738P | EXPOSURE-RESPONSE RELATIONSHIP TO ASSESS THE RISK OF NEUTROPENIA IN PATIENTS WITH HEPATOCELLULAR CARCINOMA (HCC) TREATED WITH TIVANTINIB

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Background

Tivantinib is a selective MET inhibitor that is extensively metabolized in the liver. In a randomized, placebo-controlled, phase 2 study in patients (pts) with advanced HCC, tivantinib monotherapy improved time to progression by 56%. However, in that study at the standard phase 2 dose of 360 mg twice daily (BID), tivantinib exposure was increased, and the absolute incidence of severe neutropenia increased approximately 6% compared to pts with solid tumors from previous studies. An exposure-response analysis was conducted to explore the relationship between neutropenia and tivantinib pharmacokinetics (PK).

Methods

Tivantinib plasma concentration and incidence of grade ≥ 2 neutropenia were pooled from phase 1/1b and 2 studies. A population PK model (NONMEM v.7.1.0) was used to predict tivantinib exposure in HCC. The relationship between tivantinib exposure and neutropenia was evaluated by logistic regression analysis (S plus v8.0).

Results

Data were available from 289 cancer pts, including 73 pts with HCC and mild-to-moderate hepatic impairment. Cases of grade ≥ 3 (n = 28) and grade ≥ 2 (n = 40) neutropenia were included in the analysis. Based on the population PK analysis, tivantinib clearance was reduced approximately 67% in HCC pts, resulting in approximately 3 times higher exposure compared with other cancer pts. There was a significant ($P < .001$) relationship between tivantinib exposure and incidence of grade ≥ 2/3 neutropenia. By reducing the tivantinib starting dose from 360 to 240 mg BID, the incidence of grade ≥ 3 neutropenia is modeled to decrease from 28% to 16% in HCC pts. Further reduction in the risk of neutropenia (~6%) was achieved with intensive clinical monitoring and an aggressive dose-reduction schema.

Conclusions

Based on the current analysis, the increased incidence of neutropenia in HCC pts compared to pts with other solid tumors resulted from increased tivantinib exposure due to hepatic impairment. Consistent with the model, the risk of neutropenia was successfully managed in HCC pts by implementing dose reduction and tighter clinical monitoring without compromising efficacy.

Disclosure

H. Zahir: H Zahir is an employee of Daiichi Sankyo, Inc.

H. Kastrissios: H Kastrissios is an employee of Pharsight Corporation and was retained by Daiichi Sankyo to provide scientific consulting services on tivantinib.

M. Jansen: M Jansen is an employee of Daiichi Sankyo, Inc.

R. Savage: R Savage is currently an employee of ArQule. I participate in the ESPP employee stock purchase plan and receive stock options as part of my compensation package as an employee of ArQule.

G. Abbadessa: G Abbadessa is an employee of ArQule, Inc. and owns Arqule stock options.

F. Chai: F Chai is an employee of ArQule, Inc., the sponsor of the studies. F Chai holds ArQule stock.

B. Schwartz: B Schwartz is currently an employee (Chief Medical officer) of ArQule and own stock in the company.

R. Miller: R Miller is a full time employee of Daiichi Sankyo Pharma Development.

T. Tokui: T Tokui is an employee of Daiichi Sankyo Co., Ltd.

All other authors have declared no conflicts of interest.

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