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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

Scott Paulson, MD[1], Allen L. Cohn, MD[2], Alexandria T. Phan, MD, FACP[3], Li Ding, MS, MA[4], Willis H. Navarro, MD[4], Michael J. Demeure, MD[5].

[1]Texas Oncology, Baylor Charles A. Sammons Cancer Center, Dallas, TX; [2]Rocky Mountain Cancer Center, Denver, CO; [3]Medical College of Wisconsin, Milwaukee, WI; [4]Aadi Bioscience, Inc., Pacific Palisades, CA; [5]Hoag Memorial Hospital Presbyterian, Newport Beach, CA and Translational Genomics Research Institute, Phoenix, AZ.

BACKGROUND

Neuroendocrine tumors (NETs; ~2% of all malignancies) commonly arise from the gastrointestinal (GI) tract, pancreas, and lung, often presenting as metastatic disease. The PI3K/Akt/mTOR pathway is implicated in the pathogenesis and progression of NETs. Everolimus, an oral mTOR inhibitor (mTORi), is an option for treatment of NETs of the GI tract, lung, or pancreas, but response rates observed in the RADIANT-3 and -4 studies were modest at 4–10%. *nab*-Sirolimus, an intravenous nanoparticle albumin-bound mTOR inhibitor (mTORi), is approved in the US for adults with advanced malignant perivascular epithelioid cell tumors based on a 39% response rate. Preclinical data demonstrated improved tumor accumulation, mTOR target inhibition, and tumor growth suppression of nab-sirolimus versus other mTORis. This study will evaluate efficacy and safety of *nab*-sirolimus in patients with advanced or metastatic NETs.

METHODS

This phase 2, multicenter, open-label, single-arm clinical study (NCT05997056) will enroll ~21 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 systemic therapy other than somatostatin analogs (SSTa). Patients with functional NETS are eligible if they have been on a stable dose of SSTa for ≥12 weeks and had disease progression during SSTa treatment. Eligible patients must have ≥1 measurable target lesion (per Response Evaluation Criteria in Solid Tumors [RECIST] v1.1), Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate organ function/hematologic parameters. Patients who have received a prior mTORi, including *nab*-sirolimus, or have tumors with known inactivating *TSC1* or *TSC2* alterations will be excluded. Patients will receive *nab*-sirolimus 100 mg/m2 by intravenous infusion on days 1 and 8 of a 21-day cycle (Simon's 2-stage design). Treatment will continue until disease progression, unacceptable toxicity, or discontinuation based on investigator or patient discretion. The primary endpoint is investigator-assessed overall response rate per RECIST v1.1. Secondary endpoints include duration of response, disease control rate, time to response, progression-free survival, overall survival, and safety. Exploratory endpoints include correlation of baseline molecular biomarkers with clinical outcomes. Stage 1 enrollment will enroll 12 patients. If ≥1 response is achieved in Stage 1, the trial will continue with Stage 2 of enrollment.

RESULTS

To date, 9 patients have been enrolled in Stage 1 and ≥1 response has been achieved..

CONCLUSIONS

Stage 1 of enrollment is currently open. The criterion has been met for continuing to Stage 2 of enrollment.

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