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PD-L1 Assessment for Targeted Therapy Testing in Cancer: Urgent Need For Realistic Economic and Practice Expectations

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Recent years have witnessed the explosion of a new generation of therapeutic agents in the form of monoclonal antibodies and small molecule inhibitors that are designed to target specific protein receptors expressed on, or in, cancer cells; hence the term targeted therapy agents. Among the first to be developed of such agents are Trastuzumab (anti-HER2 – FDA approved 1998) and Rituxumab (anti-CD20 – FDA approved 2006). Fast forward to 2016, and several dozen similar agents are available not only for the targeted therapy of cancer, but chronic diseases as well (1), with many more products in the approval pipeline (2). Some of these agents have become the “first line” therapy choice, others are employed as neoadjuvant therapy, instead of (or in addition to) the standard “old-fashioned” chemotherapy. For example, EGFR small molecular inhibitors are making their way to become the first-line treatment targeted therapy in non-small cell lung cancer (NSCLC).

All this is exciting, but in order for these targeted therapy agents to achieve maximum effectiveness, accurate detection of the altered gene or “over-expressed” membrane protein receptor is of paramount importance. Current methods include molecular analysis of tissue extracts, and slide-based fluorescence in situ hybridization (FISH) or immunohistochemistry (IHC) testing (1,2). In this context these tests fall under the general rubric of companion (or complementary) diagnostics.

In the United States, governmental regulatory agencies, in particular the Food and Drug Administration (FDA), have established the precedent for co-development of the ‘companion diagnostic’ in joint clinical trials with the corresponding targeted therapy. In this process a working definition of an IVD (in vitro diagnostic) companion diagnostic emerged from the FDA including certain intrinsic criteria - “it provides information that is essential for the safe and effective use of a corresponding therapeutic product,” and its use is “stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic agent (3,4).” Hence use is mandated in order to administer the companion drug. In some co-development trials the ‘test’ did not meet statistical thresholds for classification of responders versus non-responders, and such tests have been termed complementary diagnostics; their use may be recommended but is not required.

As a result of these precedents, biopharmaceutical companies have partnered with (or in some cases acquired) IVD manufacturers to co –develop and validate assays in clinical trials,

the results of which are submitted to the FDA for approval of drug and test. Often, the submission and review processes have been done on a “fast-track” accelerated basis.

This approach has created a paradigm shift for the practicing pathologist, with attendant opportunities and problems. There is the opportunity to be directly involved in the evaluation of patient eligibility for these promising therapeutic agents. As expected, though, with this come significant challenges. To quote Dr. Elizabeth Hammond (personal communication), testing for these targeted therapy agents is reminiscent of performing an intra-operative “frozen section” evaluation, where the pathologist has an immediate shot at ‘making the call’ as to whether the patient is eligible for a specified therapy, or not. However, unlike the frozen section where the final permanent (FFPE - formalin fixed paraffin embedded) H&E section provides a check and is the ultimate arbiter of diagnosis, in the instance of the companion diagnostic, the test result stands alone as the basis for the clinician to make his or her decision.

This type of overall process has not necessarily gone smoothly, with difficulties at several levels. Some of the FDA approved IVD tests have not performed as well as expected following commercialization, lacking in reproducibility. Suboptimal performance of FDA cleared IVD tests may result from several factors, important among which are unknown variations in sample preparation, deficiencies in technical sensitivity and specificity the IHC antibody, deviation by the pathology laboratory from the strict approved assay protocol, variety among platforms and difficulties for pathologists in following and reproducing complex scoring guidelines. Because of the ‘need for speed’ IVD manufacturers have sometimes allowed insufficient time to perform wide-scale comparative studies between reagents, and have not always been able to select (or generate) the reagent with the better performance; an issue further complicated by constraints of IP (intellectual property) ownership and requirements of the pharmaceutical partner.

There is no more timely example of this scenario than the story of Programmed Cell Death-1 (PD-1) and testing for its ligand (PD-L1) in melanoma, NSCLC (non small cell lung cancer), and other tumors. Admittedly the biology is complex. When cancers grow in vivo, antigens released by tumor cells are captured by antigen presenting cells, which in turn sensitize and recruit activated T-lymphocytes to attack the tumor. The tumor cells at some point may “outsmart” the activated T-cells by producing PD-L1 or PD-L2, which are ligands for the PD-1 receptor on the immune cells, rendering the receptor ineffective, and ‘turning off’ the immune response (5–7). Blocking the PD-L1/PD-1 axis inhibits this ‘turning off’ mechanism and thus enables immune cells to evade deactivation by PD-L1, with the effect of reactivating any immune response that may be present at the tumor site.

