PRECISION 1: A phase 2, multicenter, open-label tumor-agnostic trial of *nab*-sirolimus for malignant solid tumors harboring pathogenic inactivating alterations in *TSC1* and *TSC2*

TPS526

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Objective

- **This trial is designed to evaluate the efficacy, safety, and tolerability of *nab*-sirolimus in a patient population with advanced malignancies and limited therapeutic options**

KEY POINTS

- ***nab*-Sirolimus is an mTOR inhibitor (mTORi) approved in the US for the treatment of adult patients with advanced malignant PEComa**
- **Data from the AMPECT exploratory analysis and an expanded access program suggest *nab*-sirolimus may provide clinically relevant benefit with a manageable safety profile in patients with solid tumors harboring inactivating alterations in *TSC1* and/or *TSC2***
- ***TSC1* and/or *TSC2* inactivating alterations have been observed in patients with GU cancers with a frequency of up to 9.8% in bladder, 5.9% in kidney, and 0.7% in prostate cancers; however, there are no specific treatment options for patients with these alterations**
- **PRECISION 1 (NCT05103358) is a registrational, tumor-agnostic trial for patients with solid tumors driven by *TSC1* or *TSC2* inactivating alterations; the trial is currently enrolling patients with solid tumors with *TSC1* or *TSC2* inactivating alterations**

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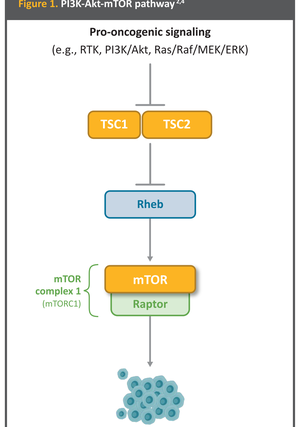
INTRODUCTION

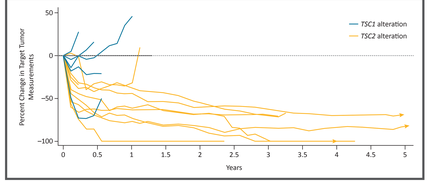
- Genitourinary (GU) cancers have a poor prognosis as indicated by low 5-year survival rates in patients with advanced bladder (8.3%), kidney (17.8%), and prostate (34.1%) cancers[1]
- Overactivation of the PI3K-Akt-mTOR pathway has been implicated in a number of cancers including GU cancers[2], and can result from inactivation of the tumor suppressor genes *TSC1* and *TSC2*[3] (**Figure 1**)

Figure 1. PI3K-Akt-mTOR pathway[2,4]



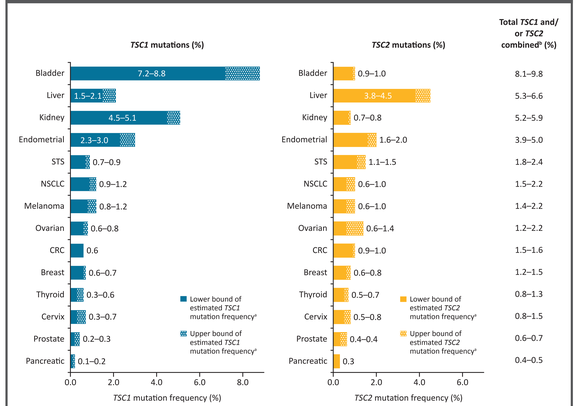
- *nab*-Sirolimus, a nanoparticle albumin-bound, IV-administered mTOR inhibitor, is approved in the United States for the treatment of adult patients with advanced, malignant perivascular epithelioid cell tumors (PEComa)[4] a group of rare aggressive tumors that can originate in GU tissues[5,6]
- In the open-label, phase 2 AMPECT trial (NCT02494570), patients treated with *nab*-sirolimus for malignant PEComa showed a clinically meaningful overall response rate, median duration of response of more than 3 years, and durable disease control and survival[7]
- Results from the AMPECT exploratory biomarker analysis demonstrated rapid and durable responses in patients with *TSC1* or *TSC2* inactivating alterations and suggested significant clinical benefit (**Figure 2**)[8]

Figure 2. Exploratory biomarker analysis from AMPECT demonstrated rapid and durable responses in the subset of patients with known *TSC1* or *TSC2* inactivating alterations treated with *nab*-sirolimus (n=14)



