Phase 2, Multicenter, Global, Open-Label Basket Trial of *nab*-Sirolimus for Patients With Inactivating Alterations in *TSC1* and *TSC2* (PRECISION 1)

B011

Debra L Richardson, MD[1]; Gopa Iyer, MD[2]; Li Ding, MS, MA[3]; Anita N. Schmid, PhD[3]; Willis H. Navarro, MD[3]; David J. Kwiatkowski, MD, PhD[4]; Jordi Rodon Ahnert, MD, PhD[5]

[1]Stephenson Cancer Center, OU Health, Oklahoma City, OK; [2]Memorial Sloan Kettering Cancer Center, New York, NY; [3]Aadi Bioscience, Pacific Palisades, CA; [4]Brigham and Women's Hospital, Boston, MA; [5]MD Anderson Cancer Center, Houston, TX

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 mTORi utilizing nanoparticle albumin technology to enhance antitumor activity as shown in animal models**
- **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***
- **Combined, *TSC1* and/or *TSC2* inactivating alterations have been found in ~3% of patients with endometrial cancers; 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; enrollment began in March 2022, and is open to patients with endometrial cancers with *TSC1* or *TSC2* inactivating alterations**

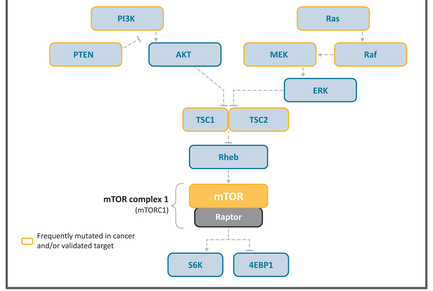
AACR Special Conference in Cancer Research: Endometrial Cancer: Transforming Care Through Science; Boston, MA; November 16–18, 2023

Correspondence: MedInfo@AadiBio.com

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[2,4]



- The utility of oral mTOR inhibitors (mTORis), such as sirolimus, as pan-cancer agents may be restricted by low bioavailability and dose-limiting toxicity[2,3]
- To improve the pharmacologic properties of sirolimus, *nab*-sirolimus, a nanoparticle albumin-bound form of sirolimus, was developed for intravenous use
- In 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[4]
- *nab*-Sirolimus is approved in the United States for the treatment of adult patients with advanced, 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**)[7]
- The safety profile in the overall study population was consistent with other mTORis with no new or unexpected safety signals[8]
  - 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
- 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[9]
- Inactivating alterations in *TSC1* and/or *TSC2* have been observed in several types of cancer, including in ~3% of patients with endometrial cancers, combined; however, no treatment options exist specifically for patients with these alterations (**Figure 3**)
- 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 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)

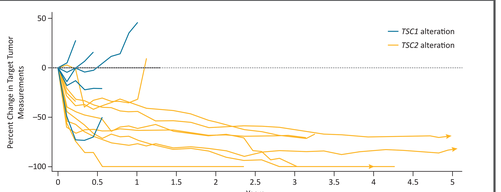
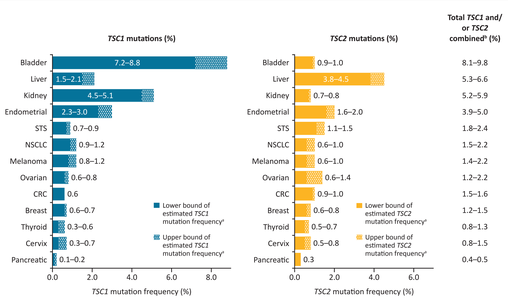


Figure 3. Estimated Frequency of Pathogenic and/or Inactivating Alterations in *TSC1* or *TSC2* by Tumor Type

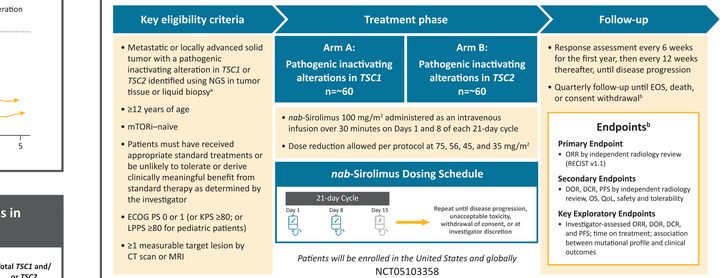


[a]Real-world frequencies were derived from tissue-based NGS results for nonhematologic malignancies included in the Foundation Medicine FoundationInsights™ web platform (n=438,974) and data provided by Tempus Labs (n=128,914) with analysis restricted to known or likely oncogenic *TSC1* or *TSC2* inactivating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

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* 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; it 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; **KPS**, Karnofsky Performance Scale; **LPPS**, Lansky Play-Performance Scale; **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 alterations in *TSC1* or *TSC2* 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

Acknowledgments & Disclosures

Editorial assistance was provided by Heather Caballes, PhD of Twist Medical and was funded by Aadi Bioscience, Inc.

DLR reports advisory boards/consulting for Merana, Immunogen, AstraZeneca, GlaxoSmithKline, Eisai and Profound Bio. **GI** reports consulting/advisory for Janssen, Mirati Therapeutics, Basilea, Flare Therapeutics, LOXO at Lilly; speakers fees from Gilead Sciences, the Lynx Group; Research Funding: Mirati Therapeutics, Novartis, Debiopharm Group, Bayer, Janssen, Seagen, Flare Therapeutics. **LD**, **ANS**, and **WHN** are employees of and own stock in Aadi Bioscience. **DJK** reports research funding from Aadi Biosciences, Genentech, Revolution Medicines; and consulting fees from Aadi Biosciences, Bridgebio, Genentech, and Guidepoint. **JRA** reports research funding from Bayer, Novartis; and personal fees from Eli Lilly, Peptomyc, and Servier.

References

1. He Y, et al. *Signal Transduct Target Ther.* 2021;6(1):425.
2. Saxton RA, et al. *Cell.* 2017;169(2):361–371.
3. Pavavra F, et al. *Oxid Med Cell.* 2017;9820181.
4. Hou S, et al. AACR-NCI-EORTC, October 7–10, 2021 [virtual]. Poster P138.
5. FYARRO (sirolimus albumin-bound particles for injectable suspension). Package insert. Aadi Bioscience, Inc.: Pacific Palisades, CA; 2021.
6. Wagner AJ, et al. *J Clin Oncol.* 2021;39(33):3660–3670.
7. Cranmer, LD, et al. AACR, April 14–19, 2023, Orlando, FL. Poster LB288.
8. Wagner AJ, et al. CTOS, November 16–19, 2022, Vancouver, BC. Poster 167.
9. Dickson MA, et al. ASCO, June 4–8, 2021 [virtual]. Abstract 339405.