nab-Sirolimus for patients with advanced malignant PEComa with or without prior mTOR inhibitors: Biomarker results from AMPECT and an expanded access program

Mark A Dickson, MD[1]; Vinod Ravi, MD[2]; Richard F Riedel, MD[3]; Kristen N Ganjoo, MD[4]; Brian A Van Tine, MD, PhD[5]; Rashmi Chugh, MD[6]; Lee D Cranmer, MD, PhD[7]; Erlinda Maria Gordon, MD[8]; James L Chen, MD[9]; Martina C Murphy, MD[10]; Anita N Schmid, PhD[11]; Neil Desai, PhD[11]; Norma Alonzo Palma, PhD[11]; David J Kwiatkowski, MD, PhD[12]; Andrew J Wagner, MD, PhD[13]

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Duke Cancer Institute, Duke University Medical Center, Durham, NC; [4]Stanford University, Stanford, CA; [5]Washington University in Saint Louis, St. Louis, MO; [6]University of Michigan, Ann Arbor, MI; [7]University of Washington/Fred Hutchinson Cancer Research Center, Seattle, WA; [8]Sarcoma Oncology Center, Santa Monica, CA; [9]The Ohio State University, Columbus, OH; [10]University of Florida, Gainesville, FL; [11]Aadi Bioscience, Pacific Palisades, CA; [12]Brigham and Women's Hospital, Boston, MA; [13]Dana-Farber Cancer Institute, Boston, MA

Abstract# 11574

INTRODUCTION

- Inactivating alterations in *TSC1* or *TSC2* are considered targetable biomarkers for mTOR inhibition[1]
- *nab*-Sirolimus is an albumin-bound mTOR inhibitor (mTORi) approved for the treatment of adult patients with locally advanced unresectable or metastatic malignant PEComa, a tumor that frequently has inactivating alterations in *TSC2* or *TSC1*[2,3]
- The AMPECT trial (NCT02494570) of *nab*-sirolimus efficacy and safety was the first prospective study in advanced malignant PEComa[4]
  - In exploratory biomarker analyses, known inactivating alterations in *TSC1* or *TSC2* were associated with response
- To allow access to *nab*-sirolimus treatment for patients with serious conditions who were excluded from AMPECT, an expanded access program (EAP; NCT03817515) bridged the gap between closure of enrollment in the AMPECT trial and *nab*-sirolimus market access
- We report data from the final analysis of AMPECT patients, who were naïve to mTORi, and from patients with malignant PEComa with prior mTORi exposure treated with *nab*-sirolimus in the EAP

METHODS

AMPECT

- AMPECT was a phase 2, open-label, single-arm, multicenter study in patients with advanced malignant PEComa to determine the efficacy and safety of *nab*-sirolimus through intravenous infusion (data cutoff as of June 2021)

Key Eligibility Criteria

- Age ≥18 years
- Centrally confirmed inoperable metastatic or locally advanced malignant PEComa
- ECOG PS 0–1
- No prior mTOR inhibitor therapy
- Adequate organ function

Treatment

- *nab*-Sirolimus 100 mg/m^2 administered as an intravenous infusion over 30 minutes on Days 1 and 8 of each 21-day cycle

***nab*-Sirolimus Dosing Schedule**

Cycle 1			Cycle 2			Cycle 3		
Day 1	Day 8	Day 21	Day 1	Day 8	Day 21	Day 1	Day 8	Day 21

Repeat until disease progression or unacceptable toxicity

Primary Endpoint

- ORR by central review per RECIST v1.1

Other Endpoints

- DOR, DCR (CR, PR, or SD of ≥12 weeks' duration), safety/tolerability, and subgroup analyses based on tumor molecular profiling by next generation sequencing (when available)

CR, complete response; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; mTOR, mechanistic target of rapamycin; *nab*, nanoparticle albumin-bound; PEComa, perivascular epithelioid cell tumor; PR, partial response; PS, performance status; SD, stable disease.

