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

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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 GI cancers with a frequency of up to 6.6% in liver cancer, 1.6% in colorectal adenocarcinoma, and 0.5% in pancreatic cancer; 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

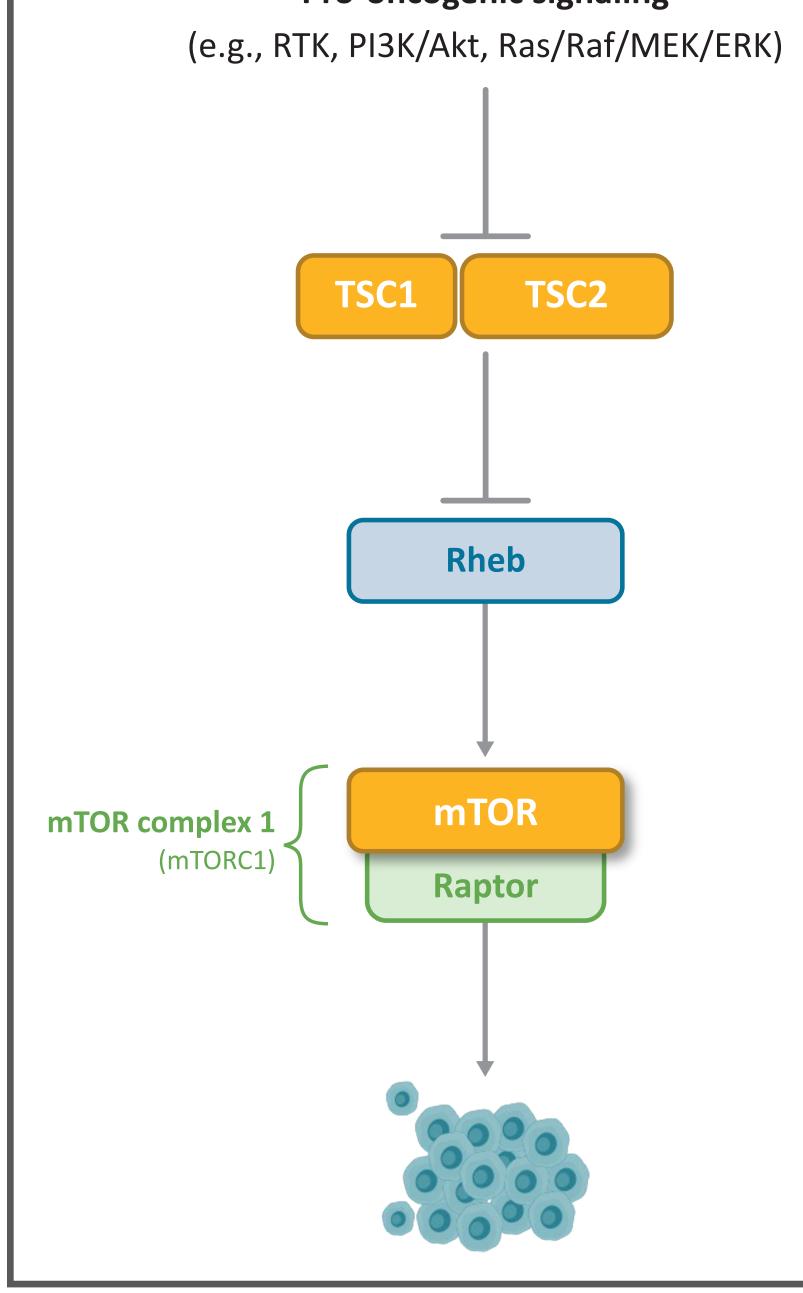
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INTRODUCTION

- Gastrointestinal (GI) cancers have a poor prognosis as indicated by low 5-year survival rates in patients with advanced colorectal (15.6%) and liver (3.5%) cancers¹
- Overactivation of the PI3K-Akt-mTOR pathway, has been implicated in a number of cancers, including GI cancers², and can result from inactivation of the tumor suppressor genes TSC1 and TSC2³ (Figure 1)





