Phase 2, Multicenter, Open-Label Basket Trial of *nab*-Sirolimus for Malignant Solid Tumors Harboring Pathogenic Inactivating Alterations in *TSC1* and *TSC2* (PRECISION 1)

#TPS3168

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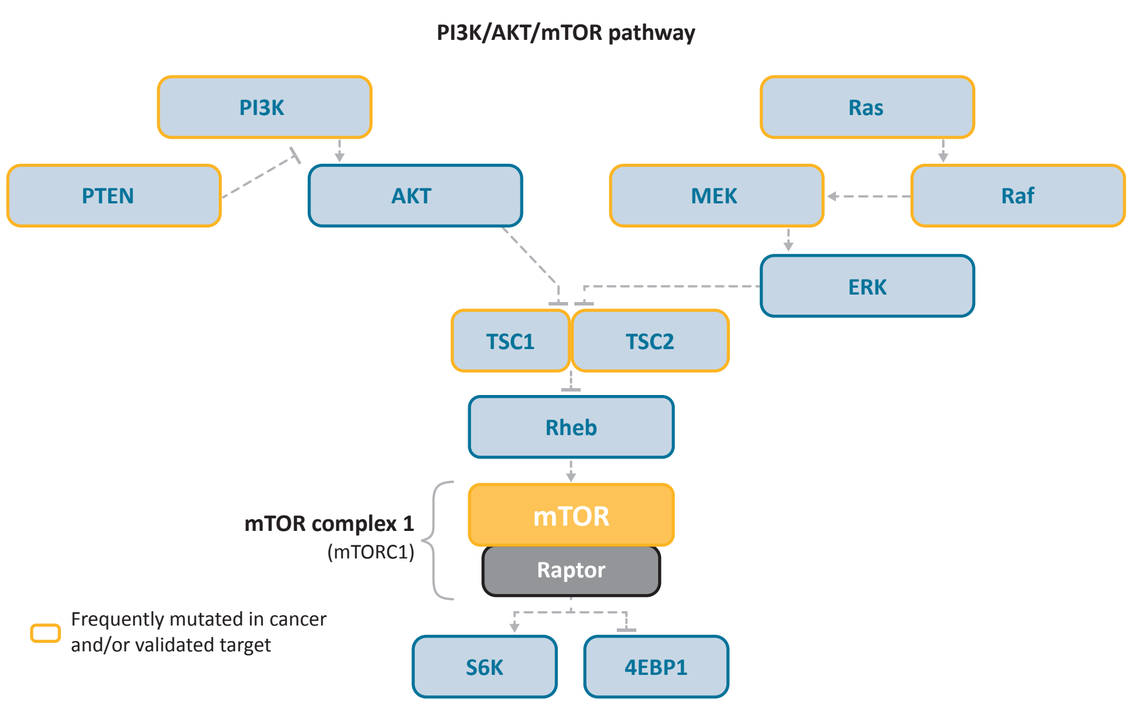
KEY POINTS

- *nab*-Sirolimus is an mTORi utilizing *nab* technology to enhance antitumor activity as shown in non-clinical animal models
- Data from the AMPECT exploratory analysis and an expanded access program suggest *nab*-sirolimus will provide clinically relevant benefit with a manageable safety profile in patients with solid tumors harboring inactivating alterations in *TSC1* and/or *TSC2*
- PRECISION 1 is a registrational basket trial for patients with solid tumors driven by *TSC1* or *TSC2* alterations; enrollment began in March 2022
- 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
- Collaboration with leading next-generation sequencing vendors will expedite the identification of patients with qualifying *TSC1* or *TSC2* alterations; study access will be facilitated through a "just-in-time" approach to trial location activation

