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A Phase-1b study of tivantinib (ARQ 197) in adult patients with hepatocellular carcinoma and cirrhosis

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Background: The mesenchymal-epithelial transition factor (MET) receptor is dysregulated in hepatocellular carcinoma (HCC), and tivantinib (ARQ 197) is an oral, selective, MET inhibitor.

Methods: This Phase-1b study assessed tivantinib safety as primary objective in patients with previously treated HCC and Child-Pugh A or B liver cirrhosis. Patients received oral tivantinib 360 mg twice daily until disease progression or unacceptable toxicity.

Results: Among 21 HCC patients, common drug-related adverse events (AEs) were neutropaenia, anaemia, asthenia, leucopaenia, anorexia, diarrhoea, and fatigue. No drug-related worsening of liver function or performance status occurred, but one Child-Pugh B patient experienced drug-related bilirubin increase. Four patients had drug-related serious AEs, including one neutropaenia-related death. Haematologic toxicities were more frequent than in previous tivantinib studies but were manageable with prompt therapy. Best response was stable disease (median, 5.3 months) in 9 of 16 evaluable patients (56%). Median time to progression was 3.3 months.

Conclusion: Tivantinib demonstrated a manageable safety profile and preliminary antitumour activity in patients with HCC and Child-Pugh A or B cirrhosis.

The current standard of care for patients with advanced hepatocellular carcinoma (HCC) is systemic treatment with sorafenib (Bruix and Sherman, 2011; EASL-EORTC, 2012; Forner *et al*, 2012). Sorafenib significantly improved overall survival compared with placebo in two large, randomised, phase 3 trials (Llovet *et al*, 2008; Cheng *et al*, 2009). There is no standard therapy for patients who are intolerant of sorafenib or experience disease progression after sorafenib treatment (NCCN, 2011).

The hepatocyte growth factor (HGF)/mesenchymal-epithelial transition factor (MET) receptor tyrosine kinase pathway is frequently dysregulated in human cancers and has a critical role in the pathophysiology of HCC (Boix *et al*, 1994; Wang *et al*, 2001; Xie *et al*, 2010). In HCC, activation of the HGF/MET pathway is associated with an aggressive phenotype and poor prognosis (Kaposi-Novak *et al*, 2006). Tivantinib (ARQ 197) is an oral, selective, MET inhibitor that disrupts MET-dependent downstream signalling by inhibiting constitutive and HGF-mediated MET phosphorylation (Munshi *et al*, 2010). Tivantinib inhibits MET activation in human HCC and other tumour cell lines and has demonstrated antitumour activity in human tumour xenograft models (Munshi *et al*, 2010; Previdi *et al*, 2012; Salvi *et al*, 2007). In clinical studies, tivantinib appears to be well tolerated and has antitumour activity as monotherapy or in combination with other agents (Rosen *et al*, 2011; Sequist *et al*, 2011; Yap *et al*, 2011).

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In dose-escalation studies, the recommended phase 2 dose (RP2D) of tivantinib was defined as 360 mg twice daily (BID) (Rosen *et al*, 2011; Yap *et al*, 2011). However, these studies did not include many patients with HCC and chronic liver disease, which may affect drug metabolism (Verbeeck, 2008). This phase 1 study evaluated the safety of tivantinib in patients with documented HCC and liver cirrhosis, focusing especially on the effect of tivantinib on liver function.

MATERIALS AND METHODS

Patients. Adult patients (⩾18 years of age) with histologically or cytologically confirmed advanced HCC, Barcelona Clinic Liver Cancer (BCLC) stage A–C (Forner *et al*, 2012), and Child-Pugh A cirrhosis with no clinical ascites were eligible (see Online Supplementary Information for additional eligibility requirements). The protocol was later amended to include patients with Child-Pugh B cirrhosis (without ascites at physical examination) and to allow validated non-pathologic HCC diagnosis ((Bruix and Sherman, 2005; Forner *et al*, 2008). This open-label, single-arm study (ClinicalTrials.gov ID: NCT00802555) was conducted in accordance with the Declaration of Helsinki and good clinical practice, and all patients provided written informed consent.

