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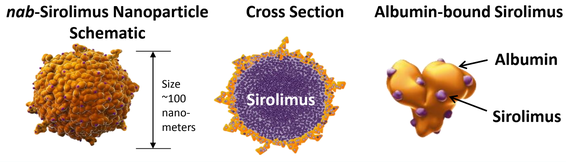
Mutational and Biomarker Correlative Analysis of mTOR Pathway Aberrations in Patients With Advanced Malignant Perivascular Epithelioid Cell Tumors (PEComa) Treated With *nab*-Sirolimus: Results From AMPECT, an Open-label Phase 2 Registrational Trial

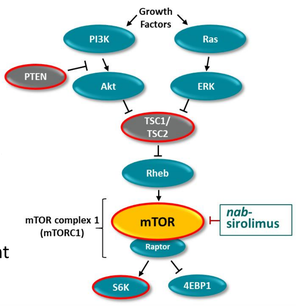
Andrew J. Wagner, MD, PhD,[1] Mark A. Dickson, MD,[2] Vinod Ravi, MD,[3] Richard F. Riedel, MD,[4] Kristen N. Ganjoo, MD,[5] Brian A. Van Tine, MD, PhD,[6] Rashmi Chugh, MD,[7] Lee D. Cranmer, MD, PhD,[8] E. Maria Gordon, MD,[9] Jason L. Hornick, MD, PhD,[10] Heng Du, MD,[10] Berta Grigorian,[11] Anita N. Schmid, PhD,[11] Shihe Hou, PhD,[11] Katherine Harris, DrPH,[11] Neil P. Desai, PhD,[11] **David J. Kwiatkowski, MD, PhD** [10]

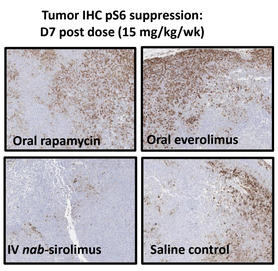
1. Dana-Farber Cancer Institute, Boston, MA
2. Memorial Sloan Kettering Cancer Center, New York, NY
3. MD Anderson Cancer Center, Houston, TX
4. Duke Cancer Institute, Durham, NC
5. Stanford University, Stanford, CA
6. Washington University in Saint Louis, St. Louis, Missouri
7. University of Michigan
8. Univ Washington/F Hutchinson Cancer Res Ctr, Seattle, WA
9. Sarcoma Oncology Center, Santa Monica, CA
10. Brigham and Women's Hospital, Boston, MA
11. Aadi Bioscience, Pacific Palisades, CA

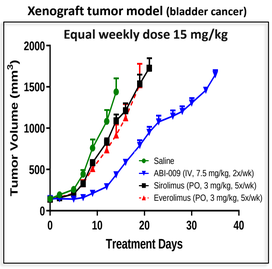
INTRODUCTION

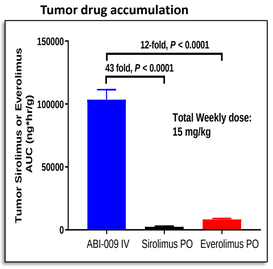
- Advanced malignant PEComa is a rare, aggressive sarcoma, with no approved treatment. Loss-of-function mutation of *TSC1* or *TSC2* and mTOR pathway overactivation has been described in this disease.
- Case reports of mTOR inhibitor treatment show substantial clinical benefit.[1,2]
- Oral mTOR inhibitors have poor and variable absorption and often require therapeutic monitoring.
- *nab*-Sirolimus (ABI-009) is a novel albumin-bound intravenous mTOR inhibitor with significantly higher anti-tumor activity, significantly higher intratumoral drug accumulation, and significantly higher mTOR target (pS6) suppression at equal dose vs oral mTOR inhibitors in preclinical models.[3-5]
- The AMPECT trial evaluated *nab*-sirolimus in patients with advanced malignant PEComa and met its primary endpoint (Abst ID: 3206452):
  - Independently assessed ORR was 39% with 95% CI of 21.8% - 57.8%
  - Durable responses (median 15+ mo, 8/12 ongoing)
  - Acceptable safety profile
- The AMPECT trial is the first trial to prospectively evaluate mutational status and biomarkers in this patient population.









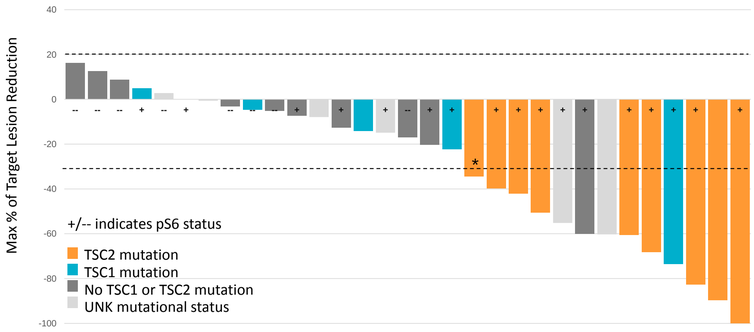


METHODS

- 34 patients with advanced malignant PEComa were treated with 100 mg/m^2 *nab*-sirolimus on a 2/3 weeks schedule. 31/34 patients were evaluable for efficacy (received ≥1 dose of ABI-009, had a post-baseline scan, had a centrally confirmed PEComa). Primary endpoint was overall response rate (ORR) by independent review. The target ORR of ~30% in 30 evaluable patients was to exclude the lower bound of the 95% CI of 14.7%. An exploratory endpoint was to identify predictive biomarkers for response.
- Pre-treatment tumors (archival or fresh tissue biopsies) were collected from all patients. The following analyses were performed on all available samples:
  - Oncopanel (next generation sequencing, n = 25 analyzable samples): Targeted exome sequencing was performed to identify mutations using the CLIA-certified Oncopanel assay at BWH Department of Pathology. The Oncopanel assay surveyed exonic DNA sequences of 447 cancer genes and 191 regions across 60 genes for rearrangement detection.
  - phospho-S6 for mTOR activation by IHC (n = 25 analyzable samples)
  - FISH for TFE3 translocation (n = 22 analyzable sample)

