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Tivantinib added to erlotinib in nonsmall-cell lung cancer: the primary end point was not MET…

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The transmembrane tyrosine kinase receptor mesenchymal–epithelial transition (MET) factor, activated by its ligand hepatocyte growth factor (HGF), is involved in cell proliferation, survival, motility, and metastasis [1]. The MET pathway is known to crosstalk with the epidermal growth factor receptor (EGFR) and KRAS signaling pathways, which are critical in the molecular pathogenesis of many solid tumors, including nonsmall-cell lung cancer (NSCLC) with intrinsic or acquired resistance to EGFR inhibitors [2]. While *MET* amplification is a quite uncommon event in lung cancer, MET protein overexpression has been detected, by immunohistochemistry, in 27%–77% of NSCLC samples with nonsquamous histology and 1%–57% of NSCLC samples with squamous cell histology [1].

Tivantinib is an oral drug that binds to the dephosphorylated MET kinase [3]. Although it has shown cytotoxic activity via molecular mechanisms that are independent from its ability to bind MET [4], the drug is under clinical development as a highly selective MET inhibitor. A pivotal randomized phase II study of tivantinib plus erlotinib versus erlotinib alone was conducted in 167 patients with advanced NSCLC, chemotherapy-pretreated and naive to EGFR tyrosine kinase inhibitors [5]. The study did not meet its primary end point, because no significant prolongation of progression-free survival (PFS) was shown, but interesting results were observed in exploratory analyses according to tumor histology and molecular characteristics: in detail, the addition of tivantinib seemed to be associated with a better outcome in both PFS and overall survival (OS) in the nonsquamous NSCLC subgroup, with better PFS in patients with wild-type *EGFR* and with a statistically significant PFS improvement in the small subgroup of patients with *KRAS* mutations [5]. In the article accompanying this editorial, Yoshioka et al. present the results of the ATTENTION phase III randomized trial comparing the combination of tivantinib plus erlotinib to placebo plus erlotinib in Asian patients with previously treated, advanced nonsquamous NSCLC [6]. The limited number of patients in many of the subgroup analyses of the abovementioned phase II trial made somehow risky the interpretation of those exploratory analyses. However, the ATTENTION study was conducted in an *EGFR* wild-type population. This ethnicity is known to be characterized by a higher proportion of tivantinib 'poor metabolizers' that are at higher risk of toxicity compared with Caucasian patients. To reduce this risk, the drug dose was administered on the basis of the CYP2C19 status (360 and 240 mg twice daily in extensive and poor metabolizers, respectively). Despite this wise dose assignment, the ATTENTION study was interrupted early because of higher incidence of interstitial lung disease (and of related deaths) in the experimental group. As for efficacy, despite a prolonged PFS, the study did not show a significant benefit in terms of OS from the addition of tivantinib to erlotinib.

At least in principle, one of the main factors that could contribute to the negative results of the Asian trial could be the insufficient statistical power, which was lower than planned. Interestingly, the MARQUEE randomized phase III study, that was based on the same treatment comparison but conducted in a much larger, mostly Caucasian population, has been recently published [7]. In that trial, patients with advanced nonsquamous NSCLC, previously treated with one or two treatment lines, including a platinum doublet, were randomly assigned to receive erlotinib 150 mg daily plus oral tivantinib 360 mg twice daily, or erlotinib plus placebo until disease progression. As detailed in Table 1, similarly to the trial by Yoshioka et al. the primary end point was OS. As for the study hypothesis, the planned hazard ratio was actually the same (0.75), but the MARQUEE trial was designed with higher statistical power (90% versus 80%) and lower risk of false-positive result (0.01 versus 0.05). As a consequence, sample size in the MARQUEE study was much larger than the Asian trial. Disappointingly, also this study was negative, and it was discontinued for futility at the interim analysis. Again, despite a PFS improvement, the addition of tivantinib was not associated with a significant improvement in OS.

Table 1.
Comparison of results reported with MET inhibitors (onartuzumab or tivantinib) in addition to erlotinib in pretreated patients with advanced NSCLC, in the intent-to-treat population and in subgroups based on MET expression

From a 'biological' point of view, the prolongation of PFS demonstrated in both trials could be interpreted as a proof of principle of the activity of the combination in this setting but, from a clinical point of view, the difference was quite small in absolute terms (difference between median PFS in favor of experimental arms was 0.9 and 1.7 months in ATTENTION and MARQUEE, respectively).