Expanded Access Program

- Based on early signal of clinical benefit from the AMPECT study, this expanded access protocol bridged between the closure of the enrollment in AMPECT and the regional marketing approval of the product in order to allow patients with malignant PEComa to be treated with nab-sirolimus

Patient Population of Retrospective Analysis

- Age ≥18 years
- Advanced malignant PEComa with prior exposure to mTOR inhibitors
- ECOG PS 0–2

Treatment

- *nab*-Sirolimus 100 mg/m^2 administered as an intravenous infusion over 30 minutes on Days 1 and 8 of each 21-day cycle

***nab*-Sirolimus Dosing Schedule**

Cycle 1			Cycle 2			Cycle 3		
Day 1	Day 8	Day 21	Day 1	Day 8	Day 21	Day 1	Day 8	Day 21

Repeat until disease progression or unacceptable toxicity

Data Collection

- Post-hoc evaluation of response via electronic medical record review
- Tumor molecular profile by next generation sequencing (when available)

ECOG, Eastern Cooperative Oncology Group; mTOR, mechanistic target of rapamycin; *nab*, nanoparticle albumin-bound; PEComa, perivascular epithelioid cell tumor; PS, performance status.

SAFETY

- There were no Grade 4 or 5 treatment-related AEs (TRAEs) in AMPECT
- The most common TRAEs in AMPECT were mucositis, fatigue, and rash (**Table 1**)
  - Four patients with a response had TRAEs that were managed with dose reduction; these patients maintained response on the lower dose
- AEs reported by the treating physician in the EAP were consistent with what was reported in AMPECT

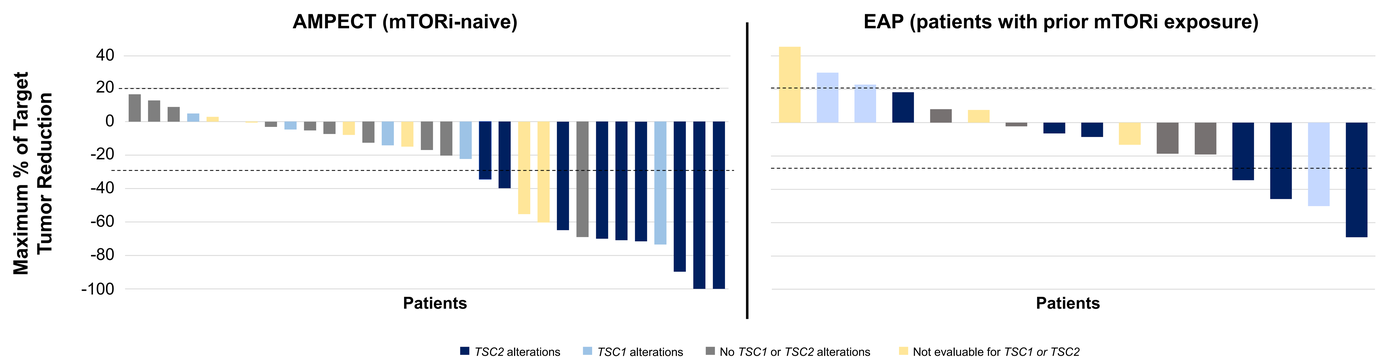
Table 1. Most frequent TRAEs and Grade 3 TRAEs in AMPECT

TRAEs	Any grade (>25%)	Grade 3
Hematologic TRAEs		
Anemia	18 (53)	5 (15)
Thrombocytopenia	12 (35)	1 (3)
Nonhematologic TRAEs		
Mucositis	27 (79)	6 (18)
Fatigue	21 (62)	1 (3)
Rash	21 (62)	--
Nausea	16 (47)	--
Diarrhea	14 (41)	--
Hyperglycemia	14 (41)	3 (9)
Weight decreased	14 (41)	--
Dermatitis	12 (35)	--
Hypertriglyceridemia	11 (32)	1 (3)
Hypercholesterolemia	11 (32)	--
Decreased appetite	12 (33)	--
Dysgeusia	9 (26)	--
Headache	10 (29)	--
ALT	9 (26)	1 (3)
Edema	9 (26)	--
Pruritus	9 (26)	--
Vomiting	9 (26)	1 (3)

ALT, alanine aminotransferase; TRAE, treatment-related adverse event.