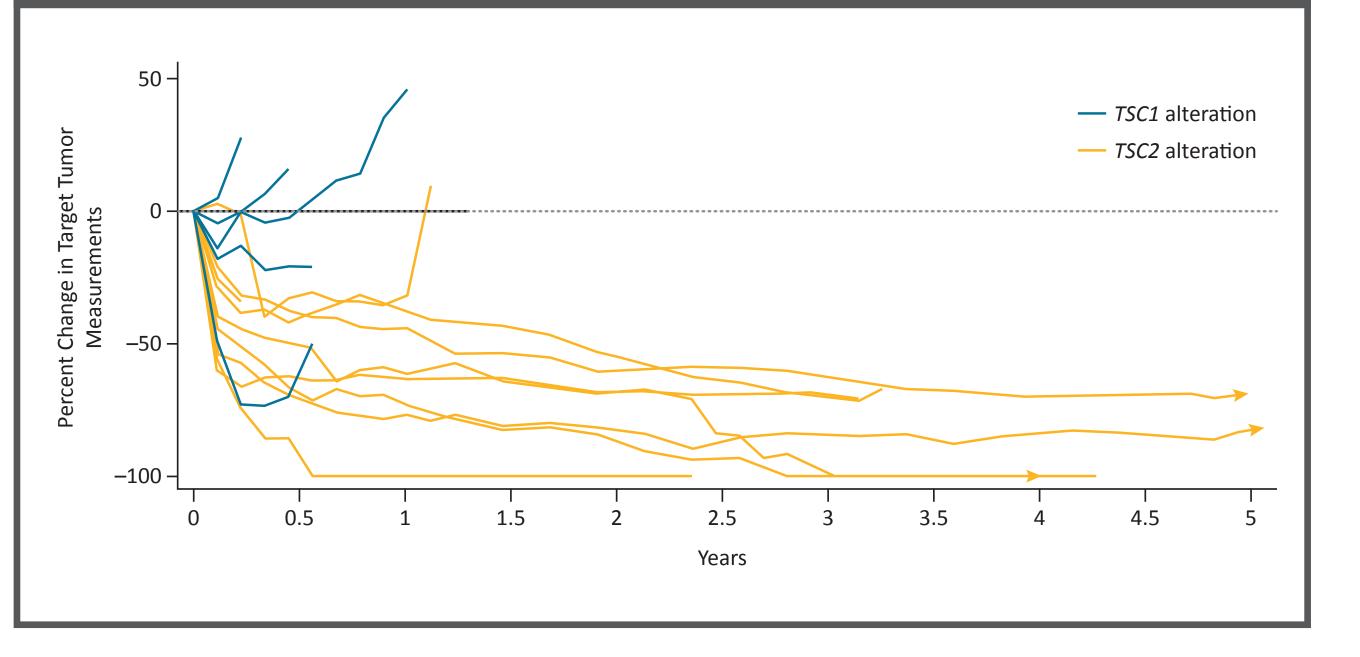
Acknowledgments & Disclosures

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- Pro-oncogenic signaling
 - TSC2

- *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 tumor (PEComa)⁴ a group of rare aggressive tumors that can originate in GI tissues^{5,6}
- In the open-label, phase 2 AMPECT trial (NCT02494570), patients treated with nab-sirolimus for malignant PEComa showed clinically meaningful overall response rate, median duration of response of more than 3 years, and durable disease control and survival
- 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

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 signals⁸
- 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

- Bladder Kidney NSCLC Melanoma

^aReal-world frequencies were derived from tissue-based NGS results for nonhematologic malignancies included in the Foundation Medicine Foundation Insights[™] 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. ^bThe 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].

