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"COMPANION DIAGNOSTICS": Has their time come and gone?

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SUMMARY

Rapid development of molecularly targeted drugs requires a "companion diagnostic", which could delay drug development and limit availability of active drugs for relevant patients. Were the negative results from MetMab studies in patients with advanced NSCLC due to drug failure or failure of the right companion diagnostic?

In this issue of *Clinical Cancer Research*, Koeppen et al describe the background for the use of the MET IHC- assay as "companion diagnostics" (1). The article describes categorization of positive and negative assay results. The authors demonstrated reproducibility of 88% between two observers, which is good, but for an assay to be clinically valid an inter-laboratorial robustness should be encouraged. Many questions remain to be solved, among them inter-laboratorial reproducibility, which might have been addressed but was not specifically reported. Ornatuzumab, (Genenetech/Roche) is a promising new targeted agent in Non-Small Cell Lung Cancer (NSCLC) based on very encouraging results from a prospective randomized phase 2 study in which patients with advanced NSCLC were randomized to erlotinib plus onartuzumab or erlotinib plus placebo (2). The rational for the study was established through the fact that erlotinib is approved in "all comers" as second- and third-line therapy of advanced NSCLC based on a phase III study comparing erlotinib to placebo in this setting (3). Furthermore, preclinical studies, particularly in EGFR mutant tumors, had shown that MET pathway activation is an acquired resistance mechanism for EGFR Tyrosine Kinase Inhibitor (EGFR TKI) therapy and hence to overcome resistance to EGFR TKI, adding a MET-inhibitor had biologic rationale (4). The phase II onartuzumab study failed to meet the primary endpoint of improved PFS in the entire population, but subset analysis showed improved PFS and OS in patients with high MET protein expressing

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tumors using IHC as defined in the Koeppen paper where a positive assay was defined by ≥ 50% of the tumor having 2+ or higher staining intensity (1,2). A worse outcome occurred in the MET IHC negative subgroup (2). The results led to a prospective randomized phase III study in patients with the “MET IHC high” subgroup of patients, which did not improve outcome with the onartuzumab combination (5). Did the phase III trial fail because the drug failed or because the biomarker failed? Could the failure of the biomarker have been driven by FDA requirements of a companion diagnostic?

Several factors might account for the lack of superiority in the onartuzumab phase III study such as the much smaller number of MET IHC patients in the phase II study. Furthermore, the studies were performed in a study population independent of EGFR mutation status and the role of MET activation as an acquired resistance mechanism to EGFR TKI therapy was initially described in EGFR mutant tumors (4). Thus, the study might also have been done in EGFR mutant population where the outcome might have favored the combined therapy. EGFR FISH did not prove to be a better selection criterion in the onartuzumab phase II study but has been demonstrated to be a promising biomarker in a study of crizotinib in MET positive patients presented at ASCO this year (6). However, whether MET FISH alone by using a more granular assessment method alone or in combination with MET IHC is a better selection paradigm for MET inhibitors needs to be evaluated in future studies. Other autocrine/paracrine markers of pathway activation should also be explored but were not explored perhaps in part to FDA requirements. In addition to all these challenges it is also possible that the mechanism of action of this antibody is not the most optimal way to target the c-met receptor and other approaches (e.g. ligand binding antibodies or small molecule tyrosine kinase inhibitors) in selected subgroups could be superior.

Many issues are raised related to the “companion diagnostics”, which is currently defined as drug specific. Different drug companies are pursuing their own “proprietary” assay, which goes through phase II studies and phase III studies with very little transparency for the scientific community! Several companies are currently pursuing their own MET-assay, mostly based on IHC, in order to have their drug FDA approved. The same situation is occurring with other assays and therapeutic targets in NSCLC, e.g. PD-1/PDL-1 targeted therapies. It is the hope that several of these new targeted therapies will be approved both in the US and in other regions. However, that will certainly raise some issues for the scientific community in general and for the pathology community in particular; how will the pathologist deal with different assays (different antibodies ,different equipment and different cut-off values for positive/negative results) for the several drugs targeting the same target?

We are fully aware of the agents’ different mechanisms of action and differences between small molecules (TKIs) and monoclonal antibodies, but even within the same drug family (i.e. monoclonal antibodies) there might eventually be several FDA approved assays, each specific for the relevant agent.

Standards for assay validation need to be established. Every assay used for selection of patients to any therapy needs to be a validated and standardized assay performed in a CLIA-certified laboratory. However, would it be possible to look for a standardized assay, which can be suitable for several agents targeting the same target across the “company borders”?

The request for a specific companion diagnostics to be approved with every specific agent, leads to “proprietaries” and “secrecies”, which limit the academic communities for any type of validation of the specific assay.

The next question will be the clinical utility and applicability of the assays in the oncology community, and will the use of only the “FDA approved test” limit the distribution of drug to potential patient beneficiaries? For patients with advanced NSCLC, crizotinib (Xalkori®, Pfizer) was approved for ALK-positive patients selected by a “FDA approved assay”. However, as time goes by, several studies have shown excellent correlation between ALK-FISH (Abbot, IL), which is the only FDA approved ALK-assay , and ALK-IHC (7), and several reports have communicated excellent responses to crizotinib in ALK-FISH negative, but IHC positive patients (8,9). While ALK-FISH is skill dependent and costly, the IHC assay is easy, relatively cheap and can be used easily for screening for ALK-gene rearrangements. It is likely that many NSCLC patients, who could be candidates for ALK-therapy do not get this therapy due to restriction of ALK-inhibitors only to patients selected by the FDA approved ALK-FISH assay. This restriction seems to be a unique US phenomenon; in Europe new active agents are approved in a defined patient subpopulation selected by a “validated test”. Thus, while one company is developing a “FDA approved” assay, which goes along with their specific drug, others and newer methodologies are developed to identify the potential targeted subpopulation. However, to get the new assay approved to go along with the drug, eventually a new clinical trial might need to be initiated or at least substantial clinical data provided, which cost time and money! The goal is to have a validated (“CLIA certified”) test for each biomarker/drug. Due to the development of “companion diagnostics”, there is a very high demand of adequate specimens for studying biomarkers based on different assay platforms. As such, multiplex assays are rapidly being developed, including Next Generation Sequencing (NGS), which addresses mutations, gene copy number/fusions and gene expression. The request for 10-15 slides with adequate tumor content is a significant barrier for patients entering clinical trials with new targeted therapies!

While we are aiming to find new ways to identify as rapidly as possible new targeted agents for cancer therapy, for example through a “Master protocol” mechanisms (10), it might be time to rethink how we can speed up the assay standardizations and streamline the validation processes in order to support the regulatory process for a more speedy drug development and to ensure that the “companion diagnostic” is supportive for a wide distribution of active drugs to patients, who will benefit, and not a limitation.

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