Study design and treatment. Oral tivantinib (360 mg BID) was administered 1 h before or 2 h after eating in 28-day treatment cycles. Dose reductions (up to 2) were allowed in patients with grade 3 or 4 drug-related adverse events (AEs) with no dose re-escalation (see Online Supplementary Information). The primary objective was safety, with the goal of defining the RP2D in cirrhotic HCC patients. If during the first month of treatment no more than two of 25 patients experienced a drug-related decrease in liver function, hepatic AE, or two-point decline in performance status, 360 mg BID would be the RP2D (see Online Supplementary Information). Secondary objectives included time to progression (TTP), objective response rate, disease control rate, and tivantinib pharmacokinetics.

Patient assessments. Adverse events were assessed using National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (CTCAE, 2006). Clinically significant laboratory abnormalities were reported as AEs. The efficacy population included all patients who received at least one complete cycle of therapy and had at least one post-baseline tumour assessment. Tumour response was assessed using Response Evaluation Criteria In Solid Tumours version 1.1 every 8 weeks until disease progression, unacceptable toxicity, death, or study withdrawal.

Pharmacokinetic assessments. Blood samples (6 ml) for 24 h pharmacokinetic analysis were collected on study days 1/2 and 15/16 (see Online Supplementary Information). Plasma concentration-time data were analysed by non-compartmental methods using WinNonLin 4.0 (Pharsight Corporation, Mountain View, CA, USA).

Statistical analysis. Data were analysed using standard statistical methods (see Online Supplementary Information).

RESULTS

Demographics and baseline characteristics. Twenty-one patients were enrolled between March 2009 and November 2010, of whom 19 (91%) had received previous sorafenib therapy and seven had received more than one previous therapy. Demographics and baseline characteristics are shown in Table 1. Four patients had Child-Pugh B status (with ⩽8 points), eight had distant metastases, and seven had vascular invasion at study entry.

Table 1. Patient demographic and baseline characteristics

	Patients (*N* = 21)
Median age, years (range)	69 (47–80)
Sex, *n* (%)	
Male	19 (91)
Female	2 (9)
Ethnic origin, *n* (%)	
Black African	1 (5)
White	20 (95)
ECOG performance status, *n* (%)	
0	8 (38)
1	13 (62)
Histologic classification, *n* (%)	
Hepatocellular carcinoma (liver cell carcinoma)	19 (91)
Trabecular-acinar carcinoma	1 (4.5)
Other[a]	1 (4.5)
Aetiology of underlying liver disease, *n* (%)	
Hepatitis C	13 (62)
Alcohol use	5 (24)
Unknown	2 (10)
Hepatitis B	1 (5)
Child-Pugh status, *n* (%)	
A	17 (81)
B	4 (19)
AJCC TMN disease stage, *n* (%)	
3	4 (19)
4	17 (81)
BCLC status, *n* (%)	
A	0
B	8 (38)
C	13 (62)
Median number of previous systemic therapies, *n* (range)	1 (1–3)[b]
Median time since last treatment, days (range)	93 (21–565)

Abbreviations: AJCC = American Joint Committee on Cancer; BCLC = Barcelona Clinic Liver Cancer; ECOG = Eastern Cooperative Oncology Group; TMN = tumour/metastasis/node stage.
[a]One patient had no biopsy available but had a radiographic diagnosis of hepatocellular carcinoma and was granted a waiver.
[b]Seven patients received more than one previous therapy, and four patients each received three previous systemic therapies (one received a waiver, two were listed as protocol deviations, and one was not listed as a protocol deviation); the most common systemic therapies other than sorafenib were chemotherapy, tamoxifen, tumour necrosis factor, and sunitinib.

Median baseline plasma alpha-fetoprotein level was 234 ng ml^{-1} (range, 2–63,918 ng ml^{-1}) and was higher than 200 ng ml^{-1} in 11 patients.

