"Companion Diagnostics": Has Their Time Come and Gone?

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In this issue of Clinical Cancer Research, Koeppen and colleagues describe the background for the use of the MET IHC assay as a "companion diagnostic" (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 interlaboratorial robustness should be encouraged. Many questions remain to be solved, among them interlaboratorial reproducibility, which might have been addressed but was not specifically reported. Onartuzumab is a promising new targeted agent in non–small cell lung cancer (NSCLC) based on very encouraging results from a prospective randomized phase II study in which patients with advanced NSCLC were randomly assigned to treatment with erlotinib plus onartuzumab or erlotinib plus placebo (2). The rationale 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 with 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 (TKI) therapy and, hence, to overcome resistance to EGFR TKI, adding a MET inhibitor had a biologic rationale (4). The phase II onartuzumab study failed to meet the primary endpoint of improved progression-free survival (PFS) in the entire population, but subset analysis showed improved PFS and overall survival in patients with high MET protein–expressing tumors using IHC as defined in the Koeppen study, in which 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). These results led to a prospective randomized phase III study in the "MET IHC high" subgroup of patients, which did not improve outcome with the onartuzumab combination (3). 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, one of which might be the much smaller number of MET IHC patients in the earlier phase II study. Furthermore, the studies were performed in a 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 an EGFR-mutant tumors (4). Thus, the study might also have been done in an EGFR-mutant population in which 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 based on findings presented at the American Society of Clinical Oncology meeting this year (6). However, whether MET FISH using a more granular assessment method alone or in combination with MET IHC is a better selection paradigm for MET inhibitors needs to be examined in future studies. Other autocrine/paracrine markers of pathway activation should also be explored but were not, perhaps in part due to FDA requirements. In addition to all of 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 TKIs) in selected subgroups could be superior.

Many issues are raised related to the companion diagnostics, which are currently defined as drug specific. Different drug companies are pursuing their own proprietary assay, which goes through phase II 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, to have their drug FDA approved. The same situation is occurring with other assays and therapeutic targets in NSCLC, for example, PD-1/PD-L1.
targeted therapies. It is hoped that several of these new targeted therapies will be approved both in the United States and elsewhere. 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 cutoff 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, with each being 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 validated and performed in a laboratory that meets the requirements of the Clinical Laboratory Improvement Amendments (CLIA). 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 diagnostic to be approved with every specific agent leads to “proprieties” and “secrecies,” which limit the academic communities for any type of validation of the specific assay.

The next question will concern the clinical utility and applicability of the assays in the oncology community, and whether the use of only the FDA-approved test limits the distribution of a drug to potential patient beneficiaries. For patients with advanced NSCLC, crizotinib (Xalkori; Pfizer) was approved for ALK-positive patients selected by an FDA-approved assay. However, over time, several studies have shown excellent correlation between ALK–FISH (Abbott), 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). Although ALK–FISH is still 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 patients with NSCLC, who could be candidates for ALK therapy do not receive it due to restriction of ALK inhibitors only to patients selected by the FDA-approved ALK–FISH assay. This restriction seems to be a unique phenomenon in the United States; in Europe new active agents are approved in a defined patient subpopulation selected by a validated test. Thus, although one company may develop an FDA-approved assay to go along with their specific drug, other, newer methodologies may be 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 costs time and money. The goal is to have a validated (CLIA certified) test for each biomarker/drug. The development of companion diagnostics has led to a very high demand for adequate specimens for studying biomarkers based on different assay platforms. As such, multiplex assays are rapidly being developed, including next-generation sequencing, which addresses mutations, gene copy number/fusions and gene expression. The request for 10 to 15 slides with adequate tumor content is a significant barrier for patients entering clinical trials with new targeted therapies.

Although 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” mechanism (10), it might be time to rethink how we can speed up the assay standardizations and streamline the validation processes to support the regulatory process for more speedy drug development and to ensure that the companion diagnostic is supportive for wide distribution of active drugs to patients who will benefit, and not a limitation.

Disclosure of Potential Conflicts of Interest

F.R. Hirsch is a consultant/advisory board member for Agena, Bristol-Myers Squibb, Genentech-Roche, Lilly, Novartis, and Pfizer, and reports receiving commercial research grants from Agena, Celgene, Imclone/Lilly, Genentech, and Ventana, through his institution (University of Colorado). P.A. Bunn was a consultant/advisory board member for Genentech and Pfizer. R.S. Herbst is a consultant/advisory board member for Biothera, Diatech, Kollzan, and N-of-One, and reports receiving a commercial research grant from Genentech. No other potential conflicts of interest were disclosed.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc): R.S. Herbst
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R.S. Herbst
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