Prospective studies in ultra-rare sarcomas: nab-sirolimus in PEComa as an example

EMA/EORTC Soft Tissue and Bone Sarcoma Group Joint Workshop

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Dana-Farber Cancer Institute

Disclosures*

Consulting/Honoraria:

Aadi Bioscience, BioAtla, Boehringer-Ingelheim, Cogent Biosciences, Daiichi Sankyo, Deciphera Pharmaceuticals, Eli Lilly, InhibRx, Kymera Therapeutics, PharmaEssentia, Servier

Research Support to My Institution:

Aadi Bioscience, Boehringer-Ingelheim, Cogent Biosciences, Daiichi Sankyo, Deciphera Pharmaceuticals, Eli Lilly, Foghorn Therapeutics, Rain Therapeutics

Board of Directors (uncompensated):

Sarcoma Alliance for Research through Collaboration (SARC)

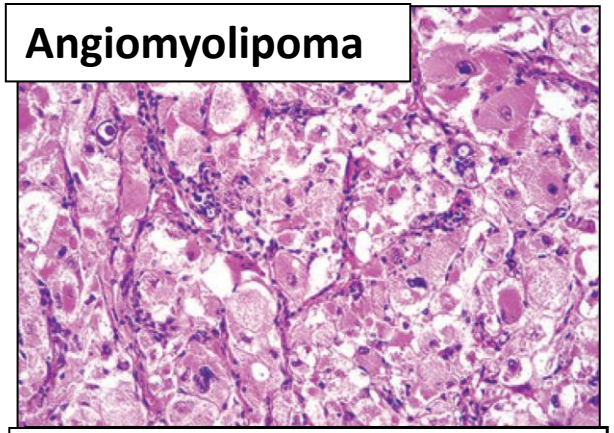
* Last 2 years

Perivascular Epithelioid Cell Tumors (PEComa)

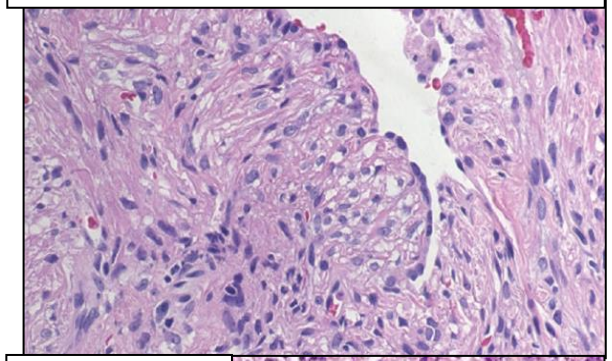
- Family of tumors consisting of angiomyolipoma (AML), lymphangioleiomyomatosis (LAM), PEComa, and other similar tumors
  - Epithelioid but occasionally spindled cells
  - Clear to granular eosinophilic cytoplasm
  - Focal association with blood vessel walls
  - Immunoreactivity for:
    - HMB-45 and/or Melan-A (melanocytic)
    - Actin and/or desmin (smooth muscle)

- AML and LAM can be sporadic or associated with Tuberous Sclerosis
  - Loss of TSC1 or TSC2, negative regulators of mTOR