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References

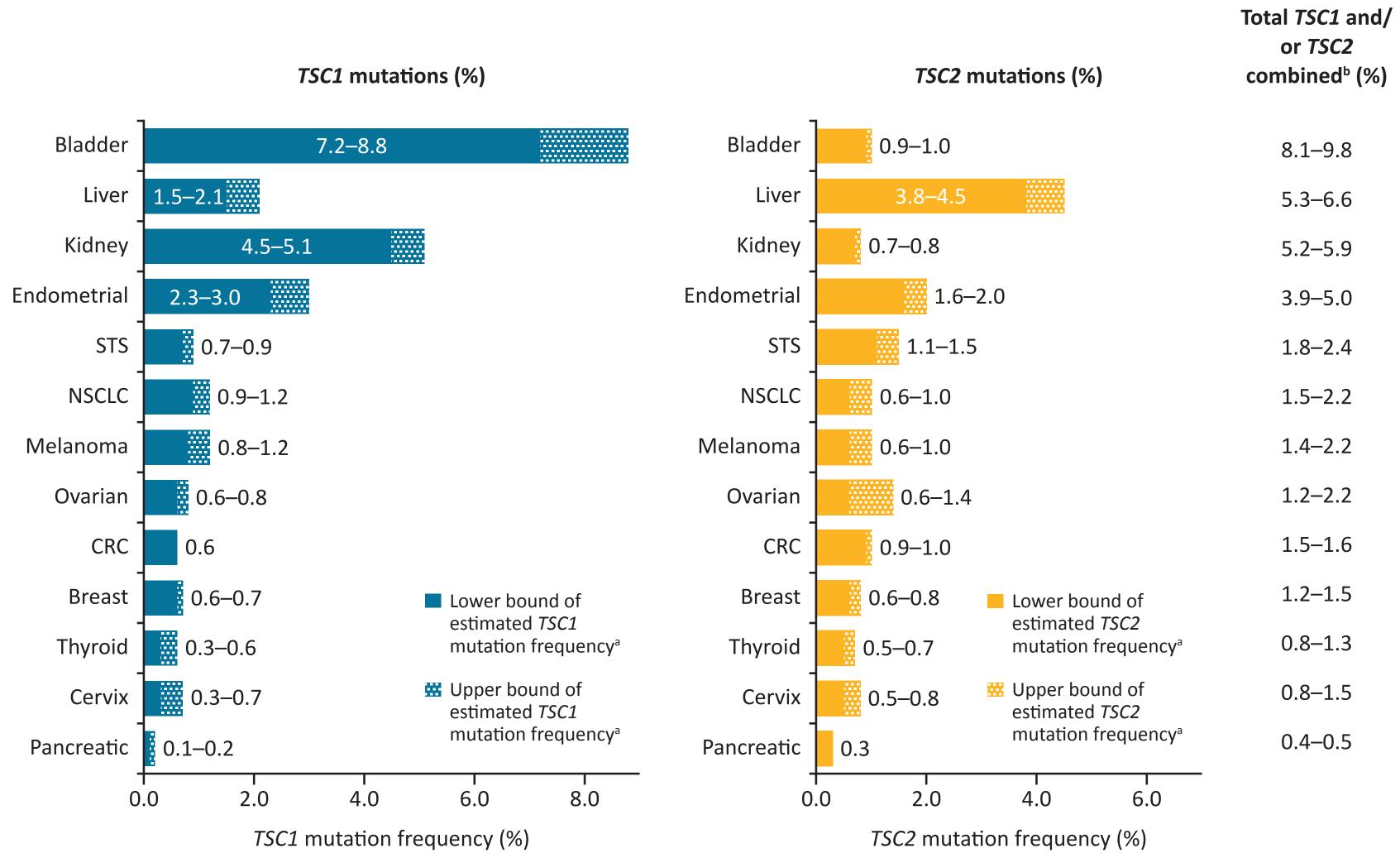
- 2. Millis SZ, et al. *Cancer.* 2019;125:1185-1199.
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• Patients with various malignancies bearing TSC1 or TSC2 inactivating alterations treated with nab-sirolimus as part of the expanded access program (NCT03817515) showed evidence of response (partial response in 5/7 patients) and manageable toxicities⁹

• Inactivating alterations in *TSC1* and/or *TSC2* have been observed in GI cancers with a combined frequency of up to 6.6% in liver cancer, 1.6% in colorectal adenocarcinoma, and 0.5% in pancreatic 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

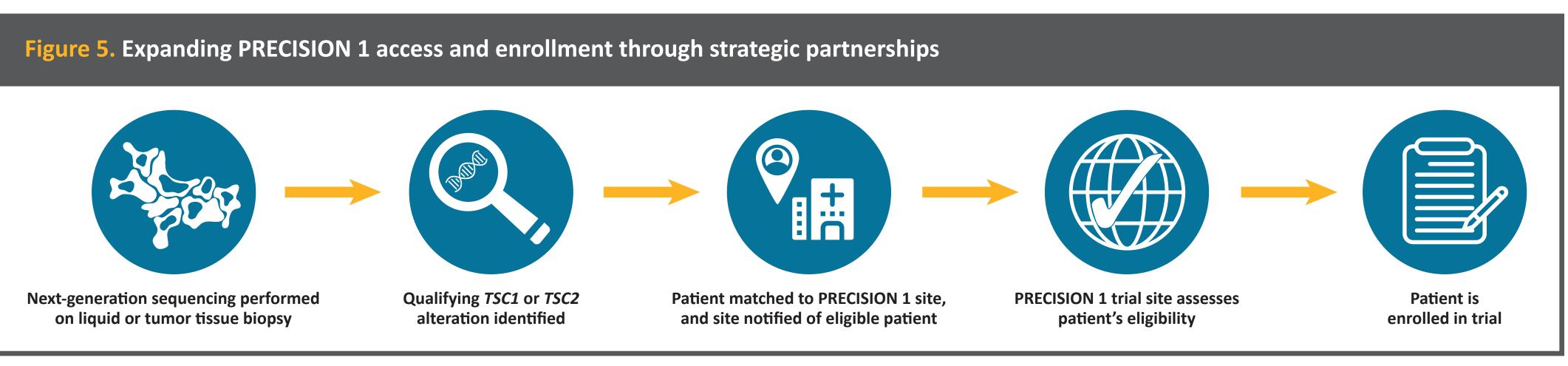
B. Estimated frequency of pathogenic and/or inactivating alterations in TSC1 or TSC2 by tumor type



