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Efficacy of mTOR Inhibition in Pulmonary Large Cell Neuroendocrine Carcinomas (LCNEC)

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BACKGROUND: Inhibition of mTOR signaling was recently reported to significantly improve the median progression-free survival in patients with progressive well-differentiated pulmonary neuroendocrine tumors. To date, there is a lack of clinical evidence that mTOR kinase inhibitors (mTORKi) would have efficacy in poorly differentiated pulmonary large cell neuroendocrine carcinomas (LCNEC)s. Given the rapid proliferation rate of these tumors, we hypothesized that complete mTOR inhibition will lead to a significant decrease in LCNEC growth compared to placebo while being less toxic than chemotherapeutic regimens, such as cisplatin containing ones.

METHODS: NSG mice bearing subcutaneously implanted non-small cell lung carcinoma cells (NCI-H1155 from ATCC) or tumor pieces from an LCNEC patient-derived xenograft (PDX) obtained from Jackson Laboratories were treated with either placebo or the mTORKi, MLN0128. Cisplatin was included as a treatment arm in the LCNEC PDX experiment to compare MLN0128 efficacy to a standard-of-care drug.

RESULTS: MLN0128 treatment significantly inhibited downstream targets of mTOR and decreased tumor volume compared to placebo-treated tumors. Moreover, in the LCNEC PDX model, both MLN0128 and cisplatin significantly decreased tumor size compared to placebo, with no significant difference between the drug treatments themselves. The average body weight (BW) of cisplatin-treated mice however, was significantly less than placebo mice, suggestive of drug toxicity. In contrast, the slight decrease in average BW of MLN0128-treated mice was not statistically different from that of placebo-treated mice.

CONCLUSION: In these preclinical studies, inhibition of mTOR significantly decreased tumor progression of pulmonary LCNECs and was better tolerated than cisplatin at the doses employed. We are currently testing longer treatment time points for the efficacy of mTORKi in LCNECs and whether mTORKi would be more beneficial in combination with chemotherapy or following it as a maintenance therapy.