AB049. P-17. A phase II study of HDAC inhibition to sensitize to immunotherapy in advanced cholangiocarcinoma

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Background: Immune checkpoint inhibitors (ICIs) have unlocked the promise of modulating the immune tumor microenvironment (TME) in the battle against cancer, but it remains unclear whether they might be useful for cholangiocarcinoma (CCA). Our laboratory has explored entinostat, a histone deacetylase inhibitor (HDACi) to alter the function of suppressive myeloid derived suppressor cells (MDSC) in favor of recruiting T cells in murine pancreatic ductal adenocarcinoma (PDAC) models, showing improved survival when given with anti-PD1 therapy. We hypothesize that the HDACi entinostat may prime an ICI-insensitive cancer into a more sensitive one.

Methods: An open-label, two-arm study enrolling patients with histologically confirmed advanced CCA or PDAC, who have progressed after at least one line of therapy. Eligibility criteria include measurable disease, PS ≤1, good end organ function and no history of autoimmune disease. Patients receive entinostat 5 mg oral once a week. After a fourteen-day lead in with entinostat monotherapy, patients receive entinostat 5 mg oral once a week plus nivolumab 240 mg every two weeks until progression or unacceptable toxicities. Patients undergo tumor biopsy and have research bloods drawn at baseline and after two weeks of entinostat lead-in therapy, and on week 6. An optional biopsy is performed at the time of progression. The study is planned with 27 subjects per histology based on a Simon's two-stage design that allows early termination for lack of efficacy. The primary objective of the trial is ORR, by RECIST 1.1. Secondary objectives include PFS, OS, safety and immunological correlates to evaluate the effect of HDAC inhibition on the TME by interrogating clinical specimens.

Results: The clinical study has been activated in November 2017. The accrual is still ongoing. Ten patients with a diagnosis of CCA and 22 with PDAC have been enrolled. Blood samples and tumor biopsies are being drawn, processed, and stored for accrued patients. The analysis will be performed in a single batched analysis at the conclusion of the study accrual.

Conclusions: This clinical trial is the first to test HDAC + immune checkpoint inhibition in pancreatobiliary cancers. If our project is successful, we have the potential to increase therapeutic options for CCA and PDAC patients (clinical trial information: NCT03250273).

Keywords: Epigenetic therapy; histone deacetylase inhibition (HDAC inhibition); immunotherapy; metastatic disease

Cite this abstract as: Baretti M, Walker R, Durham J, Christmas B, Cope L, Jaffee EM, Azad NS. A phase II study of HDAC inhibition to sensitize to immunotherapy in advanced cholangiocarcinoma. HepatoBiliary Surg Nutr 2019;8(Suppl 1):AB049. doi: 10.21037/hbsn.2019.AB049

