A Variant of a Killer Cell Immunoglobulin-like Receptor Is Associated with Resistance to PD-1 Blockade in Lung Cancer


PURPOSE
PD-(L)1-blocking antibodies have clinical activity in metastatic non-small cell lung cancer (NSCLC) and mediate durable tumor remissions. However, the majority of patients are resistant to PD-(L)1 blockade. Understanding mechanisms of primary resistance may allow prediction of clinical response and identification of new targetable pathways.

EXPERIMENTAL DESIGN
Peripheral blood mononuclear cells were collected from 35 patients with NSCLC receiving nivolumab monotherapy. Cellular changes, cytokine levels, gene expression, and polymorphisms were compared between responders and nonresponders to treatment. Findings were confirmed in additional cohorts of patients with NSCLC receiving immune checkpoint blockade.

RESULTS
We identified a genetic variant of a killer cell immunoglobulin-like receptor (KIR) that is associated with primary resistance to PD-1 blockade in patients with NSCLC. This association could be confirmed in independent cohorts of patients with NSCLC. In a multivariate analysis of the pooled cohort of 135 patients, the progression-free survival was significantly associated with presence of the allele (HR, 1.72; 95% confidence interval, 1.10-2.68; \( p = 0.017 \)). No relationship was seen in cohorts of patients with NSCLC who did not receive immunotherapy. Cellular assays from patients before and during PD-1 blockade showed that resistance may be due to NK-cell dysfunction.

CONCLUSIONS
We identified an association of the allelic variant with response to PD-1-targeted immunotherapy in patients with NSCLC. This finding links NK cells with response to PD-1 therapy. Although the findings are interesting, a larger analysis in a randomized trial will be needed to confirm KIRs as predictive
markers for response to PD-1-targeted immunotherapy.

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