- The safety profile in the overall study population was consistent with the mTORi class with no new or unexpected safety signals[4]
  - The most common any grade, nonhematologic treatment-related adverse events (TRAEs) were stomatitis (28/34, [82%]), fatigue (21/34 [62%]), and rash (21/34 [62%]); and the most common, any-grade hematologic TRAEs were anemia (18/34 [53%]) and thrombocytopenia (12/34 [35%])
  - Most TRAEs were grade 1/2 and were manageable for long-term treatment; no grade ≥4 TRAEs were observed
- Patients with various malignancies bearing *TSC1* or *TSC2* inactivating alterations treated with *nab*-sirolimus as part of the expanded access program (NCT03817515) showed evidence of response (partial response in 5/7 patients) and manageable toxicities[9]
- Inactivating alterations in *TSC1* and/or *TSC2* have been observed in GU cancers with a combined frequency of up to 9.8% of patients with bladder cancer, 5.9% of patients with kidney cancer, and 0.7% of patients with prostate cancer (**Figure 3**); however, no treatment options exist specifically for patients with these alterations
- The phase 2 PRECISION 1 trial was initiated to evaluate the potential of mTOR inhibition with *nab*-sirolimus for the treatment of patients with solid tumors harboring inactivating alterations in *TSC1* or *TSC2*

Figure 3. Estimated frequency of pathogenic and/or inactivating alterations in *TSC1* or *TSC2* by tumor type

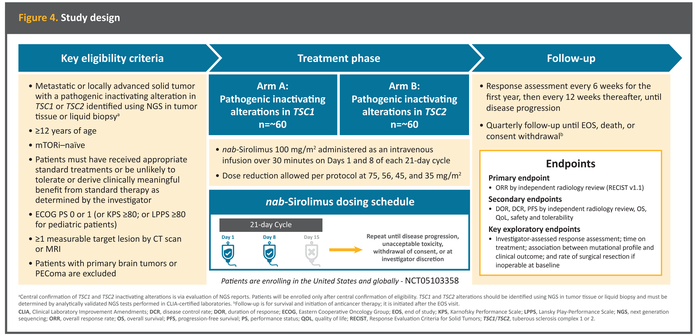


[a]Real-world frequencies were derived from tissue-based NGS results for nonhematologic malignancies included in the Foundation Medicine FoundationInsights℠ web platform (n=438,974) and data provided by Tempus Labs (n=128,914) with analysis restricted to known or likely oncogenic *TSC1* or *TSC2* inactivating alterations. Upper and lower bounds of frequency ranges were defined as the frequencies calculated from each dataset. [b]The range is reported as the sum of the highest and lowest values for each gene reported in either dataset. **CRC**, colorectal cancer; **NSCLC**, non–small cell lung cancer; **STS**, soft tissue sarcoma; ***TSC1*/*TSC2***, tuberous sclerosis complex 1/2. Data on file. Aadi Bioscience [May 2023].

STUDY DESIGN

- PRECISION 1 (NCT05103358) is a prospective, phase 2, open-label, multi-institution tumor-agnostic trial evaluating *nab*-sirolimus in patients with malignant solid tumors with pathogenic inactivating alterations in *TSC1* (Arm A) or *TSC2* (Arm B) (**Figure 4**)

Figure 4. Study design



[a]Central confirmation of *TSC1* and *TSC2* inactivating alterations is via evaluation of NGS reports. Patients will be enrolled only after central confirmation of eligibility. *TSC1* and *TSC2* alterations should be identified using NGS in tumor tissue or liquid biopsy and must be determined by analytically validated NGS tests performed in CLIA-certified laboratories. [b]Follow-up is for survival and initiation of anticancer therapy; it is initiated after the EOS visit.
CLIA, Clinical Laboratory Improvement Amendments; **DCR**, disease control rate; **DOR**, duration of response; **ECOG**, Eastern Cooperative Oncology Group; **EOS**, end of study; **KPS**, Karnofsky Performance Scale; **LPPS**, Lansky Play-Performance Scale; **NGS**, next generation sequencing; **ORR**, overall response rate; **OS**, overall survival; **PFS**, progression-free survival; **PS**, performance status; **QOL**, quality of life; **RECIST**, Response Evaluation Criteria for Solid Tumors; ***TSC1*/*TSC2***, tuberous sclerosis complex 1 or 2.

- Partnerships with leading next-generation sequencing companies (Foundation Medicine, Tempus, and Caris) and US Oncology will facilitate identification of patients with qualifying inactivating alterations in *TSC1* or *TSC2* and expand access to the study through just-in-time trial locations and accelerated site activation (**Figure 5**)

Figure 5. Expanding PRECISION 1 access and enrollment through strategic partnerships

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