In cancer immunotherapy, one PD-L1 test to rule them all?

December 1 2016, by Garth Sundem

Clinical trials have proven the power of immunotherapies targeting PD-L1 or PD-1 in a range of cancers. However, these same trials show that only some patients benefit - tumors must depend on PD-L1 to be affected when medicines block its action. In response, the companies Merck, AstraZeneca, Genentech/Roche, and Bristol-Myers Squibb together with the diagnostic companies Ventana and Dako have developed four tests to predict which tumors do and do not express on PD-L1 and thus which tumors will respond to the therapies. An ambitious collaboration between these companies and research organizations including the International Association for the Study of Lung Cancer, the American Association for Cancer Research, and academic medical centers including the University of Colorado Cancer Center, results in a study published online today in the *Journal of Thoracic Oncology* comparing these four tests.

The study, called the "Blueprint PD-L1 IHC Assay Comparison Project," used all four tests to evaluate 38 samples of human non-small cell lung cancer. In all four tests, half of the tumors were positive for PD-L1 and 5 of the tumors were negative. However, in 14 of 38 cases (37 percent), some tests considered the sample positive while others considered it negative. The disagreement implies that the choice of test used to determine a tumor's PD-L1 dependence may influence whether or not a patient is offered anti-PD-L1 therapy.

"Immunotherapy is evolving very fast and with very encouraging results in lung cancer as well as other cancers. However, a main issue is how to

select patients for these therapies. Each company is pursuing their own predictive PD-L1 assay in order to select patients. However, the PD-L1 assays are all different in terms of antibody used and cut-off values for positive/negative results," says Fred R. Hirsch MD, PhD, investigator at the University of Colorado Cancer Center and CEO of the International Association for the Study of Lung Cancer.

With support from the U.S. Food and Drug Administration, Hirsch brought together the four pharmaceutical companies and the two diagnostic companies with leading PD-L1 assays to explore their agreements and discrepancies.

Importantly, each test is paired with a drug - the drug pembrolizumab, developed by Merck, is prescribed based on results from the assay called 22C3; the drug nivolumab, developed by Bristol-Myers Squibb, is paired with an assay called 28-8; likewise, atezolizumab by Genentech/Roche and durvalumab by AstraZeneca are both paired with assays specific to the compound. In fact, this mimics the way in which targeted therapies generally earn FDA approval - a drug and a test determining which patients will benefit from the drug tend to be approved in tandem.

However, all four of these drugs target a tumor's ability to hide from the immune system by the expression of PD-L1, which interacts with the protein PD-1 expressed on immune cells in a way that deactivates these immune cells against tumor tissue. However, by blocking the interaction between PD-L1 and PD-1 the immune cells (T-lymphocytes) remain activated against tumor tissue. In theory, any of these four tests should be able to predict the benefit of any of these four drugs. Critically, each measures how much PD-L1 protein is expressed on the membranes of tumor cells and, based on clinical trial data, how much PD-L1 must be expressed in order for the drug to show benefit.

"Rather than black and white, this can be a grey area. It is not that some

tumors express PD-L1 and others do not, but rather that tumors express PD-L1 across a gradient and at some cutoff point in that gradient, the expression becomes clinically relevant," Hirsch says.

Results show that three of the four tests tend to cluster together in their results. Also, differences in these tests meant that there was no absolute cutoff in the amount of PD-L1 that made a sample positive or negative - the different tests must be evaluated by their own scales.

Now with results in hand for the first phase of this study, the comparison will continue into a second phase by comparing these test results to patient outcomes. Basically, the goal is to determine which test allowed doctors to prescribe PD-L1 inhibitors to the patients who benefit, while avoiding the use of these drugs with patients who went on to see little or no benefit.

"This is a unique study based on a unique partnership meant to solve a very important clinical problem," Hirsch says. It might not be long before the field of anti-PD-L1 cancer immunotherapies receives a peer-reviewed recommendation for the one test that will rule them all.

More information: Fred R. Hirsch et al, PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phase 1 of the "Blueprint PD-L1 IHC Assay Comparison Project", *Journal of Thoracic Oncology* (2016). DOI: 10.1016/j.jtho.2016.11.2228

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