

A Blueprint Proposal for Companion Diagnostic Comparability

Introduction

We are in an era of rapid incorporation of basic scientific discoveries into the drug development pipeline. Currently, numerous sponsors are developing therapeutic products that may use similar or identical biomarkers for therapeutic selection, measured or detected by an in vitro companion diagnostic device. The current practice is to independently develop a companion diagnostic for each therapeutic. Thus, the matrix of therapeutics and companion diagnostics, if each therapeutic were approved in conjunction with a companion diagnostic, may present a complex challenge for testing and decision making in the clinic, potentially putting patients at risk if inappropriate diagnostic tests were used to make treatment decisions.

To address this challenge, there is a desire to understand assay comparability and/or standardize analytical and clinical performance characteristics supporting claims that are shared across companion diagnostic devices. Pathologists and oncologists also need clarity on how to interpret test results to inform downstream treatment options for their patients.

Clearly using each of the companion diagnostics to select one of the several available targeted therapies in the same class is not practical and may be impossible. Likewise, having a single test or assay as a sole companion test for all of the multiple therapeutic options within a class is also impractical since the individual therapies have differing modes of action, intended use populations, specificities, safety and efficacy outcomes. Thus, a single assay or test may not adequately capture the appropriate patient population that may benefit (or not) from each individual therapeutic option within a class of therapies. Furthermore, aligning multiple sponsors' study designs and timelines in order that they all adopt a single companion test may inadvertently slow down development of critical therapeutic products and delay patient access to these life-saving products.

Any solution to this challenge will be multifaceted and will, by necessity, involve multiple stakeholders. Thus, the US Food and Drug Administration (FDA), the American Association for Cancer Research (AACR) and American Society of Clinical Oncology (ASCO) convened a workshop titled "Complexities in Personalized Medicine: Harmonizing Companion Diagnostics Across a Class of Targeted Therapies" to draw out and assess possible solutions. Recognizing that the complex scientific, regulatory and market forces at play here require a collaborative effort, an industry workgroup volunteered to develop a blueprint proposal of potential solutions using non-small cell lung cancer (NSCLC) as the use case indication.

Goal and Scope of Blueprint

The imminent arrival to the market of multiple PD1 / PD-L1 compounds and the possibility of one or more associated companion diagnostics is unprecedented in the field of oncology. Some may assume that since these products target the same biological pathway, they are interchangeable; however, each PD1/PD-L1 compound is unique with respect to its clinical pharmacology and each compound is being developed in the context of a unique biological scientific hypothesis and registration strategy. Similarly, each companion diagnostic has been optimized within the individual therapeutic development programs to meet specific development goals, e.g., 1) validation for patient selection, 2) subgroup analysis as a prognostic variable, or 3) enrichment.

Further, each companion diagnostic test is optimized for its specific therapy and with its own unique performance characteristics and scoring/interpretation guidelines.

The blueprint development group recognizes that to assume that any one of the available tests could be used for guiding the treatment decision with any one or all of the drugs available in this class presents a potential risk to patients that must be addressed.

The goal of this proposal is to agree and deliver, via cross industry collaboration, a package of information /data upon which analytic comparison of the various diagnostic assays may be conducted, potentially paving the way for post-market standardization and/or practice guideline development as appropriate.

The scope of this proposal:

- Initiation of activities that build the evidence base to increase our understanding of the analytic performance of companion diagnostic assays without delaying pivotal studies and patient access to critical new therapies.
- Understanding analytical performance of the different assays, outside of the clinical sample sets used to develop each individual assay is key – reduction to a single assay is considered to be neither feasible nor beneficial for the market.
- Studies will be restricted to tests developed via the Pre-Market Approval (PMA) pathway deployed in clinical trials as per the intended instructions for use and on the associated platform, since these are the assays and configurations with associated clinical data.
- Studies will be performed by diagnostics manufacturers in collaboration with a recognized independent body.
- Collaborative work will be independent of each company's interactions with the FDA, including FDA review and potential approval of any drug/diagnostic pair.
- Whilst the numbers of indications in which PD1 / PD-L1 inhibitors in development are numerous, focus on a single indication in the first instance is necessary. Non-small cell lung cancer (NSCLC) is an area that all companies with an active PD1 / PD-L1 program are actively pursuing, and therefore, the initial studies will focus on that disease.

PD-L1 Assay Analytical Performance Comparison

Goal: Characterize PD-L1 Investigational Use Only (IUO) assay systems from Dako and Ventana to assess the level of analytical similarity.

Study Design:

- Obtain appropriately-sized NSCLC cohort that includes a mix of sample types (e.g., resections and needle biopsies) and representative samples from the different patient populations for which each individual assay has been optimized for characteristics, such as dynamic ranges of the assays and the range of staining in tumor and/or infiltrating cells.
- Stain cohort with PD-L1 IUO assays using the appropriate clinical trial platform. This staining would be performed by respective diagnostic manufacturers to minimize logistical challenges and to assure that results are in accordance with demonstrated performance expectations.

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- Stained slides will be evaluated by the respective diagnostics companies and a third party, such as an independent pathologist(s), External Quality Assessor (EQA) or other organization, to describe analytical staining results from each assay in a simple and reproducible manner. Specific evaluation instructions will be worked out.
- The study will help answer how similar or different the assays are in terms of their analytical performance with respect to targets, intensities, frequency of staining, etc.
 - Analytical data could be additionally assessed by individual diagnostic manufacturers (to maintain confidentiality) with respect to the interpretation guidelines that have been optimized for each drug in order to judge the impact of misclassifying patients in the event the assay is not correctly matched to other drugs.

Feedback invited from workshop participants:

- Comments on the study design
- What scope of study output and format would add value to the community?

Suggestions for Implementation of Blueprint

The ultimate goal is to provide information to the medical practice community with respect to appropriate intended use populations for the individual drugs which includes scoring methods, interpretation and reporting for PD-L1 expression determined by IHC. The standards and comparability for the pre-analytical variables and technical assay parameters will be a first step toward achieving this goal. There is precedent for establishing standards and guidelines for Her2/neu and ER/PR testing by IHC that have been widely adopted by the medical practice community^{1,2}.

Taking a page from the precedent experience, we propose that a reputable scientific professional third party be engaged to help conduct a comparability study among the selected assays. This independent third party would work with the pharmaceutical and diagnostics stakeholders to create an appropriate study protocol.

The scope of this proposal would be to establish technical comparability of the assays, such as by performing an analytical evaluation of each assay to define the key performance parameters of each assay. Testing of clinical samples from any of the commercial sponsors' programs or any activity directed at clinical validation of one or more tests is out of scope for this proposal.

The respective industry stakeholders and the third party will collaborate on the study. Publication of the results would similarly be a joint effort and responsibility. Prior to publication, all commercial sponsors would have the opportunity to review and comment with final decisions resting with the third party.

¹ Wolff AC¹, Hammond ME, et al; Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update; J Clin Oncol. 2013 Nov 1; 31(31):3997-4013.

² Allred DC, Carlson RW, et al; NCCN Task Force Report: Estrogen Receptor and Progesterone Receptor Testing in Breast Cancer by Immunohistochemistry. J Natl Compr Canc Netw. 2009 Sep;7, Suppl 6:S1-S21

This proposal was developed by a working group of representatives from the pharmaceutical and diagnostic industry for discussion at the FDA-AACR-ASCO Public Workshop “Complexities in Personalized Medicine: Harmonizing Companion Diagnostics Across a Class of Targeted Therapies” held on March 24, 2015 in Washington, DC.

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