#TPS3168

Phase 2, Multicenter Open-label Basket Trial of *nab*-Sirolimus for Patients With Inactivating Alterations in *TSC1* or *TSC2* (PRECISION I)

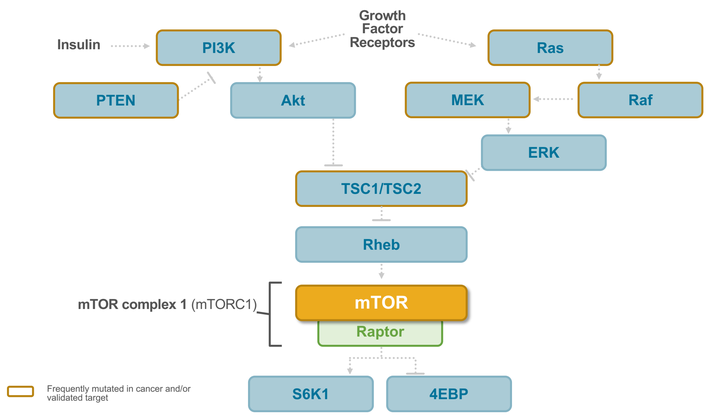
Gopa Iyer, MD[1]; Dustin Deming, MD[2]; Michael J. Demeure, MD[3]; Noah Federman, MD[4]; Meredith McKean, MD[5]; Elizabeth Katherine Lee, MD[6]; Alexander Spira, MD, PhD[7]; David J. Kwiatkowski, MD, PhD[8]; Maen A. Hussein, MD[9]; Erlinda Maria Gordon, MD[10]; David G. Crockett, MD[11]; Kristen N. Ganjoo, MD[12]; Brian Schulte, MD[13]; Lee D. Cranmer, MD, PhD[14]; Li Ding, MS, MA[15]; Anita N. Schmid, MD[15]; Willis H. Navarro, MD[15]; Jordi Rodon Ahnert, MD, PhD[16]

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]University of Wisconsin, Madison, WI; [3]Hoag Memorial Hospital Presbyterian, Newport Beach, CA; [4]University of California, Los Angeles, CA; [5]Sarah Cannon and HCA Research Institute, Nashville, TN; [6]Dana-Farber Cancer Institute, Boston, MA; [7]Virginia Cancer Specialists, Fairfax, VA; [8]Brigham and Women's Hospital, Boston, MA; [9]Florida Cancer Specialists North Division, St. Petersburg, FL; [10]Sarcoma Oncology Research Center, Santa Monica, CA; [11]Nebraska Cancer Specialists, Omaha, NE; [12]Stanford Cancer Center, Stanford, CA; [13]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; [14]Fred Hutchinson Cancer Center, Seattle, WA; [15]Aadi Bioscience, Pacific Palisades, CA; [16]MD Anderson Cancer Center, Houston, TX

INTRODUCTION

- Tuberous sclerosis complex subunit 1 and 2 (*TSC1, TSC2*) form a heterodimeric 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]



4EBPI, 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 no treatment options exist specifically for patients with *TSC1* or *TSC2* inactivating alterations (**Table 1**)

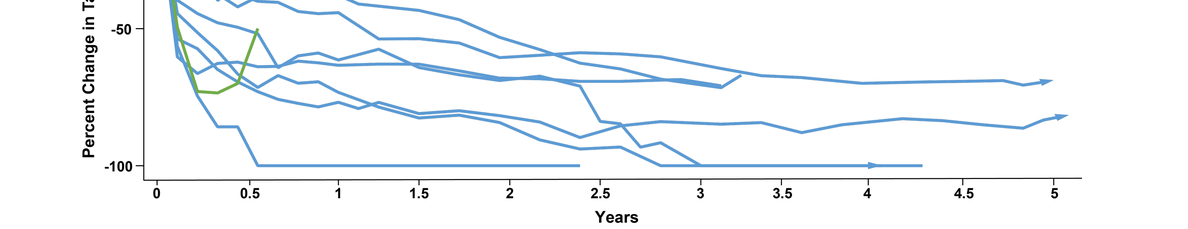
Table 1. Estimated Frequency of Definite Impact *TSC1* or *TSC2* Alterations

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.

- 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 similar weekly doses of sirolimus and everolimus[3] (**Figure 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.