INTRODUCTION

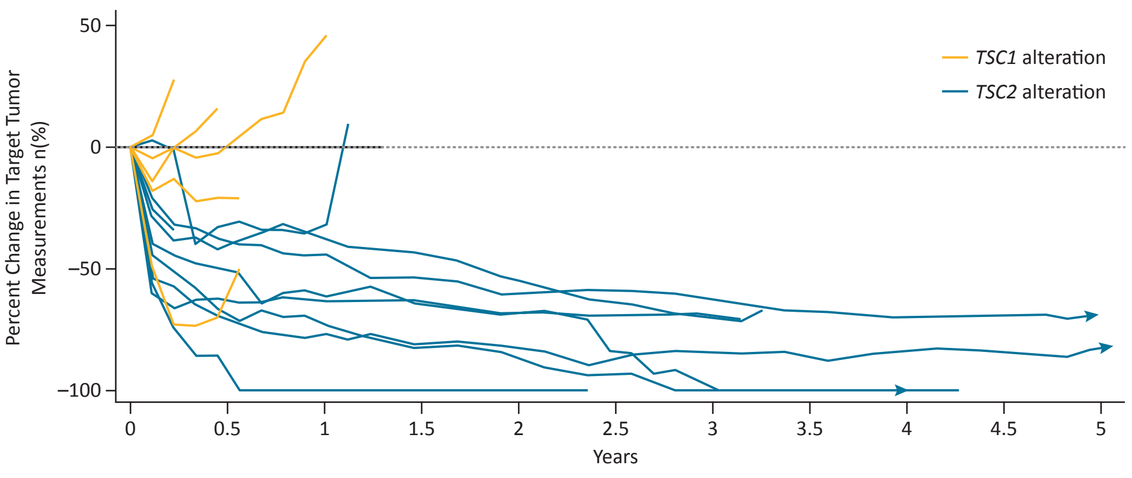
- *TSC1* and *TSC2* form a protein complex and together are critical negative regulators of mTOR complex 1 activation[1] (**Figure 1**)

Figure 1. PI3K-AKT-mTOR Pathway[2,3]



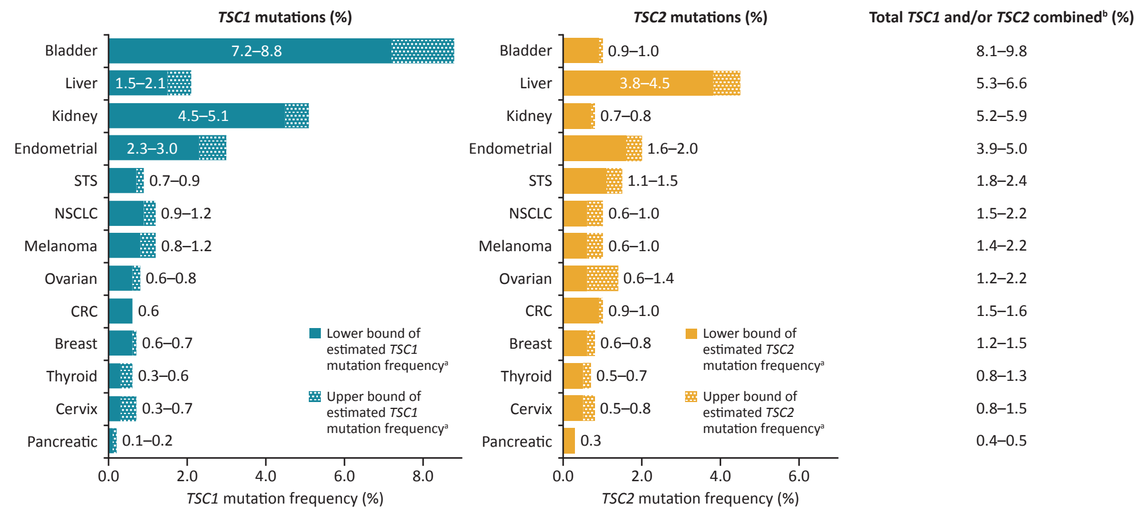
- The utility of oral mTOR inhibitors (mTORis), such as sirolimus, as pan-cancer agents may be restricted by low bioavailability and dose-limiting toxicity[2,4]
- To improve the pharmacologic properties of sirolimus, *nab*-sirolimus, a nanoparticle form of human albumin-bound sirolimus, was developed for intravenous use
- In preclinical animal models, *nab*-sirolimus demonstrated significantly higher intratumor drug concentrations, greater tumor growth inhibition, improved survival, and greater inhibition of the downstream marker of mTOR activity, phosphorylated-S6 ribosomal protein, relative to equal weekly doses of sirolimus and everolimus[3]
- *nab*-Sirolimus is a novel albumin-bound mTORi and is approved in the United States for the treatment of adult patients with locally advanced, unresectable or metastatic malignant perivascular epithelioid cell tumor (PEComa)[5] based on clinical efficacy and safety results from the AMPECT trial (NCT02494570)[6]
- 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**)[6,7]
  - The most common nonhematologic treatment-related adverse events (TRAEs) were stomatitis (28/34 [82%]), fatigue and rash (21/34 [62%] each), and the most common hematologic TRAEs were anemia (18/34 [53%]) and thrombocytopenia (12/34 [35%])
  - Most treatment-emergent adverse events (TEAEs) were grade 1/2 and were manageable for long-term treatment; no grade ≥4 TRAEs were observed
  - The overall safety profile was consistent with other mTORis with no new or unexpected safety signals

Figure 2. Exploratory Biomarker Analysis From AMPECT Demonstrated Rapid and Durable Responses in Patients With *TSC1* or *TSC2* Inactivating Alterations Treated with *nab*-Sirolimus (n=14)