Target tumor reductions were observed in patients with *TSC1* and *TSC2* inactivating alterations in both the AMPECT trial and the EAP

Waterfall plot of the efficacy of *nab*-sirolimus for tumor reduction in patients with malignant PEComa in AMPECT and on the EAP



Data cut as of June 2021.

Data cut as of July 2021.

EAP, expanded access program; mTORi, mechanistic target of rapamycin inhibitor; PEComa, perivascular epithelioid cell tumor.

CONCLUSIONS

- *nab*-Sirolimus provided clinical benefit in mTORi-naïve patients with malignant PEComa in the AMPECT trial and in patients with malignant PEComa with prior mTORi therapy in an EAP
- Although AMPECT and the EAP cannot be directly compared, response rates showed similar trends regardless of prior mTORi exposure and in patients with *TSC1* or *TSC2* alterations
- Based on the emerging biomarker results, a tissue-agnostic pan-tumor Phase 2 study in patients with *TSC1* and *TSC2* alterations has been initiated and is currently enrolling patients (NCT05103358)

EFFICACY

AMPECT

- 31 patients with malignant PEComa and no prior mTORi exposure are shown as of June 2021
- ORR was 39% (12/31 patients), including 2 CRs, and DCR was 71%
  - Median DOR was not reached after 3 years of follow-up, indicating that >50% of patients will have a DOR >36 months
  - No clinically relevant differences by baseline characteristics were noted
  - Patients obtained benefit regardless of *TSC1* and *TSC2* alteration status
  - During long-term follow-up, 2 patients ineligible for tumor resection at baseline had successful resection after treatment with *nab*-sirolimus

Table 2. Best overall response in all evaluable patients and patients with known inactivating alterations in *TSC1* or *TSC2* in AMPECT

	Patients	CR or PR[a]	SD	PD
All evaluable patients	31	12/31 (39%)	16/31 (52%)	3/31 (10%)
TSC1 or *TSC2* alteration	14	9/14 (64%)	5/14 (36%)	0

4/31 patients, all with response, were ongoing at the data cutoff.
[a]Confirmed responses.
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

EAP

- 16 patients with malignant PEComa and prior mTORi exposure were treated on the EAP from July 2019–July 2021; prior mTORi included sirolimus, everolimus, temsirolimus, and sapanisertib; 12 patients had exposure to 1 prior mTORi and 4 patients had exposure to ≥2 prior mTORis; and 50% had had progressive disease as best response on previous mTORi
- The DCR was 63% (10/16)

Table 3. Best overall response in all evaluable patients and patients with known inactivating alterations in *TSC1* or *TSC2* on the EAP

	Patients	PR[a]	SD	PD
All evaluable patients	16	4/16 (25%)	8/16 (50%)[b]	4/16 (25%)
TSC1 or *TSC2* alteration	9	4/9 (44%)	3/9 (33%)	2/9 (22%)

6/16 patients including 2 without alterations in *TSC1* or *TSC2* were ongoing at the time of data cutoff.
[a]Confirmed responses. [b]6/16 patients had SD for ≥12 weeks.
EAP, expanded access program; PD, progressive disease; PR, partial response; SD, stable disease.

REFERENCES

1. Huang J, et al. *Biochem J* 2008 ; 412(2) :179–90.
2. FYARRO (sirolimus albumin-bound particles for injectable suspension). Package insert. Pacific Palisades, CA. Aadi Bioscience, Inc.; 2021.
3. Martignoni G, et al. *Virchows Arch* 2006;452:119–132.
4. Wagner AJ, et al. *J Clin Oncol* 2021;39(33):3660–70.

ACKNOWLEDGMENTS

This study was funded by Aadi Bioscience, Inc. Editorial support was provided by Hilary Durbano, PhD, of AlphaBioCom, LLC, King of Prussia, PA, USA, and funded by Aadi Bioscience, Inc.

Presented at American Society of Clinical Oncology Annual Meeting 2022, June 3-7, Chicago, IL and Virtual