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PD-L1 and PD-L2 mRNA are associated with outcome and high negative predictive value in immunotherapy-treated non-small cell lung cancer

Aileen I. Fernandez1, Niki Gavrielatou1, Leena McCann2, Saba Shafi1, Myrto K. Moutafi1, Sandra Martinez-Morilla4, Ioannis A. Vathiotis1,5, Thazin Nwe Aung1, Vesal Yaghoobi1,6, Yalai Bai1, Jodi Weidler1, Michael Bates1, and David L. Rimm1,9

1 Department of Pathology, Yale University School of Medicine, New Haven, CT, USA, 2 Oncology Research and Development, Cepheid, Sunnyvale, CA, USA, 3 Department of Pathology, The Ohio State University, Columbus, OH, USA, 4 Oncology Translational Science, Boehringer Ingelheim, Ridgefield, CT, USA, 5 Department of Medicine, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece, 6 Department of Pathology, Hartford Hospital, Hartford, CT, USA, 7 Medical and Scientific Affairs, Oncology, Cepheid, Sunnyvale, CA, USA, 8 Department of Internal Medicine (Medical Oncology), Yale University School of Medicine, New Haven, CT, USA

BACKGROUND

What are immune checkpoint inhibitors (ICI)? When a foreign tumor cell presents itself, it can talk with cells and instruct the human immune system to not kill the cancer, functioning as “brakes”. Immune checkpoint inhibitor therapies (ICI) function by releasing these natural brakes of the human immune system (Figure 1). By blocking this communication, ICIs allow the immune cell to perform its function and kill the foreign tumor cell.

Selecting who to treat with ICIs. Currently in clinic, we look at a tumor and decide who is going to receive ICIs by measuring the amount of a specific protein called programmed death ligand 1 (PD-L1). However, using this criteria for selection, only 1/5 patients with non-small cell lung cancer (NSCLC) who receive ICIs have a good response, as measured by improved survival. This means that only looking at the expression of PD-L1 is not sufficient for determining who to treat.

This proposed research aims to find an alternative way to identify which persons with NSCLC will respond, and not respond, to this kind of treatment.

METHODS Tissues from patients with NSCLC treated with ICIs from 2011 to 2020 were retrospectively collected. Tissues were pre-ICI treatment to allow to look at tissues that have not been altered by ICI treatment. The tumor-specific areas of these tissues were selected and analyzed using a research use only version of a clinical test. This is an inexpensive, simple diagnostic assay that is easy to operate. It measures mRNA levels. We looked at the mRNA of 4 target immune genes, CD274 (PD-L1), PDCD1LG2 (PD-L2), CD8A, and IRF1 (depicted in Figure 1) and a control gene. Gene expression levels were analyzed for associations with response.

MAIN FINDINGS

- PD-L1 protein is associated with survival (TPS >50) and is weakly correlated with PD-L1 mRNA
- Lower PD-L1 mRNA is associated with worse outcome (decreased overall survival and no benefit at 24 months; Figure 2 below) and a high negative predictive value (92% NPV, meaning a negative test has a 92% chance of being associated with no benefit).

Figure 2 Patients with no benefit at 24 months post-treatment had significantly lower PD-L1 mRNA. Using a calculated cutoff for "low" PD-L1 mRNA (gray dotted line on left graph), see high NPV. So, the patients whose tumors fall within the gray circle have a high likelihood of not responding.

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
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<tr>
<td>0.72</td>
<td>0.67</td>
<td>0.33</td>
<td>0.92</td>
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Figure 1 ICI function. PD-1 binds PD-L1, giving a signal to protect the cancer cell. ICIs block this interaction, leading to immune attack of tumor cells. Created with Biorender.com, based on Winslow, 2016

TAKEAWAY: This assay, because of its high NPV, has the potential to identify patients who are not likely to benefit from ICIs and could be spared the risk of immune-related adverse effects