- 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[8]
- Inactivating alterations in *TSC1* and/or *TSC2* have been observed in several types of cancer, but no treatment options exist specifically for patients with these alterations (**Figure 3**)

Figure 3. Estimated Frequency of Pathogenic and/or Inactivating *TSC1* or *TSC2* Alterations by Tumor Type



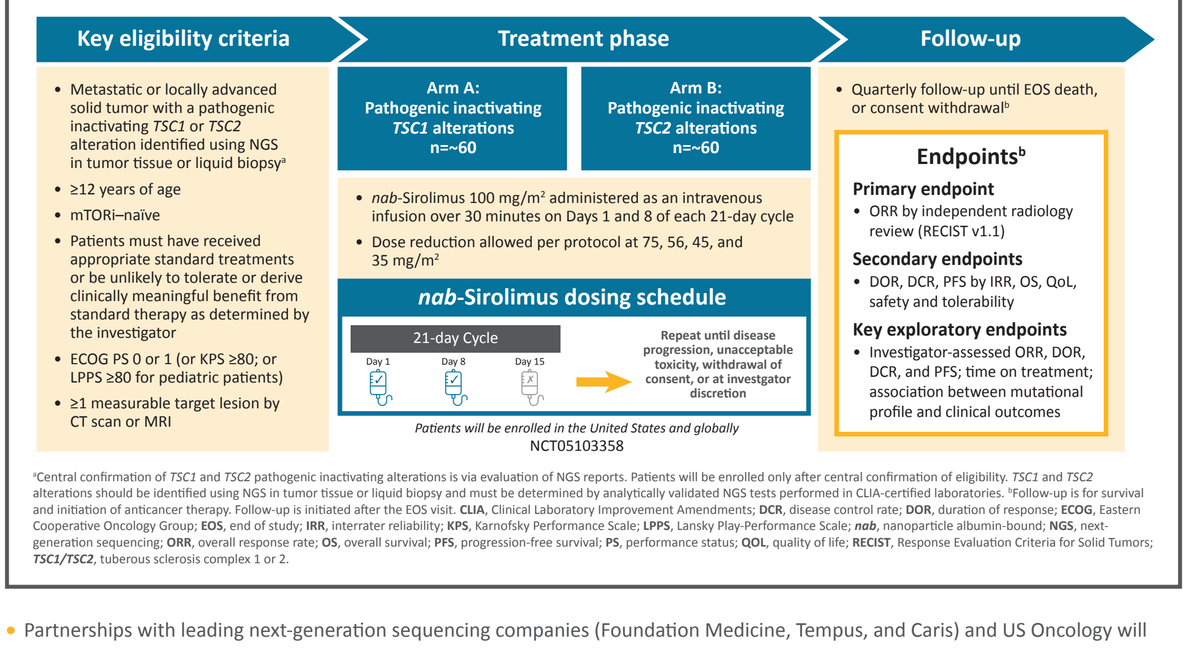
[a]Real-world frequencies were derived from tissue-based NGS results for nonhematologic malignancies included in the Foundation Medicine FoundationInsights™ web platform (n=438,974) and data provided by Tempus Labs (n=128,914) with analysis restricted to known or likely oncogenic *TSC1* or *TSC2* inactivating 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].

- 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 *TSC1* or *TSC2* inactivating alterations

STUDY DESIGN

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

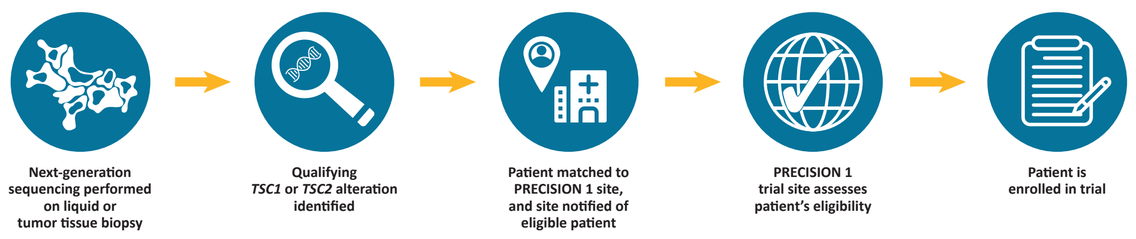
Figure 4. Study Design



[a]Central confirmation of *TSC1* and *TSC2* pathogenic 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. Follow-up 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; **IRR**, interrater reliability; **KPS**, Karnofsky Performance Scale; **LPPS**, Lansky Play-Performance Scale; ***nab***, nanoparticle albumin-bound; **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 *TSC1* or *TSC2* alterations 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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