Treatment duration and dose modifications. At time of analysis, all patients had discontinued study treatment: 17 (81%) because of radiographic or clinical disease progression, and four (19%) because of AEs. Overall, 16 patients (76%) received at least two cycles of study drug (range, 1–15 cycles), and median treatment duration was 1.8 months (range, 0.1–15.9 months). Nine patients (43%) were treated for >2 months; two patients continued to

receive treatment for 1.5 months and >24 months, respectively, after confirmed radiographic disease progression because of continued clinical benefit. Five patients (24%) required tivantinib dose reductions because of AEs, and eight (38%) required dose interruptions (<2 weeks) because of AEs and subsequently were able to resume treatment at the same dose.

Safety and tolerability. All patients received at least one dose of tivantinib and were evaluable for safety. The most common drug-related AEs were neutropaenia, anaemia, leucopaenia, asthenia, anorexia, diarrhoea, and fatigue (Table 2). Grade 3 or greater drug-related AEs were observed in 11 patients (52%), including neutropaenia in eight patients (38%). Neutropaenia was the primary reason for dose reduction, interruption, or discontinuation.

Serious AEs that were definitely, probably, or possibly related to tivantinib in the opinion of the investigator were reported in four patients (19%). These included grade 3 anaemia ($n=1$); grade 3 anaemia and grade 4 neutropaenia ($n=1$); grade 4 leucopaenia and grade 4 neutropaenia ($n=1$); and grade 4 leucopaenia, grade 4 neutropaenia, and grade 5 septic shock ($n=1$). Septic shock secondary to neutropaenia was the only drug-related AE leading to death.

A total of 77 myelosuppression events considered related to study drug were reported in 14 patients. Additionally, four cardiac events were reported that were considered possibly or probably related to study drug. No patient experienced drug-related worsening of liver function or decreased Eastern Cooperative Oncology Group performance status during the first cycle, except for one patient with Child-Pugh B cirrhosis who experienced elevated bilirubin that was considered possibly drug related.

Pharmacokinetics. The plasma concentration-time profile of tivantinib was characterised by mean peak levels occurring 4 h and 2 h post dose on days 1 and 15, respectively (Supplementary Figure S1). However, considerable interpatient variability (coefficient of variation range, 43–73%) was observed in tivantinib pharmacokinetic parameters (Supplementary Table S1). Significant tivantinib accumulation in plasma was observed after multiple oral doses.

Table 2. Common (>10%) drug-related adverse events

	Patients, *n* (%) (*N* = 21)	
Adverse event	**All grades**	**Grade 3 and 4**
Any drug-related TEAE	20 (95)	11 (52)
Haematologic		
Neutropaenia	11 (52)	8 (38)
Anaemia	10 (48)	5 (24)
Leucopaenia	8 (38)	4 (19)
Thrombocytopaenia	3 (14)	0
Lymphopaenia	2 (10)	0
Non-haematologic		
Asthenia	10 (48)	2 (10)
Anorexia	8 (38)	0
Diarrhoea	6 (29)	0
Fatigue	6 (29)	1 (5)
Alopecia	4 (19)	0
Peripheral oedema	3 (14)	0
Hyperbilirubinemia	3 (14)	1 (5)
Vomiting	3 (14)	0

Abbreviation: TEAE = treatment-emergent adverse event.

Tumour response. Sixteen of 21 patients (46%) were evaluable for tumour response. Among five non-evaluable patients (24%), three had no post-therapy tumour assessment and two had not completed one full cycle of treatment at the time of confirmed disease progression. No objective responses were reported. Best response of stable disease was observed in nine of 16 evaluable patients (56%; Figure 1). A tumour reduction of ~20% was observed in one patient who experienced prolonged stable disease. Median TTP was 3.3 months (range, 1.7–5.3 months) in the evaluable population (Supplementary Figure S2) and 1.8 months (range, 1.6–5.3 months) in the intent-to-treat population.

