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

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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.

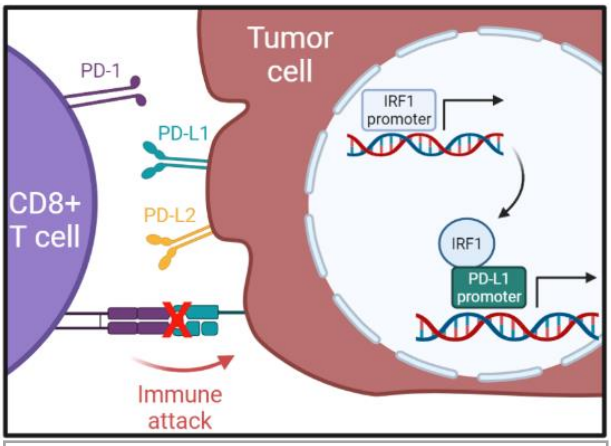


Figure 1 ICI function. PD-1 binds PD-L1, giving a signal to protect the cancer cell. ICIs block this interaction, leading to immune attack of tumor cells. Created with Biorender.com, based on Winslow, 2016

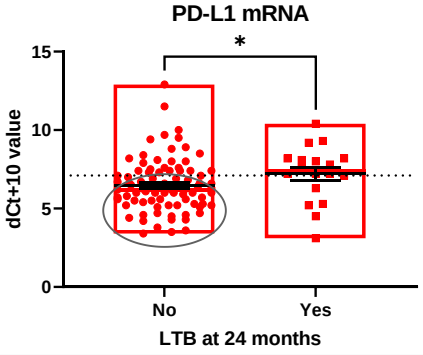
Selecting who to treat with ICIs. Currently in clinic, we look at a tumor and decide who is going to receive ICIs by measuring the amount of a specific protein called programmed cell death ligand 1 (PD-L1). However, using this criteria for selection, only 1/5 patients with non-small cell lung cancer (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).



	Optimal Cutpoint
Sensitivity	0.72
Specificity	0.67
PPV	0.33
NPV	0.92

Figure 2. Patients with no benefit at 24 months post- treatment had significantly lower PD-L1 mRNA. Using a calculated cutpoint 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.

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

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