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Clinical Cancer Research

Letter to the Editor

Tivantinib (ARQ197) Displays Cytotoxic Activity That Is Independent of Its Ability to Bind MET—Letter

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We read with interest the article by Basilico and colleagues (1), testing the *in vitro* activity of tivantinib.

The article ignores highly suggestive clinical evidence supporting the conclusion that the principal mechanism of action of tivantinib is the inhibition of MET, as shown in a double-blind, randomized, placebo-controlled, phase II trial (randomized controlled trial, RCT) in patients with advanced hepatocellular carcinoma. A statistically significant improvement was observed in tumor stabilization and overall survival in MET-high patients on tivantinib, whereas no clinical benefit was observed in the MET-low cohort. Furthermore, survival of MET-high patients on tivantinib and MET-low patients on placebo overlapped, suggesting the detrimental role of MET was neutralized by the treatment (2).

In addition, data from a RCT in non–small cell lung cancer where tivantinib was combined with erlotinib showed statistical benefit for patients with nonsquamous histology, with pronounced benefit in the MET-high group (3, 4). A recent public disclosure of data from the subsequent phase III study announced that only MET-high patients gained overall survival benefit from tivantinib (ArQule form 10-Q release, May 2013).

In contrast, the article by Basilico and colleagues reports preclinical data to support the hypothesis that tivantinib is not a MET inhibitor. Such data were generated under particular conditions in cells, but the importance of MET increases after stress and is related to the surrounding environment. Furthermore, the HepG2 hepatoblastoma cells used in the experiments do not represent the prognosis and drug sensitivity of a hepatocellular carcinoma surrounded by influential stromal cells, in a cirrhotic liver. Therefore, such data may not be relevant to the clinical setting.

Translating preclinical data to clinical trial recommendations should be viewed cautiously, as should broad conclusions derived from isolated *in vitro* studies, in contrast with other relevant literature, including a recent work published by Katayama and colleagues (5). Indeed, this article shows that tivantinib inhibits MET and interacts with tubulin in a way entirely different from that proposed by Basilico and colleagues (1).

The understanding of the biology of MET and tivantinib is evolving. We are aware that certain preclinical data suggest potential nonkinase targets of tivantinib in addition to MET. However, the signals generated in human trials repeatedly show that clinical benefit of tivantinib is observed in MET-high patients. Therefore, we strongly support selecting patients for phase III trials with tivantinib on the basis of the growing evidence from robust RCTs. This seems to be an eminently rational approach, preferable to selecting patients based on data from unconfirmed preclinical findings.

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