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

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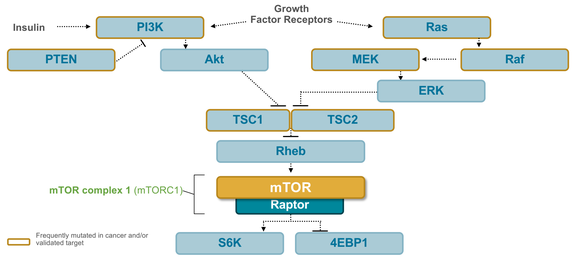
INTRODUCTION

- Tuberous sclerosis complex subunit 1 and 2 (*TSC1, TSC2*) form a protein complex and together are critical negative regulators of mechanistic target of rapamycin (mTOR) complex 1 activation[1] (**Figure 1**)

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



4EBP1, 4E binding protein 1; Akt, Akt serine/threonine protein kinase; ERK, extracellular signal-regulated kinases; MEK, mitogen-activated protein kinase; mTOR, mechanistic target of rapamycin; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; Raf, rapidly accelerated fibrosarcoma protein; Raptor, regulatory-associated protein of mTOR; Ras, rat sarcoma virus homolog; Rheb, Ras homolog enriched in brain; S6K, ribosomal protein S6 kinase; TSC, tuberous sclerosis complex; TSC1/TSC2, tuberous sclerosis complex 1/2.

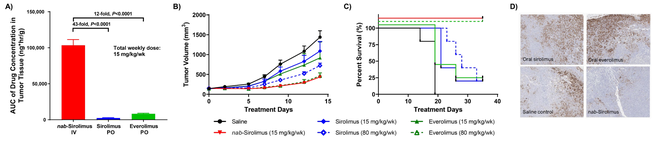
- Inactivating alterations in *TSC1* and/or *TSC2* have been observed in several types of cancer, but no treatment options exist specifically for patients with *TSC1* or *TSC2* inactivating alterations (**Table**)

Table. Estimated Frequency of Definite Impact *TSC1* or *TSC2* Alterations

Tumor Type	*TSC1* Alterations, %[a]	*TSC2* Alterations, %	*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
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

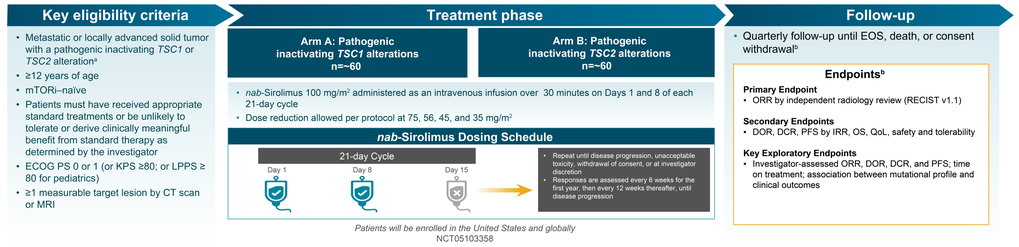
[a]The proportion of patients with definite impact alterations (ie, alterations known to have a biological impact, including frameshift, nonsense, and splice-site mutations and deep deletions) derived from analysis of TCGA and cBioPortal by Gulati et al. (Data on file). *TSC1*, *TSC2*, tuberous sclerosis complex subunit 1, 2.

Figure 2. (A) Intratumor Drug Concentration, (B) Tumor Growth Inhibition, (C) Survival, and (D) mTOR Activity



Results from *PTEN*-null UMUC3 bladder cancer model. AUC, area under the curve; IV, intravenous, *nab*, nanoparticle albumin-bound; PO, per os (orally); pS6, ribosomal protein S6.

STUDY DESIGN

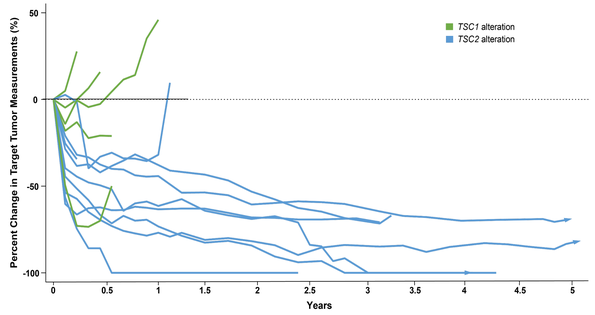


[a]Central confirmation of *TSC1* and *TSC2* pathogenic inactivating alterations is via evaluation of NGS reports. Patients will be enrolled only after central confirmation of eligibility. *TSC1* and *TSC2* alterations should be identified using NGS in tumor tissue or liquid biopsy and must be determined 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; mTORi, mechanistic target of rapamycin inhibitor; *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. Reproduced from Schulte et al.[7]

INTRODUCTION (cont.)

- 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 (IV) 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 (pS6) ribosomal protein, relative to equal weekly doses of sirolimus and everolimus[3] (**Figure 2**)
- *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 (overall response rate 38.7%) 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 3**)[6,7]
  - The most common nonhematologic TRAEs were stomatitis (28/34 [82%]) and 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 treatment-related TEAEs were observed
  - The overall safety profile was consistent with other mTORis with no new or unexpected safety signals emerging in the AMPECT trial
- **Patients with various malignancies bearing *TSC1* or *TSC2* 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]**
- 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

Figure 3. Exploratory Biomarker Analysis From AMPECT Demonstrated Rapid and Durable Responses in Patients With *TSC1* or *TSC2* Alteration Treated With *nab*-Sirolimus (n=14)



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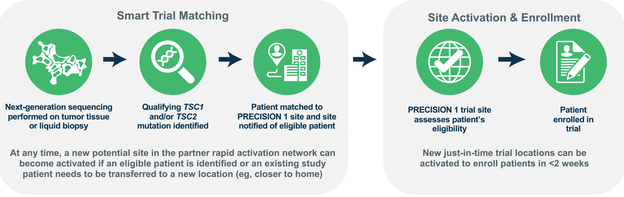
STUDY DESIGN AND FUTURE PARTNERSHIPS

- PRECISION 1 (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) (**Study Design inset**)
- 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 4**)

Figure 4. Expanding PRECISION 1 Access and Enrollment Through Strategic Partnerships



SUMMARY

- *nab*-Sirolimus is an mTORi utilizing *nab* technology that enhances antitumor activity in non-clinical animal models
- Available 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

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