF) therapy but only transiently, and that continuous inhibition of VEGF might be necessary for MET to exert a relevant oncogenic effect. Alternatively, a so-called filtering effect might have occurred while patients were receiving sorafenib or being screened for this study whereby patients with more aggressive tumours who progressed faster on sorafenib and deteriorated in terms of liver function or physical status became ineligible, while patients with less-aggressive tumours were enrolled in the study and ultimately had good survival. Those patients who were enrolled might not have benefited from tivantinib because MET no longer had a key role in their disease

progression. Finally, because the median overall survival of the patients who received placebo in this trial was longer than in any other study to date, the immunohistochemistry test used in this study might not have exclusively selected patients who were MET-high.

Similar to the current study, tivantinib did not improve progression-free survival compared with placebo in a Japanese phase 3 study (JET-HCC)[28] in patients with MET-high hepatocellular carcinoma previously treated with sorafenib. Although the reasons for these negative results are not clear, they could be related to primary resistance to MET inhibitors or an absence of persistent MET activation after sorafenib therapy is suspended. A phase 1 study[29] of tivantinib plus sorafenib showed preliminary evidence of the antitumour activity of the combination in patients previously treated with sorafenib, thereby supporting the relevance of combined inhibition of MET and angiogenesis in advanced hepatocellular carcinoma. This approach was investigated in CELESTIAL, a phase 3 trial (NCT01908426) comparing cabozantinib, a multitargeted TKI with activity against both the MET and angiogenic pathways, with placebo in patients with hepatocellular carcinoma who had received previous sorafenib therapy and up to two previous systemic cancer therapies. This trial[30] showed an overall survival benefit for patients receiving cabozantinib compared with placebo. However, CELESTIAL did not select for patients with MET-high tumours, and the predictive relevance of MET expression in this study is unknown.

Tivantinib is not the only drug that has shown no clinical benefit as second-line therapy in advanced hepatocellular carcinoma. Brivanib, ramucirumab, everolimus, and ADI-Peg 20 (an arginine-degrading enzyme conjugated to polyethylene glycol) did not improve overall survival compared with placebo in phase 3, randomised studies[23–26] of patients with advanced hepatocellular carcinoma who had disease progression after previous systemic therapy. These results clearly highlight the challenges in developing effective new drugs for the management of patients with advanced hepatocellular carcinoma who have disease progression on, or were intolerant of, previous therapies.

Study limitations include the fact that the tivantinib formulation was different in the phase 2 (capsule) and phase 3 studies (tablet), and patients could have been underexposed to tivantinib after this formulation change. Based on the population pharmacokinetics analysis presented, exposure to 120 mg twice daily tablets was similar to 240 mg twice daily capsules. However, a full pharmacokinetics analysis was not done and, therefore, we cannot assess differences in rates of absorption, drug elimination, and metabolism between the two formulations. Furthermore, MET expression or MET status was not assessed at the patient level after tivantinib treatment to evaluate the molecular effect of this treatment; we did not collect samples of circulating MET or HGF, nor were enough biopsies taken before and after tivantinib in the METIV-HCC study. However, in a publication based on the randomised phase 2 study[12] of tivantinib in advanced hepatocellular carcinoma, the researchers reported several correlations between circulating MET, HGF, and tivantinib efficacy. Additionally, previous animal model and phase 1 clinical studies[9,10] for tivantinib treatment, which obtained biopsies before and after therapy, reported a reduction in phosphorylated MET after therapy. Although this METIV-HCC trial was negative, it shows the feasibility of doing integral tissue biomarker studies as a requirement for enrolment in clinical trials of patients with advanced hepatocellular carcinoma. We analysed more than 1100 biopsies and only four serious adverse events caused by bleeding were reported after biopsy. Preclinical studies[31] have shown that MET expression increases after VEGF inhibition and hypoxia. Paired biopsy results from this study also highlight MET plasticity in patients treated with sorafenib; therefore, it is important to rebiopsy after treatment with sorafenib and to have complete information on previous therapies and tumour site. A limitation of the current biomarker analysis is that patients who were MET-high before sorafenib therapy were not reassessed for MET expression after sorafenib therapy. We postulated that these patients remained MET-high and might be similar to most of the MET-high patients enrolled in the phase 2 study. Preclinical and phase 1 studies[9,10] of paired tumour biopsies obtained before and after treatment with tivantinib reported that MET activity was reduced after tivantinib administration, thereby confirming MET plasticity and the need to do a biopsy at the correct time. Incorporating tissue biomarker analysis in clinical studies might help to better define and stratify patients with advanced hepatocellular carcinoma and, ultimately, improve clinical outcomes.

Additional studies will be needed to address whether MET has prognostic significance in patients with advanced hepatocellular carcinoma after sorafenib treatment. Phase 3, randomised studies are also needed to establish whether MET inhibition is still a potential therapy in some subsets of patients with advanced hepatocellular carcinoma.

Contributors

All authors were responsible for data interpretation, manuscript preparation, and the decision to submit for publication.

Declaration of interests

LR reports grants and non-financial support from ArQule Inc and Daiichi Sankyo (Daiichi Sankyo Group), during the conduct of the study; and personal fees from Eli Lilly, Bayer, and ArQule Inc, outside the submitted work. EA reports non-financial support from Bayer, Novartis, Amgen, and IPSEN, outside the submitted work. MP-R reports grants from ArQule Inc, during the conduct of the study, and reports grants and personal fees from Bayer Healthcare and personal fees from Lilly, Bristol-Myers Squibb (BMS), Novartis, and Onxeo, outside the submitted work. PM reports personal fees from BMS, Gilead, Verlyx, Merck Sharp & Dohme (MSD), Intercept, AbbVie, Bayer Healthcare, and Sanofi, outside the submitted work. BD reports personal fees and non-financial support from Bayer and BMS and personal fees from Lilly, MSD, Eisai, and Merck, outside the submitted work. LB reports grants from ArQule Inc, during the conduct of the study, and grants from Bayer, BMS, Sirtex, Eli Lilly, Bracco, and Meda-Pharm, outside the submitted work.

VM reports grants from Ipsen, Bayer, and BTG, outside of the submitted work. WH reports that his institution received funding for the clinical trial from ArQule Inc and Daiichi Sankyo, during the conduct of the study; his institution received funding for other clinical trials not related to the current study from ArQule Inc, outside the submitted work. ND reports grants from ArQule Inc, during the conduct of the study, and reports personal fees from ArQule Inc, Bayer, SIRTEX, and Eisai, outside the submitted work. MR reports grants and personal fees from Bayer and BMS, and grants from BTG and Gilead, outside the submitted work. JK reports personal fees from Merck and Taiho and grants from AstraZeneca and Pfizer, outside the submitted work. JT reports personal fees from Daiichi Sankyo and Bayer Healthcare, outside the submitted work. CLL reports grants from Daiichi Sankyo, during the conduct of the study, and reports grants and personal fees from Bayer and Eisai and grants from Lilly, outside the submitted work. MD reports personal fees from Bayer, Pfizer, and Novartis, outside of the submitted work. WS reports personal fees and non-financial support from Bayer Healthcare, personal fees from BMS, and grants from AbbVie, outside the submitted work. GA, BS, and ML are employees of ArQule Inc. JB reports grants and compensation for consulting from Bayer and Biocompatibles, compensation for consulting from Daiichi Sankyo, ArQule Inc, BMS, Kowa, Lilly, Roche, Onxeo, Sirtex, Abbott, and Glaxo, compensation for consulting and advisory boards from Novartis and Terumo, and compensation for advisory boards from Eisai, outside the submitted work. All other authors declare no competing interests.

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