New drug combination shows promising activity in non-small cell lung cancer patients

27 August 2019

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Patients with non-small cell lung cancer (NSCLC) now have more improved treatment options compared to standard of care with the addition of several new agents called immune-checkpoint inhibitors (ICI). Despite these changes, many patients still develop progressive disease after ICI treatment. In a new study published in *Clinical Cancer Research*, Moffitt Cancer Center researchers describe promising results from an early clinical trial that may offer patients who progress after ICI an additional treatment option.

Several ICI agents have been approved in recent years to treat NSCLC, including nivolumab, atezolizumab and pembrolizumab. ICIs function by stimulating the immune system to target cancer cells for destruction. However, patients may become resistant to ICIs and develop progressive disease. Many of these patients who have poor responses to ICIs have low numbers of T cells in their tumor environment. Therefore, the cancer community has been trying to find drugs that work in conjunction with ICIs to increase the number and activity of T cells in a tumor.

Several preclinical studies, including studies conducted at Moffitt, have shown that drugs call histone deacetylase inhibitors (HDAC inhibitors) are capable of stimulating the immune system and enhancing the response to ICIs. "In our preclinical studies, we reported that HDAC inhibitors improve response to PD-1 blockade in mouse models of lung cancer by increasing T cell trafficking to tumors and enhancing T cell function," explained Amer Beg, Ph.D., senior member of the Department of Immunology at Moffitt.

Given the positive results of preclinical studies with ICIs and HDAC inhibitors, Moffitt researchers wanted to assess the potential benefit of these agents in patients with NSCLC. They conducted a phase 1/1b study of pembrolizumab plus the HDAC inhibitor vorinostat in 33 patients with advanced or metastatic NSCLC.

"To our knowledge, this represents the first publication of the clinical trial combination of ICI with an HDAC inhibitor in lung cancer. We found that this combination was well tolerated and demonstrated preliminary anti-tumor activity in patients who were refractory to prior ICI treatment," said Jhanelle Gray, M.D., assistant member of the Department of Thoracic Oncology at Moffitt.

The researchers report that the most common adverse events during treatment were fatigue (33%), nausea (27%) and vomiting (27%). Immune-activating drugs are often associated with adverse events related to increased immune system activity. The immune-related adverse events experienced by patients during the study were similar to those reported previously for pembrolizumab, with the most common event being hypothryroidism in 15%

of patients. The combination of pembrolizumab and vorinostat also demonstrated preliminary anti-tumor activity. Of 30 patients who were evaluable for efficacy, 4 had a partial response to treatment and 16 developed stable disease, for a disease control rate of 67%.

During the study, the researchers conducted a correlative analysis to determine if any blood or tissue biomarkers were associated with better patient outcomes to the combination treatment. They discovered that patients who had higher levels of T cells within the stromal environment before treatment had improved outcomes to therapy. According to the researchers, these observations suggest that vorinostat may sensitize tumors to ICIs by causing the T cells to migrate from the stroma to the tumor bed.

The researchers will further investigate this hypothesis and the activity of pembrolizumab and vorinostat in the ongoing phase 2 trial in patients with advanced/metastatic NSCLC who did not previously receive ICI treatment. "We believe our results lay the groundwork for future trials to assess impact of epigenetic agents on ICI response, and the discovery of biomarkers to assess the dynamic nature of the immune response early in patient's treatment course," said Beg.

More information: Jhanelle E. Gray et al, Phase 1/1b study of pembrolizumab plus vorinostat in advanced/metastatic non-small cell lung cancer, *Clinical Cancer Research* (2019). DOI: 10.1158/1078-0432.CCR-19-1305

Provided by H. Lee Moffitt Cancer Center & Research Institute

APA citation: New drug combination shows promising activity in non-small cell lung cancer patients (2019, August 27) retrieved 27 November 2022 from https://medicalxpress.com/news/2019-08-drug-combination-non-small-cell-lung.html

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