Phase 2, multicenter, open-label basket trial of *nab*-sirolimus for patients with malignant solid tumors harboring pathogenic inactivating alterations in *TSC1* or *TSC2* genes (PRECISION I)

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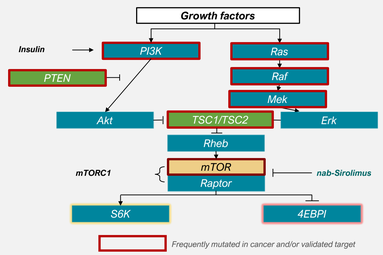
INTRODUCTION

- Tuberous sclerosis complex subunit 1 or 2 (*TSC1 or TSC2*) are critical negative regulators of mechanistic target of rapamycin (mTOR) complex 1 activation[1]



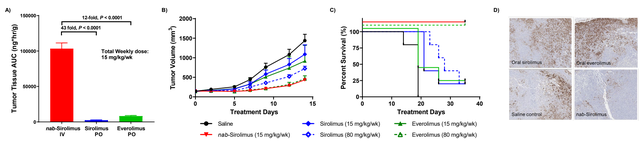
4EBP1, eukaryotic translation initiation factor 4E-binding protein; Akt, protein kinase B; Erk, extracellular signal-regulated kinase; Mek, mitogen-activated protein kinase kinase; mTOR, mechanistic target of rapamycin; mTORC1, mTOR complex 1; *nab*, nanoparticle albumin-bound; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; Raf, rapidly accelerated fibrosarcoma; Raptor, regulatory-associated protein of mTOR; Ras, rat sarcoma virus homolog; Rheb, Ras homolog enriched in brain; S6K, ribosomal S6 kinase; *TSC1/TSC2*, tuberous sclerosis complex subunit 1 or 2.

- Inactivating alterations in *TSC1* and/or *TSC2* have been observed in several types of cancer, but there are currently no approved treatment options for these patients

Tumor type	Definite impact *TSC1* mutations[a]	Definite impact *TSC2* mutations[a]	Eligible *TSC1* or *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%**
Kidney	1.51%	0.45%	**1.96%**
NSCLC	0.77%	1.16%	**1.93%**
Melanoma	1.14%	0.68%	**1.82%**
CRC	0.99%	0.39%	**1.38%**
Thyroid	0.83%	--	**0.83%**
Cervix	--	0.71%	**0.71%**
Pancreatic	0.57%	--	**0.57%**
Breast	0.41%	0.10%	**0.51%**

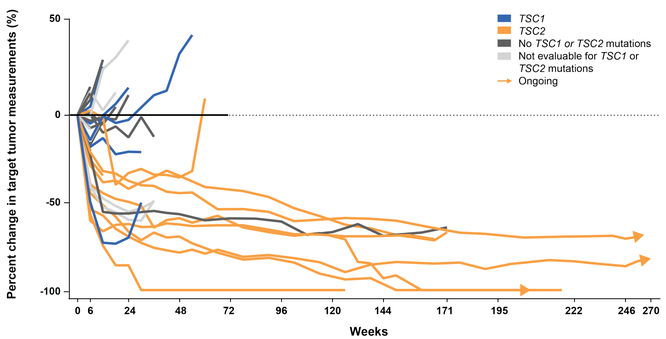
[a]The proportion of patients with definite impact alterations (ie, alterations known to have a biological impact; this includes frameshift, nonsense, and splice-site alterations and deep deletions) was derived from the NIH NCI Genomic Data Commons Data Portal (NIH NCI Genomic Data Commons). CRC, colorectal carcinoma; NCI, National Cancer Institute; NIH, National Institutes of Health; NSCLC, non-small cell lung cancer; *TSC1*, tuberous sclerosis complex subunit 1; *TSC2*, tuberous sclerosis complex subunit 2.

- The utility of oral mTOR inhibitors, such as sirolimus as pan-cancer agents, may be restricted by low bioavailability and dose-limiting toxicity[2,3]
- To improve the pharmacologic properties of sirolimus, *nab*-sirolimus, a nanoparticle form of human albumin-bound sirolimus, was developed for intravenous (IV) use
- In preclinical animal models, *nab*-sirolimus demonstrated significantly **A)** higher intratumor drug concentrations, **B)** greater tumor growth inhibition, **C)** improved survival, and **D)** greater inhibition of the downstream marker of mTOR activity, phosphorylated-S6 (pS6) ribosomal protein, relative to equal weekly doses of sirolimus and everolimus



AUC, area under the curve; IV, intravenous; PO, per os (orally); *nab*, nanoparticle albumin-bound; pS6, ribosomal protein S6.