The discovery of this biologic phenomenon lead to a race among several biopharmaceutical companies to develop clinically effective monoclonal antibodies against PD-L1 (or PD-1) and accelerate clinical trials to obtain FDA approval for these targeted therapies. As a result, cancer patients who experience disease progression either during or after first-line therapy are now offered targeted therapy with antibodies such as Nivolumab (anti-PD-1), Pembrolizumab (anti-PD-1), Atezolizumab (anti-PD-L1), or Durvalumab (anti-PD-L1) (8). Note that for Nivolumab and NSCLC, the therapy targets PD-1, but the IVD detects PD-L1

(4), and different approved tests (utilizing different anti-PD-L1 clones, methods, platforms and scoring guidelines) are employed for each of these PD-1/PD-L1 axis therapies (6). Furthermore the same clone, method and platform may have different scoring parameters for different tumor types, in a separately approved IVD device. If the biology is complex, then practical exploitation unfortunately reaches new heights of complexity.

Not surprisingly with multiple different approved IVD tests each for a different targeted therapy (albeit against the same biological target), there is confusion among oncologists and pathologists as to how properly to test and report PD-L1 expression results; despite (or even because of) the availability of several FDA-cleared assays (9)!

In contrast to other IVDs such as HER2, EGFR and ALK tests, where the College of American Pathologists (CAP) and other oncology/pathology cooperative groups have stepped in to take a leadership role in designing clinically-oriented and meaningful testing guidelines (10;11), the lack of such involvement in PD-L1 testing has created a vacuum that is being filled by industry, but with incomplete collaboration and disclosure, inhibited by competitive considerations. Biopharmaceutical groups and their consultants are attempting to develop consensus testing guidelines (Blueprint Study; unpublished data), but in the absence of participation by CAP or similar unbiased expert groups. It is crucial that the CAP, as an organization representing the pathology community in the US, and comparable groups elsewhere such as NordiQC (Nordic Immunohistochemistry Quality Control), CIHCQC (Canadian Immunohistochemistry Quality Control), UKNEQAS (United Kingdom Quality Assurance System) and other similar organizations that are now emerging, assume leadership positions in bringing together expertise best suited to design meaningful guidelines that are not based on pre-existing bias by the manufacturers.

The other major practical problem is the cost of these approved anti- PD-L1 based tests, and other similar targeted therapy IVD assays cleared by the FDA. The economic burden of performing any one of the FDA-approved PD-L1 assays is prohibitive, and it is impossible for a hospital laboratory to perform the several different approved PD-L1 tests (on different automated instrument platforms) that would be required for clinicians at an institution to select from the full menu different available approved PD-1/PD-L1 targeted therapies. The direct cost of the antibody alone is much higher than total reimbursement rates paid by Medicare or commercial payers for CPT IHC codes 88360 and 88361, without factoring in the cost of the detection system, or the real indirect costs of overhead, technologists, pathologists, etc.. There is no easy solution, certainly not one likely to be embraced by all. Either the manufacturers should significantly reduce the sale price of these FDA-cleared assays, or the AMA (American Medical Association) committees should design and CMS (Center for Medicare Services) approve new CPT codes specifically for FDA-cleared IHC (and other) assays, having much higher reimbursement rates than the rates currently paid. This unfortunate reality, created by the costly FDA-approval process for each individual IVD test, is forcing immunohistochemistry laboratories in the US, already dealing with significant financial challenges, into one of two options; either to devise their own laboratory developed tests (LDT) in order to be able to 'afford' performing PD-L1 testing, or to send out such tests, shifting the burden elsewhere, but possibly to the detriment of interactive patient care within the institution. The likely end result is that very few laboratories will be

offering the FDA-cleared assays, and most laboratories will be offering LDT assays, with no uniform validation process. The good news is that some preliminary studies show little difference in performance when comparing the FDA-cleared IHC assays to non-FDA cleared LDT assays, when comparing different antibodies under optimized conditions (12); indeed in some cases there is superiority of the non-FDA approved assays (unpublished data). However, the lack of cross validation of such assays may pose a severe and growing problem.

While the focus of the preceding section is upon US practice, similar problems exist in other countries commensurate with increased usage of targeted therapies. With regard to IHC-based guidelines, there are several excellent expert quality assurance and control organizations, such as the CAP IHC committee, NordiQC, CIHCQC, UKNEQAS and others, plus the newly formed ISIMM (International Society of Immunohistochemistry and Molecular Morphology - <http://isimm.org>) that are more than capable of facilitating the design of meaningful and unbiased methods, controls and guidelines.

This editorial serves as a plea for their active, indeed pro-active, involvement.

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