# T-4

## Phase 2, Multicenter, Open-label Basket Trial of nab-Sirolimus for Malignant Solid Tumors Harboring Pathogenic Inactivating Alterations in TSC1/2 (PRECISION I)

*Gopa Iyer, MD[1], Michael J. Demeure, MD[2], Li Ding, MS, MA[3], Anita N. Schmid, PhD[3], Willis Navarro, MD[3], David J. Kwiatkowski, MD, PhD[4], Jordi Rodon Ahnert, MD, PhD[5].*

*[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Hoag Memorial Hospital Presbyterian, Newport Beach, CA; [3]Aadi Biosciences, Inc., Pacific Palisades, CA; [4]Brigham and Women's Hospital, Boston, MA; [5]MD Anderson Cancer Center, Houston, TX.*

### BACKGROUND

*nab*-Sirolimus, approved in the US for patients with advanced malignant PEComa, is a novel albumin-bound mTOR inhibitor (mTORi) that inhibits the mTOR pathway via suppression of the mTORC1 complex. When *TSC1* or *TSC2* is inactivated via mutation or loss, the mTOR pathway may be aberrantly activated. *TSC1* and *TSC2* alterations occur in a range of common cancers. Clinically, in the AMPECT exploratory analysis of *nab*-sirolimus in advanced malignant PEComa (NCT02494570), 8/9 (89%) and 1/5 (20%) patients with inactivating alterations in *TSC2* and *TSC1*, respectively, had confirmed response. Most treatment-related adverse events in AMPECT were grade 1/2 (none grade ≥4), consistent with mTORi-class adverse events (Wagner, *J Clin Oncol*, 2021). Based on clinical observations from AMPECT and the underlying mechanism of action of *nab*-sirolimus, PRECISION I (NCT05103358) was designed to assess nab-sirolimus safety and efficacy in a tumor-agnostic study of advanced cancers with *TSC1* and *TSC2* inactivating alterations.

### METHODS

Eligible patients are ≥12yo and mTORi-naïve, possess advanced malignant solid tumors with *TSC1* and *TSC2* inactivating alterations identified using next-generation sequencing (NGS) in tumor tissue or liquid biopsy (confirmed by central review of NGS reports), and have received appropriate standard treatments, per investigator.

*nab*-Sirolimus 100 mg/m2 will be given intravenously over 30 min on D1 and D8 of each 21-day cycle. Primary endpoint: overall response rate per independent radiographic review (IRR) using RECIST v1.1. Other endpoints include duration of response, time to response, progression-free survival by IRR, overall survival, patient-reported QOL, and safety.

Enrollment began March 2022. Collaboration with leading NGS providers will expedite the identification of patients with qualifying *TSC1* and *TSC2* mutations; ongoing study access is facilitated through a just-in-time approach to trial site activation. Based on the prevalence of *TSC1* and *TSC2* inactivating alterations, the most frequent tumor types expected are given in bold in the Table.

*Table. Estimated frequency of definite impact TSC1/TSC2 alterations*

| Tumor Type | *TSC1* Alterations[a] | *TSC2* Alterations[a] | *TSC1*/*TSC2* Combined |
|---|---|---|---|
| **Bladder** | 6.33 | 1.70 | 8.03 |
| **Hepatobiliary** | 1.27 | 3.31 | 4.58 |
| **Endometrial** | 2.10 | 1.22 | 3.32 |
| **Soft tissue sarcoma** | 1.28 | 1.71 | 2.99 |
| **Ovarian** | 1.85 | 0.92 | 2.77 |
| **Esophagogastric** | 0.65 | 1.46 | 2.11 |
| Non-small cell lung cancer | 0.77 | 1.16 | 1.93 |
| Colorectal carcinoma | 0.99 | 0.39 | 1.38 |
| Breast | 0.41 | 0.10 | 0.51 |

Data are %. [a]Proportion of patients with definite impact alterations (ie, alterations known to have a biological impact, including frameshift, nonsense, and splice-site mutations and deep deletions) derived from analysis of TCGA and cBioPortal by Gulati et al. Data on file.

## RESULTS

N/A

## CONCLUSIONS

Trial in progress

## ABSTRACT ID 23649