RESULTS

- **Oncopanel:** The results of this analysis were provided for 7 genes for which mutations were identified frequently, or for which previous studies had suggested a role in PEComa development.

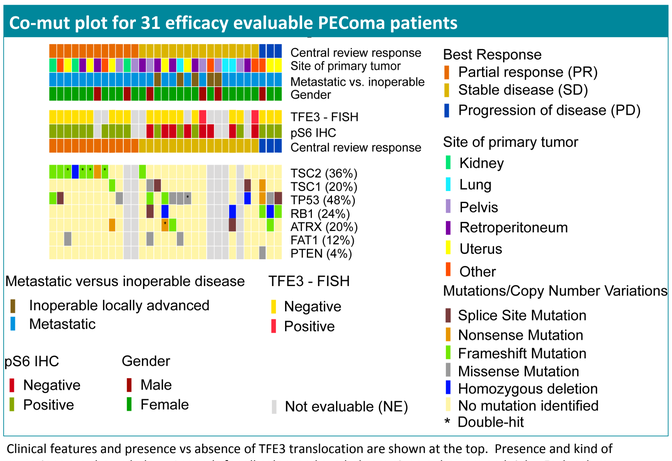


TSC1/TSC2 Mutational Analysis N = 25	Independent Review: Responders (PR) n = 10	Independent Review: Non-responders (SD+PD) n = 15
TSC2 (n = 9)	8/9 (89%)	1/9 (11)*
TSC1 (n = 5)	1/5 (20%)	4/5 (80%)
No *TSC1* or *2* (n = 11)	1/11 (9%)	10/11 (91%)
	P < 0.001 (Chi Square)	
Unknown status (n = 6)	2/6 (33%)	4/6 (66%)

** 1 patient with TSC2 mutation had an unconfirmed PR and thus best response is an SD*

pS6 IHC N = 25	Independent Review: Responders (PR) n = 10	Independent Review: Non-responders (SD+PD) n = 15
pS6 + (n = 17)	10/17 (59%)	7/17 (41%)
pS6 - (n = 8)	0	8/8 (100%)
	P = 0.008 (2x2 Fisher)	
Unknown status (n = 6)	3/6 (50%)	3/6 (50%)

Co-mut plot for 31 efficacy evaluable PEComa patients



Clinical features and presence vs absence of TFE3 translocation are shown at the top. Presence and kind of mutations are shown below. Legends for all colors and symbols are given at bottom and right. Each column represents a different patient on AMPECT.

- 43% (3/7) efficacy evaluable patients with uterine primary PEComa, a hard to treat subset, had a PR.
  - No trend emerged for primary tumor sites vs response.
- Mutations in *TSC2,* but not *TSC1,* were significantly associated with response.
- pS6 expression by IHC was significantly associated with response; while absence was associated with non-response.
- 11 patients with *TSC1* or *TSC2* mutations were analyzable for pS6 by IHC; 10/11(91%) expressed pS6. In contrast, only 5/11 (45%) without *TSC1* or *TSC2* mutations expressed pS6 (*p*=NS, Fisher).
- TFE3 translocation (2/22, both patients SD) was infrequent, and was not associated with pS6.
- Mutations in TP53 were present in both nonresponders (9/15, 60%) and responders (3/10, 30%) (*p*=NS, Fisher's exact test).
- Mutations in other genes (ATRX, RB1, FAT1, PTEN) was not associated with response.
  - Of note, TP53, ATRX, RB1 are also all commonly mutated in leiomyosarcoma.

CONCLUSIONS

- TSC2 mutations were significantly associated with response (89% of patients) to *nab*-sirolimus in this cohort of 31 efficacy evaluable patients with PEComa.
- Responses were also seen in patients with *TSC1* mutations (20%) or no *TSC1/TSC2* mutations (9%) although at much lower frequency than for *TSC2* mutations indicating *nab*-sirolimus is active regardless of mutational status.
- Lack of pS6 expression was a negative predictor of response.
- This first prospective study in advanced malignant PEComa suggests that *nab*-sirolimus may offer an important benefit in a rare and aggressive sarcoma for which there are no approved therapies.
- A prospective tumor agnostic trial of *nab*-sirolimus for patients with tumor mutations in *TSC2* is warranted.

REFERENCES

1. Wagner et al., JCO 2010
2. Dickson et al., Int J Cancer 2013
3. Hou et al., AACR 2019, #348
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5. Aadi Bioscience internal data

David J. Kwiatkowski: dk@rics.bwh.harvard.edu Andrew Wagner: Andrew_Wagner@dfci.harvard.edu

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