Tivantinib for second-line treatment of advanced hepatocellular carcinoma: a randomised, placebo-controlled phase 2 study.

Abstract:
Tivantinib (ARQ 197), a selective oral inhibitor of MET, has shown promising antitumour activity in hepatocellular carcinoma as monotherapy and in combination with sorafenib. We aimed to assess efficacy and safety of tivantinib for second-line treatment of advanced hepatocellular carcinoma. In this completed, multicentre, randomised, placebo-controlled, double-blind, phase 2 study, we enrolled patients with advanced hepatocellular carcinoma and Child-Pugh A cirrhosis who had progressed on or were unable to tolerate first-line systemic therapy. We randomly allocated patients 2:1 to receive tivantinib (360 mg twice-daily) or placebo until disease progression. The tivantinib dose was amended to 240 mg twice-daily because of high incidence of treatment-emergent grade 3 or worse neutropenia. Randomisation was done centrally by an interactive voice-response system, stratified by Eastern Cooperative Oncology Group performance status.
and vascular invasion. The primary endpoint was time to progression, according to independent radiological review in the intention-to-treat population. We assessed tumour samples for MET expression with immunohistochemistry (high expression was regarded as \( \geq 2+ \) in \( \geq 50\% \) of tumour cells). This study is registered with ClinicalTrials.gov, number NCT00988741. 71 patients were randomly assigned to receive tivantinib (38 at 360 mg twice-daily and 33 at 240 mg twice-daily); 36 patients were randomly assigned to receive placebo. At the time of analysis, 46 (65%) patients in the tivantinib group and 26 (72%) of those in the placebo group had progressive disease. Time to progression was longer for patients treated with tivantinib (1·6 months [95% CI 1·4-2·8]) than placebo (1·4 months [1·4-1·5]; hazard ratio [HR] 0·64, 90% CI 0·43-0·94; \( p=0·04 \)). For patients with MET-high tumours, median time to progression was longer with tivantinib than for those on placebo (2·7 months [95% CI 1·4-8·5] for 22 MET-high patients on tivantinib vs 1·4 months [1·4-1·6] for 15 MET-high patients on placebo; HR 0·43, 95% CI 0·19-0·97; \( p=0·03 \)). The most common grade 3 or worse adverse events in the tivantinib group were neutropenia (ten patients [14%] vs none in the placebo group) and anaemia (eight [11%] vs none in the placebo group). Eight patients (21%) in the tivantinib 360 mg group had grade 3 or worse neutropenia compared with two (6%) patients in the 240 mg group. Four deaths related to tivantinib occurred from severe neutropenia. 24 (34%) patients in the tivantinib group and 14 (39%) patients in the placebo group had serious adverse events. Tivantinib could provide an option for second-line treatment of patients with advanced hepatocellular carcinoma and well-compensated liver cirrhosis, particularly for patients with MET-high tumours. Confirmation in a phase 3 trial is needed, with a starting dose of tivantinib 240 mg twice-daily. ArQule, Daiichi Sankyo (Daiichi Sankyo Group).