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Pembrolizumab-Based Therapy in Previously Treated High Grade Extrapulmonary Neuroendocrine Carcinomas

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BACKGROUND: The efficacy of immune checkpoint inhibitors (CPI) has not been established in extrapulmonary high-grade neuroendocrine carcinomas (EP-HGNECs), a disease for which additional treatments are needed. Pembrolizumab (PEM) has safety and preliminary efficacy in small cell lung cancer. This phase 2 study evaluates the efficacy and safety of PEM-based therapy in biomarker-unselected EP-HGNECs.

METHODS: Open-label, adaptive Simon's 2-stage study of PEM alone (Part A) and PEM plus chemotherapy (weekly irinotecan (IRI) or paclitaxel; dealers' choice) (Part B). If more than 2 out of 14 patients respond by week 18 (Stage 1 Part A), then 21 additional patients will enroll in stage 2 (Part A), corresponding to H0 10% vs. H1 26% at type I error 0.05 with power 80%. Otherwise, the study will proceed to Part B, with a safety lead-in of 6-12 patients for IRI/PEM (up to two dose levels, 1 and -1), adding 16 additional patients for a total of 22 patients treated with PEM plus chemotherapy based on one-side binomial test of H0 10% vs. H1 31% at type I error 0.05 with power 80%. Total N will be 35 (Part A) or 36-42 (Part A then B).

RESULTS: Key eligibility: poorly differentiated EP-HGNEC of all sites (excluding Merkel cell carcinoma) with progression during or after first-line systemic therapy, no prior CPI, bilirubin and creatinine ≤1.5x ULN, ECOG PS 0-1. Treatment: PEM 200 mg IV Q21 days for up to 35 treatments. Primary endpoint: Overall radiographic response rate by RECIST1.1. Secondary endpoint: Safety, response duration, overall survival, progression-free survival. Exploratory endpoints: irRECIST vs RECIST1.1, baseline PBMC and tumor immune cell profiles, T cell receptor repertoire change, tumor mutation profile, Ki67 index, PD-L1 expression. Current enrollment: 12 of planned 14 patients in Stage 1 Part A (6/2017-present). Clinical trial information: NCT03136055