DISCUSSION

Oral tivantinib was found to have a manageable safety profile (based on prospectively defined liver function criteria) and preliminary antitumour activity in patients with HCC and Child-Pugh A or B liver cirrhosis (up to 7 points), and 360 mg BID was considered the RP2D in this patient population. These results are encouraging and support further investigation of tivantinib in this setting. Neutropaenia, which occurred primarily within the first 30 days of treatment, was generally manageable with prompt dose modification, growth factors, and antibiotics. However, the frequency of grade 3 or greater neutropaenia (38%) was higher than in previous single-agent, phase 1, dose-ranging studies, in which grade 3 or greater neutropaenia occurred in <5% of patients (Rosen *et al*, 2011; Yap *et al*, 2011). Moreover, one patient in the current study died from septic shock secondary to neutropaenia. In a subsequent phase 2 study in previously treated patients with HCC and Child-Pugh A cirrhosis, the tivantinib dose was reduced to 240 mg BID and a modified dose-reduction schema was implemented because of grade 3 or greater neutropaenia (Santoro *et al*, 2012).

Pharmacokinetic data indicated plasma accumulation of tivantinib after multiple doses, with an area under the plasma concentration-time curve among HCC patients approximately two-fold higher than in patients with other solid tumours, but there was high interpatient variability. Although data are limited, there was no indication of a link between drug-related AEs and dose, tivantinib exposure, or Child-Pugh status, or a link between baseline demographic variables and tivantinib exposure. However, a population pharmacokinetics analysis subsequently showed that tivantinib exposure correlated with the incidence of grade 3 or greater neutropaenia (Zahir *et al*, 2012). These findings are consistent with evidence that tivantinib is extensively metabolised in the liver (Bagai *et al*, 2010; Bathala *et al*, 2012). Thus, a tivantinib dose of 240 mg BID with careful monitoring of haematologic toxicity is recommended in HCC patients with liver cirrhosis.

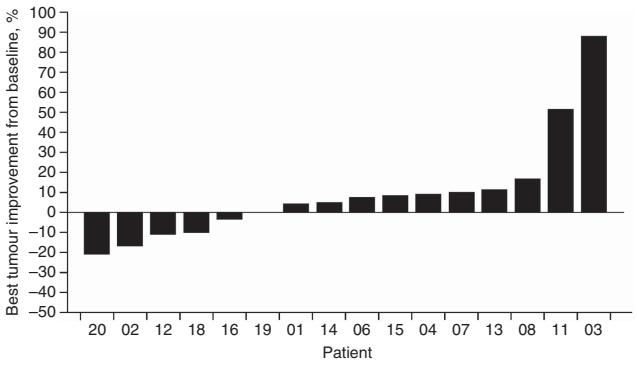

Figure 1. Maximum change from baseline in tumour burden in the evaluable efficacy population ($n=16$).

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AUTHOR CONTRIBUTIONS

AS contributed to study design. AS, CR-L, MS, PZ, and LR contributed to provision and management of study patients, data collection, data interpretation, and writing. JB was the Principal Investigator of the study and contributed to the study design, data interpretation, and writing. LC, AG, NS, ML, RS, and GA contributed to data analysis and manuscript editing. BS contributed to study design, data interpretation, data analysis, and manuscript editing.

CONFLICT OF INTEREST

JB is a consultant for Abbott, AngioDynamics, ArQule, Bayer, BioAlliance, Biocompatibles, BMS, Eisai, GlaxoSmithKline, ImClone, Jennerex, Kowa, Lilly, MedImmune, Novartis, OSI, Pharmexa, Roche, Sanofi, Schering-Plough, and Sumitomo. AS is a consultant for ArQule and Bayer. GA, ML, BS, and RS are employees of ArQule. LR received travel grants from ArQule. The remaining authors declare no conflict of interest.

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Supplementary Information accompanies this paper on British Journal of Cancer website (http://www.nature.com/bjc)