HDAC inhibition may combat resistance to anti-PD-1 therapy in patients with melanoma

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A combination of the experimental histone deacetylase (HDAC) inhibitor entinostat with the anti-PD-1 therapeutic pembrolizumab (Keytruda) showed clinical responses in patients with melanoma that had progressed on prior anti-PD-1 treatment, according to results from the ENCORE 601 phase Ib/II clinical trial presented at the AACR Annual Meeting 2019, March 29-April 3.

"While a large group of patients have derived benefit from treatment with checkpoint inhibitors, many still develop resistance to these therapies," said Ryan Sullivan, MD, assistant professor of hematology and oncology at Massachusetts General Hospital Cancer Center. "A number of studies, including this trial, are endeavoring to identify key immunotherapy combinations to overcome resistance to checkpoint blockade immunotherapy."

HDAC inhibitors can modulate the immune system by suppressing regulatory cells, such as myeloid-derived suppressor cells and regulatory T cells, and by increasing antigen expression on cancerous cells, two mechanisms that may counteract resistance to checkpoint inhibition, explained Sullivan. "Adding HDAC inhibition to anti-PD-1 treatment against tumors that have developed resistance to checkpoint blockade immunotherapy may lead to re-recognition of the tumor by the immune system and down-modulation of immune-suppressive elements in the tumor microenvironment, thereby increasing the efficacy of anti-PD-1 therapy," he added.

The purpose of the phase II ENCORE 601 trial was to assess the effectiveness of entinostat and pembrolizumab in patients with non-small cell lung cancer, melanoma, and mismatch repair-proficient colorectal cancer. This study reports on patients with unresectable or metastatic melanoma that progressed during or following treatment with anti-PD-1 immunotherapy.

In this single-arm trial, patients were treated with 5mg of entinostat once per week in conjunction with 200mg of pembrolizumab every three weeks until disease progression. The primary endpoint of the study was objective response rate (ORR) as measured by irRECIST.

Fifty-three patients were enrolled in the trial by data cutoff (January 2019). The median duration of prior anti-PD-1 treatment was 4.9 months; 66 percent of patients had no intervening therapy between prior anti-PD-1 treatment and study enrollment. Seventy percent of patients had prior treatment with ipilimumab (Yervoy), and 23 percent of patients had prior treatment with BRAF/MEK inhibitors.

Of the 53 evaluable patients, nine had a partial response and one had a complete response following the combinatorial treatment, resulting in an ORR of 19 percent. At the time of data cutoff, the median duration of response was 12.5 months; five patients had ongoing responses.

"Our results suggest that this combination may be an active regimen for patients who never responded to or progressed during treatment with PD-1 inhibitors," said Sullivan. "A key next step will be to identify a biomarker to better determine which patients will respond to this treatment."

Sullivan noted that prolonged delays and/or intervening therapy between prior anti-PD-1 treatment and trial enrollment may have influenced treatment response, representing a key limitation in the study.