MedicalXpress

New assay selects patients with lung cancer for treatment with immune checkpoint inhibitors

February 13 2019

Immune checkpoint inhibitors, such as the anti-PD-1 antibody pembrolizumab, have become important tools for managing non-small-cell lung cancer (NSCLC). Assessing the level of programmed death ligand 1 (PD-L1) expressed by a tumor can help clinicians determine how the patient should be treated. A report in *The Journal of Molecular Diagnostics* describes a novel and rapid approach for quantifying PD-L1 expression levels in tumors that requires only small amounts of tissue that can be collected using minimally-invasive bronchoscopy techniques. This approach can also be used to discriminate malignant from benign tumors and identify mutational status, all of which can guide and refine therapeutic decisions.

"The emergence of lung cancer screening trials will result in greater demand to define the molecular nature of suspect lung nodules. This test has the potential to save considerable time and money in identifying patients who are most likely to benefit from checkpoint inhibitors such as pembrolizumab," explained Steven Bozinovski, Ph.D., of the School of Health and Biomedical Sciences, RMIT University, Bundoora, Victoria, Australia.

The paper describes a new streamlined approach for comprehensive molecular profiling of bronchial specimens suspected to be NSCLC. Upon collection of a bronchoscopy specimen using brush or biopsy radial probe endobronchial ultrasound (EBUS), a small amount of tissue

is placed directly in nucleic acid stabilization buffer following rapid onsite evaluation of the malignant site. RNA and DNA are isolated from the specimen and an assay is performed to quantify the expression of matrix metalloproteinase-9 (MMP-9) and its endogenous inhibitor (TIMP3). The test itself can be performed very quickly, therefore, diagnosis of malignancy and PD-L1 status can be determined within hours following collection. The test and scoring can be readily automated to eliminate tester variability.

"In this study we demonstrate for the first time that the ratio of MMP-9:TIMP3 can accurately differentiate malignant from non-malignant tissue specimens without the need to fix tissue for histological assessment," said Prof. Bozinovski. In one case, the MMP9:TIMP3 ratio was elevated more than 300 times while cytology was normal. Nine months later, repeat cytology confirmed that the tumor was indeed malignant.

The assay also quantifies PD-L1 transcript levels, which can have an important impact on the clinical management of NSCLC. Pembrolizumab has FDA approval for the frontline treatment of patients with advanced NSCLC whose tumors have 50 percent or greater PD-L1 expression as determined using the SP263 immunohistochemistry test. Patients with lower PD-L1 expression levels are more likely to benefit from a combination of pembrolizumab and chemotherapy. This study showed a strong positive association between transcript levels of PD-L1 as measured by the new assay and the FDA-approved SP263 immunohistochemistry.

According to the investigators, enough genomic DNA from the same specimen should be available to allow multi-panel targeted next-generation sequencing to assess the total mutational burden of the tumor. Importantly, this is possible because the tissue is unfixed, maintaining the integrity of DNA and RNA. In the current report, mutations were

detected in the majority of EBUS tumor specimens, including TP53 gene mutations found in 10 of 15 NSCLC samples. Such information may further refine patient selection for a particular treatment regimen.

The test offers additional advantages including rapid turnaround time and automated analysis. "We believe our test should significantly enhance the diagnostic utility of EBUS-guided bronchoscopy specimens for the molecular testing of lung cancer patients," noted Prof. Bozinovski.

More information: "A Novel Approach to Detect PD-L1 Status and Multiple Tumor Mutations Using a Single Non-Small-Cell Lung Cancer (NSCLC) Bronchoscopy Specimen," *Journal of Molecular Diagnostics* (2019). DOI: 10.1016/j.jmoldx.2018.10.001

Provided by Elsevier