

669PD | MET AS PROGNOSTIC FACTOR AND THERAPEUTIC TARGET IN PRETREATED HEPATOCELLULAR CARCINOMA (HCC): FINAL RESULTS OF A RANDOMIZED CONTROLLED PHASE 2 TRIAL (RCT) WITH TIVANTINIB (ARQ 197)

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Background

Tivantinib (T), a selective, oral inhibitor of MET, the hepatocyte growth factor (HGF) receptor, was tolerated in HCC as monotherapy and with sorafenib.

Methods

Multi center RCT; key selection criteria: unresectable HCC, 1 prior systemic therapy, PS <2; no Child-Pugh B-C. Randomization: 2:1 to T or placebo (P); dose: 360mg BID (TA), then 240 mg BID (TB) in all patients (pts) due to G \geq 3 neutropenia; stratification: PS, vascular invasion. Tumor evaluation: by CT / MRI every 6 weeks; central radiology review by RECIST 1.1. Crossover to open label T allowed after PD. Endpoints include: time to tumor progression (TTP) in the intent-to-treat (ITT) population; disease control rate (DCR), progression free survival (PFS), overall survival (OS), efficacy in MET+ (MET \geq 2+ in \geq 50% of tumor cells by immunohistochemistry) pts, safety.

Results

107 enrolled HCC pts, 71 on T (TA: 38; TB: 33), 36 on P. Pt characteristics were generally well balanced. In ITT, median TTP: 1.6 vs 1.4 mos (HR 0.64, 90%CI 0.43-0.94; P = 0.04). Most promising results were obtained in MET+ group, TTP: 2.7 vs 1.4 mos (HR 0.43, 95%CI 0.19-0.97; P = 0.03), DCR (95%CI): 50% (28-72%) vs 20% (4-48%), OS 7.2 vs 3.8 mos (HR 0.38, 95%CI 0.18-0.81, P < 0.02). Prognostic role of several factors was evaluated in the P group. MET+ pts had a 60% higher risk of progression and a 195% higher risk of death; high HGF (cutoff: median value of 2307 pg/mL) pts showed a similar trend in terms of TTP and OS. In MET+ pts on T, the most common AEs were fatigue (7, 31.7%) and asthenia (6, 27.3%). Blood levels (PK) of T were higher than in non HCC studies. No relation between MET and HBV/HCV, HGF or PK was observed. Strict dose reduction guidelines and the TB starting dose dramatically reduced the G \geq 3 neutropenia rate without changing efficacy.

Conclusions

In this study, MET is an independent, negative prognostic factor in pretreated HCC pts; T shows pronounced activity in the MET+ patients with a manageable safety profile at TB. Larger studies are warranted.

Disclosure

R. von Roemeling: The Author is an employee of Daiichi-Sankyo and holds company stocks.

G. Abbadessa: The Author is an employee of ArQule and holds ArQule's stock options.

A. Santoro: The Author serves on the advisory board at ArQule.

All other authors have declared no conflicts of interest.

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