re 4. Study design

- tissue or liquid biopsy^a
- ≥12 years of age mTORi–naïve
- determined by the investigator
- for pediatric patients)
- or MRI
- PEComa are excluded

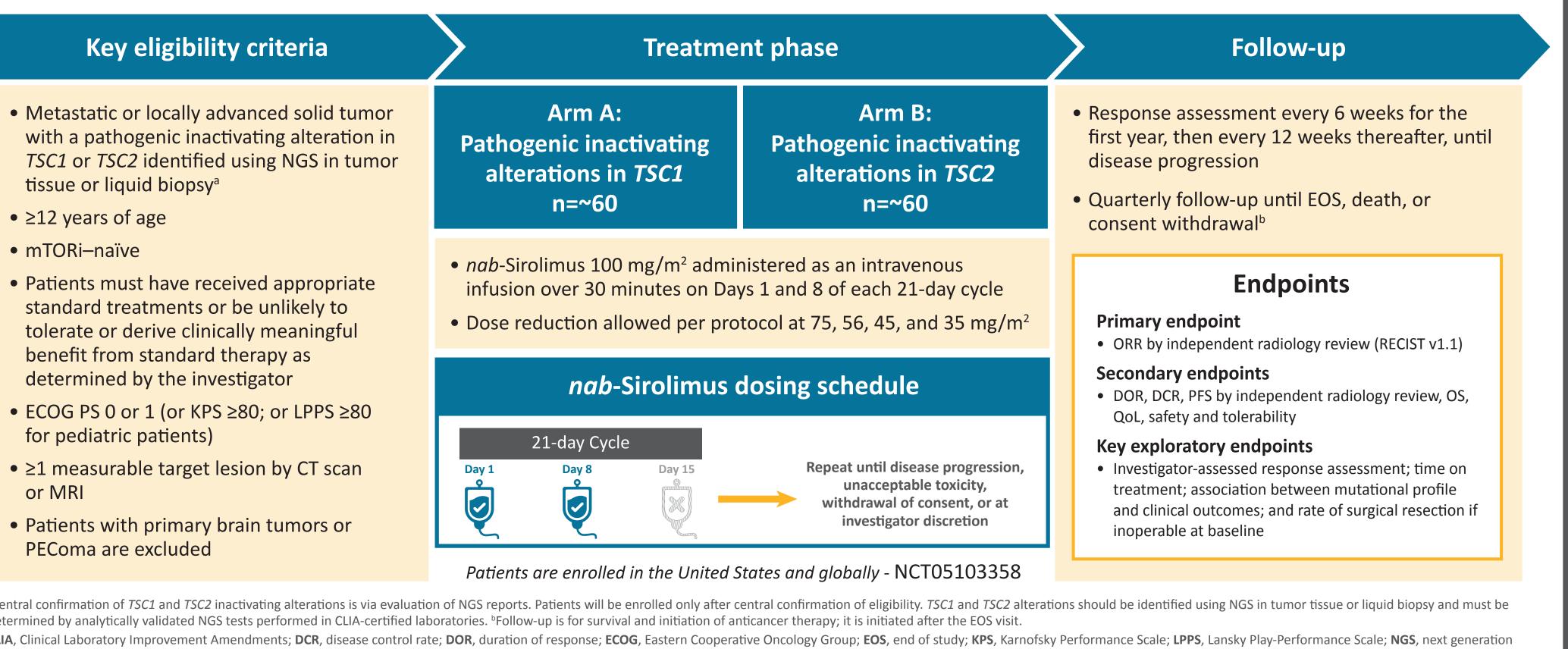
sequencing; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; QOL, quality of life; RECIST, Response Evaluation Criteria for Solid Tumors; TSC1/TSC2, tuberous sclerosis complex 1 or 2.



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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)



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)

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