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Phase 2 study of nab-sirolimus in patients with well-differentiated and advanced/metastatic neuroendocrine tumors of the gastrointestinal tract, lung, or pancreas

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BACKGROUND

Neuroendocrine tumors (NETs; ~2% of all malignancies) commonly arise from the GI tract, pancreas, and lung and often present with metastatic disease. The PI3K/Akt/mTOR pathway is implicated in the pathogenesis and progression of NETs. The oral mTOR inhibitor (mTORi), everolimus, is approved for treatment of patients with NETs of the GI tract, lung, or pancreas. However, due to the rarity and heterogeneity, nonspecific clinical symptoms, and unique indolent biology, management of NETs remains challenging. Nanoparticle albumin-bound (*nab*)-sirolimus is a novel mTORi that utilizes nanoparticle technology to preferentially target tumors. *nab*-Sirolimus is approved in the US for adult patients with malignant PEComa. In preclinical animal models, *nab*-sirolimus demonstrated higher intratumoral drug accumulation and improved target suppression relative to similar weekly doses of sirolimus and everolimus, warranting further exploration of *nab*-sirolimus (Hou et al, *Mol Cancer Ther*, 2021). This study will evaluate efficacy and safety of *nab*-sirolimus in patients with advanced/metastatic NETs.

METHODS

This is a phase 2, multicenter, open-label, single-arm study that will enroll up to 21 efficacy-evaluable patients. The study will enroll adults (≥18 years) with functional or non-functional, well-differentiated, locally advanced unresectable or metastatic NETs of the GI tract, lung, or pancreas who have received ≤2 prior lines of therapy excluding somatostatin analogs. Patients with functional NETS are eligible for enrollment if they have been on a stable dose of somatostatin analog for ≥12 weeks and experienced disease progression during treatment. Eligible patients must have ≥1 measurable target lesion (RECIST v1.1), an ECOG performance score of 0 or 1, and adequate organ function/hematologic parameters. Patients are not permitted to have previously received an mTORi, including *nab*-sirolimus, or to have tumors with known inactivating *TSC1/TSC2* alterations. Patients will receive *nab*-sirolimus 100 mg/m^2 by intravenous infusion on Days 1 and 8 of every 21-day cycle. Treatment will continue until the patient experiences disease progression or unacceptable toxicity, or until discontinuation based on the discretion of the investigator or the patient. The primary endpoint is investigator-assessed objective response rate (ORR) based on RECIST v1.1. Secondary endpoints include duration of response, disease control rate, time to response, progression-free survival, and overall survival; safety and tolerability will be assessed throughout the study.

Exploratory endpoints include correlation of baseline molecular biomarkers with clinical outcomes. Analysis of study objectives will be descriptive and hypothesis generating.

RESULTS

Enrollment is expected to commence in the third quarter of 2023.

CONCLUSIONS

Trial in progress.

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