- *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 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

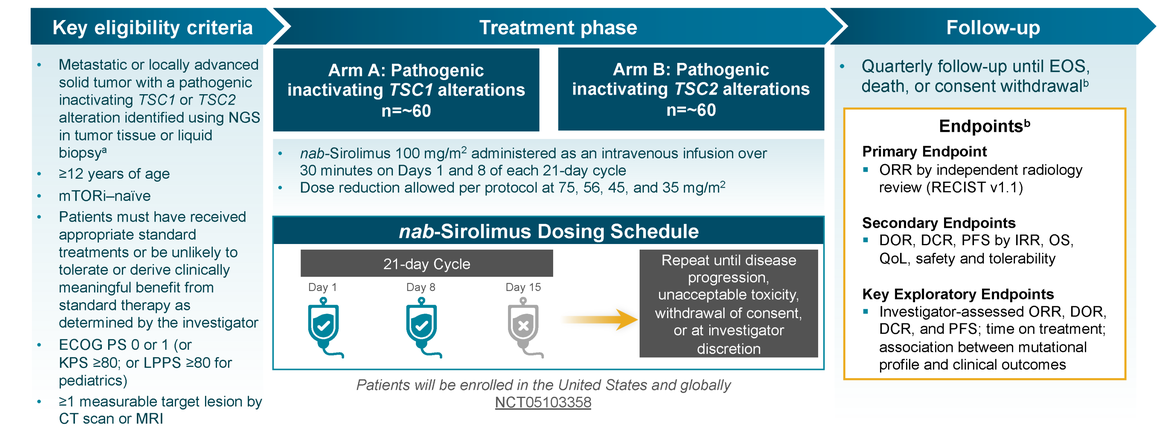
Figure 3. Exploratory Biomarker Analysis From AMPECT Demonstrated Rapid and Durable Responses in Patients With *TSC1* or *TSC2* Alteration (n=14)

- 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 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) (**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; 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]

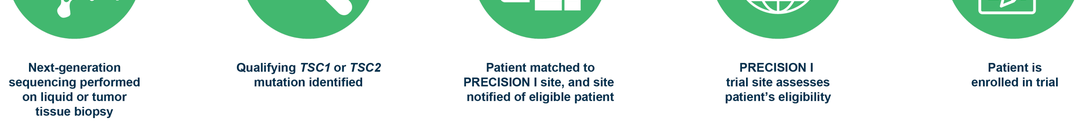
Table 2. Key Inclusion and Exclusion Criteria

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.

- 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 I Access and Enrollment Through Strategic Partnerships



SUMMARY

- *nab*-Sirolimus is an mTORi utilizing *nab* technology to enhance 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 I 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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DISCLOSURES: JRA: Research funding: Bayer, Novartis; personal fees: Eli Lilly, Peptomyc, and Servier. **MJD:** Consulting fees: Bayer, Eli Lilly, On Cusp Therapeutics, and TD2. **NF:** Consulting and speakers' fees: Bayer. **AS:** Honoraria: ARIAD Pharmaceuticals, Clovis Oncology, Novartis, Roche; consulting fees: ARIAD Pharmaceuticals, Clovis Oncology, CytomX Therapeutics, Genentech, Roche; research funding: AbbVie, Astellas Pharma, AstraZeneca, BeiGene, Boehringer Ingelheim, Clovis Oncology, MedImmune, Merck, Merrimack, Newlink Genetics, Novartis, Roche; travel fees: ARIAD Pharmaceuticals, Roche. **DJK:** Research funding: Aadi Bioscience, Genentech, Revolution Medicines; consulting fees: Aadi Bioscience, Bridgebio, Genentech, Guidepoint. **MH:** Consulting fees: Guardant Health; speakers' fees: AMAG Pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb, Heron, Incyte, Pfizer; stock ownership: Celgene. **EMG:** Stock and other ownership interests: Counterpoint Biomedica, Delta NextGene; research funding: Bristol Myers Squibb. **KNG:** Consulting fees: Daiichi Sankyo, Deciphera, Foundation Medicine. **LDC:** Research funding: Aadi Bioscience, Advenchen Laboratories, CBA Research, Exelixis, Iterion Therapeutics, Lilly, Merck, Monopar, Philogen, Zentalis; consulting fee: Aadi Bioscience. **LD, ANS, WHN, and LMI:** Employment and stock ownership: Aadi Bioscience, Inc. **BS, DD, MAM, EL, DGC, and GI:** no conflicts of interest.

ACKNOWLEDGMENTS: Medical writing and editorial assistance were provided by Cynthia D. Gioiello, PharmD, and Stephen Bublitz, ELS, of MedVal Scientific Information Services, LLC, and were funded by Aadi Bioscience, Inc.

Correspondence: MedInfo@AadiBio.com

Presented at the American Society of Clinical Oncology Annual Meeting, June 2-6, 2023, Chicago, IL