In both trials, subgroup analyses according to the status of several biomarkers were carried out. In details, within this exploratory effort of identifying predictive factors, MET expression, *MET* gene copy number, HGF expression, serum HGF level and plasma vascular endothelial growth factor level were explored in the ATTENTION trial, while tumor specimens of patients enrolled in the MARQUEE trial were investigated for *EGFR* and *KRAS* mutations, MET expression and *MET* gene copy number. In the report of the ATTENTION trial, Yoshioka et al. do not show formal interaction tests and, looking simply at the forest plot, the only subgroups suggesting a potential interaction with treatment efficacy are the HGF expression by immunohistochemistry and serum HGF levels: in both cases, the efficacy of addition of tivantinib seems to be limited to the 'high' HGF subgroup. On the other hand, subgroup analyses of the larger MARQUEE trial suggest that selection of patients on the basis of the level of MET expression, evaluated by immunohistochemistry, could be useful to predict treatment efficacy. Of course, if this information is considered relevant for the development of the experimental combination in this setting, these exploratory evidences need a prospective validation. The absence of any interaction between MET expression and efficacy in the ATTENTION trial does not explicitly reinforce this hypothesis. However, it should be emphasized again that the number of patients in the Asian trial was much smaller (due to both different study design and premature study interruption), and subgroup analyses suffer from a very low statistical power.

The results of other trials conducted with anti-MET agents, not limited to NSCLC but also in other solid tumors, may help investigators to better understand the role of the level of MET expression as a predictive factor for this targeted approach. In the setting of advanced NSCLC, onartuzumab, a monovalent monoclonal anti-MET antibody, was tested in combination with erlotinib in a phase II randomized trial versus erlotinib plus placebo [8]. There was no patient selection according to MET expression, but tumor tissue collection was mandatory in order to assess MET status by immunohistochemistry. PFS in the intent-to-treat population and PFS in MET-positive patients were co-primary end points. Interestingly, although the addition of onartuzumab to erlotinib was not effective in the intent-to-treat population, the combination generated a significant PFS and OS prolongation in MET-positive patients and, conversely, worse outcomes in MET-negative patients. These results prompted a randomized phase III trial dedicated to patients with MET-positive tumors: unfortunately, this trial did not meet the primary end point [9].

Subgroup analyses of the phase II trial that tested tivantinib as single agent in the second-line treatment of patients with hepatocellular carcinoma suggested antitumor activity in the subpopulation of patients with high MET expression [10]. Following these results, a subsequent phase III trial has been designed with a molecular selection of patients, and only patients with high MET expression are eligible for inclusion [11]. This study is still ongoing and results are awaited to understand if this could represent a 'winning' rescue strategy for tivantinib, at least in the difficult setting of advanced, pretreated hepatocellular carcinoma.

In the era of personalized medicine, taking into account the toxicity associated with specific treatments, the existence of potentially effective therapeutic alternatives and the high costs associated with new targeted therapies, the identifications of biomarkers as predictive factors of treatment efficacy is crucial for new drug development. However, the other side of the coin is that subgroup analyses may be often misleading. The recent negative confirmatory experience with

onartuzumab, together with the tricky interpretation of the phase III results of ATTENTION and MARQUEE trials with tivantinib, claim for caution when we estimate the information obtained from subgroups analyses for the generation of further hypotheses. Furthermore, dealing with molecular tumor characterization and with the issue of intrinsic and acquired resistance to treatments, the scientific community has recently faced with the great deal of tumor heterogeneity, both among different synchronous tumor sites and among different time frames in the natural history of disease [12]. The molecular profile of tumor cells after one or more lines of chemotherapy is most likely to be different from the baseline profile of the original diagnostic tissue. How can this affect specifically the predictive role of MET status for anti-MET drugs, we do not know yet. For instance, *MET* amplification, which is relatively rare in NSCLC sampled before treatment, is detected as a secondary event commonly involved in the acquired resistance to EGFR tyrosine kinase inhibitors [13]. Of course, we do not know how this information may apply to patients with NSCLC before and after treatment with chemotherapy.

While the results obtained in both the ATTENTION and MARQUEE trials do not support any current role for tivantinib in addition to erlotinib in pretreated patients with advanced, nonsquamous NSCLC, the search for treatment efficacy in specific molecular subpopulations is challenging from methodological, clinical, and technical point of view. A randomized phase II trial will hopefully contribute to know more about the role of tivantinib plus erlotinib compared with single-agent chemotherapy in pretreated patients with *KRAS* mutant NSCLC (ClinicalTrials.gov Identifier NCT01395758). As for MET and HGF expression, they emerge as potential biomarkers for the addition of tivantinib to erlotinib in MARQUEE and ATTENTION trials, respectively. However, only further prospective data could clarify if both those results can be really useful to refine the use of tivantinib or, alternatively, if they are just another brick in the big wall of mistaken subgroup analyses.