- *nab*-Sirolimus is approved in the US for the treatment of adult patients with locally advanced, unresectable or metastatic malignant perivascular epithelioid cell tumor (PEComa)[4] based on clinical efficacy and safety results from the AMPECT trial (NCT02494570)[5]

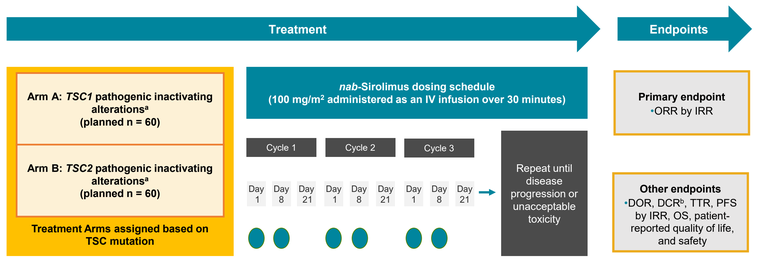


- An exploratory biomarker analysis from AMPECT demonstrated that known inactivating alterations in *TSC1* or *TSC2* were associated with response to *nab*-sirolimus in PEComa, suggesting *nab*-sirolimus might be beneficial for patients with other solid tumors harboring *TSC1* or *TSC2* alterations **(above)**[5]
  - Most treatment-emergent adverse events (TEAEs) were grade 1/2 and were manageable for long-term treatment; no grade ≥4 treatment-related TEAEs were observed
  - The overall safety profile was consistent with other mTOR inhibitors, with no new or unexpected safety signals emerging in the AMPECT trial
- Patients with various malignancies bearing *TSC1* or *TSC2* mutations 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[6]

- The phase 2 PRECISION I 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 I (NCT05103358) is a prospective, phase 2, open-label, multi-institution basket trial to determine the efficacy and safety profile of *nab*-sirolimus in patients with malignant solid tumors with pathogenic inactivating alterations in *TSC1* (Arm A) or *TSC2* (Arm B)
  - Partnerships with next-generation sequencing companies (Foundation Medicine, Tempus, and Caris) will help to identify eligible patients



[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. Pathogenic inactivating alterations are defined as truncating alterations (nonsense, frameshift, splice, intragenic loss/deletion of ≥1 exons) or deletions (patients with 2-copy deletion in *TSC1/TSC2*).
[b]DCR was defined as BOR of confirmed CR or PR (either of any duration) or stable disease ≥12 weeks following study treatment initiation by IRR.
BOR, best overall response; CR, complete response; DCR, disease control rate; DOR, duration of response; IRR, independent radiographic review; IV, intravenous; *nab*, nanoparticle albumin-bound; NGS, next-generation sequencing; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; *TSC1/TSC2*, tuberous sclerosis complex subunit 1 or 2; TTR, time to response.

Key Inclusion Criteria	Key Exclusion Criteria
≥12 years of age	Prior treatment with mTOR inhibitor
Metastatic or locally advanced malignant solid tumor with a pathogenic inactivating *TSC1* or *TSC2* alteration, where surgical resection is not an option, or likely to result in severe morbidity	Recent infection requiring systemic anti-infective treatment
Received appropriate standard treatments or be unlikely to tolerate or derive clinically meaningful benefit from standard therapy as determined by the investigator	Primary brain tumor or PEComa
ECOG performance status of 0 or 1, KPS ≥80, or Lansky play-performance scale for pediatric patients ≥80	Severe and/or uncontrolled medical or psychiatric conditions
≥1 measurable target lesion by CT scan or MRI	For patients on strong inhibitors, inducers, and known CYP3A4 substrates, discontinuation is required ≥5 half-lives prior to receiving the first dose of *nab*-sirolimus

The full list of inclusion and exclusion criteria is available at https://www.clinicaltrials.gov/ct2/show/NCT05103358.
CT, computed tomography; CYP3A4, cytochrome P450 3A4; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky performance status; mTOR, mechanistic target of rapamycin; MRI, magnetic resonance imaging; *nab*, nanoparticle albumin-bound; PEComa, perivascular epithelioid tumor; *TSC1/TSC2*, tuberous sclerosis complex subunit 1 or 2.

SUMMARY

- Available data from the exploratory analysis and an expanded access program suggest acceptable efficacy and safety of *nab*-sirolimus, an mTOR inhibitor with enhanced antitumor activity, in patients with solid tumors harboring inactivating alterations in *TSC1* and/or *TSC2*
- PRECISION 1 is a registrational trial now recruiting for patients with solid tumors driven by *TSC1* or *TSC2* alterations, an underserved patient population with no targeted therapeutic options; this trial is designed to evaluate the efficacy, safety, and tolerability of *nab*-sirolimus

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