Letter to the Editor

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

Paolo Michieli1,2, Cristina Basilico1,2, and Selma Pennacchietti1,2

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, hypoxia, metabolic stress, or it could identify a specific histologic subset of tumors with particular biologic 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 and colleagues (2) show 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 2 studies also show that tivantinib exerts its pharmacologic action in cells not dependent on MET for growth and survival (1, 2), including cells not expressing MET (1). Both Basilico and colleagues (1) and Katayama and colleagues (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 pharmacologic 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.

Disclosure of Potential Conflicts of Interest

P. Michieli is a consultant/advisory board member of arGEN-X BVBA (Zwijnaarde, Belgium) and Metheresis (Lugano, Switzerland). No potential conflicts of interest were disclosed by the other authors.

Grant Support

This study was supported by The Italian Association for Cancer Research (AIRC 2010 Special Program in Molecular Clinical Oncology 5% Project No. 9970 and AIRC 2012 IG Grant No. 12798; to P. Michieli), The Fondazione Piemontese per la Ricerca sul Cancro-ONLUS (Intramural Grant 5% 2008), and The University of Torino/Compagnia di San Paolo (Progetti di ricerca di Ateneo 2012).

Received June 4, 2013; accepted June 7, 2013; published OnlineFirst June 13, 2013.

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