CORRESPONDENCE

Re: Tivantinib (ARQ197) displays cytotoxic activity that is independent of its ability to bind MET – letter by Rimassa et al.

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We acknowledge the reasoning behind the clinical observations of Dr. Santoro’s team. However, we believe that the authors are confusing the concept of predictive biomarker with that of drug target. The possibility that tumors expressing high MET levels are more sensitive to tivantinib does not implicate that this drug exerts its antitumor activity by inhibiting MET function, but rather that MET expression predicts response to tivantinib treatment. MET could be a marker of proliferation, of hypoxia, of metabolic stress, or it could identify a specific histological subset of tumors with particular biological characteristics that make a cancer cell more susceptible to tivantinib-induced apoptosis. In the case of hepatocellular carcinoma, tumors expressing high levels of MET—the Hepatocyte Growth Factor receptor—conceivably display a higher proliferative index, and microtubule-targeting antimitotic agents like tivantinib are known to be more active on highly proliferating tumors. In any case, we suggest caution in interpreting phase II results, as these may come from assessment of a small patient cohort (like in the NCT00988741 liver study) and may not be reproduced in phase III (the NCT01244191 lung study was interrupted for futility).
The clinical activity of a targeted agent cannot be separated from its molecular mechanism of action. By definition, a MET inhibitor is a drug that inhibits MET function in cancer cells. Unfortunately, both our study (1) and the work by Katayama et al. (2) demonstrate that tivantinib does not inhibit MET activity in a variety of tumor cells, even if MET has been previously dephosphorylated using a bona fide MET inhibitor (2). These two studies also show that tivantinib exerts its pharmacological action in cells not dependent on MET for growth and survival (1,2), including cells not expressing MET (1). Both Basilico et al. (1) and Katayama et al. (2) fail to reproduce earlier studies (3,4) that led to tivantinib being tested in the clinic as a ‘highly selective MET inhibitor’, suggesting instead that this drug is a cytotoxic agent that perturbs microtubule dynamics (5). Therefore, we recommend prudence in recruiting patients into tivantinib trials based on MET expression. We do agree that translation of preclinical results into the clinic should be undertaken with caution. In fact, a more rigorous characterization of tivantinib pharmacological activity in the experimental setting would have allowed unbiased clinical testing of this drug, and would have provided more benefit to patients accrued in the trials.


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