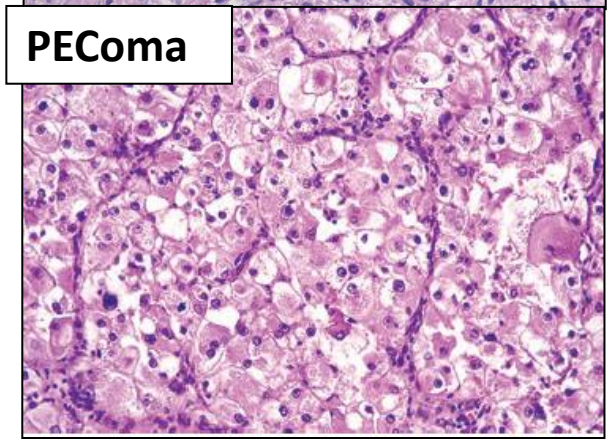
Angiomyolipoma



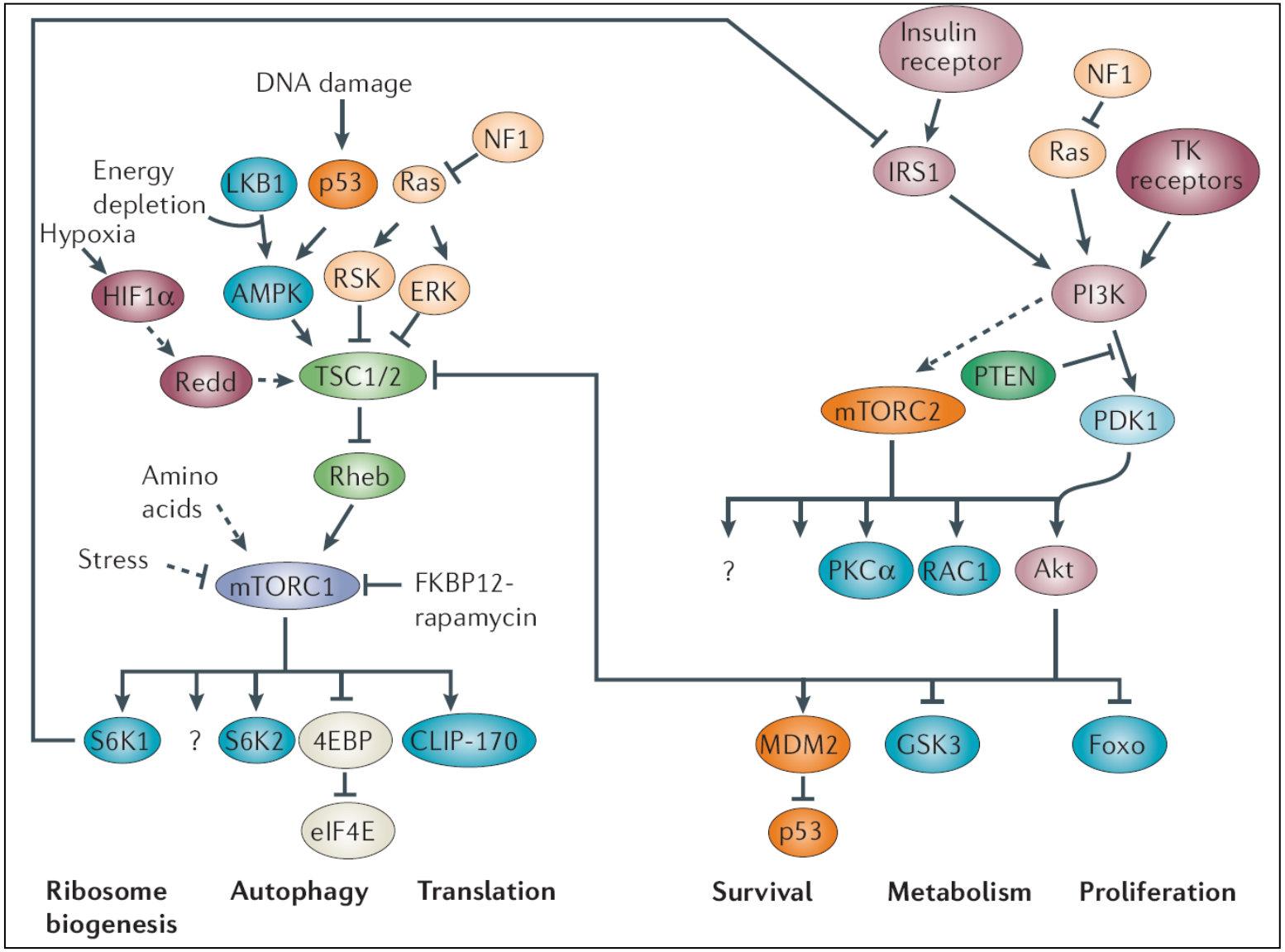
Lymphangioleiomyomatosis



PEComa

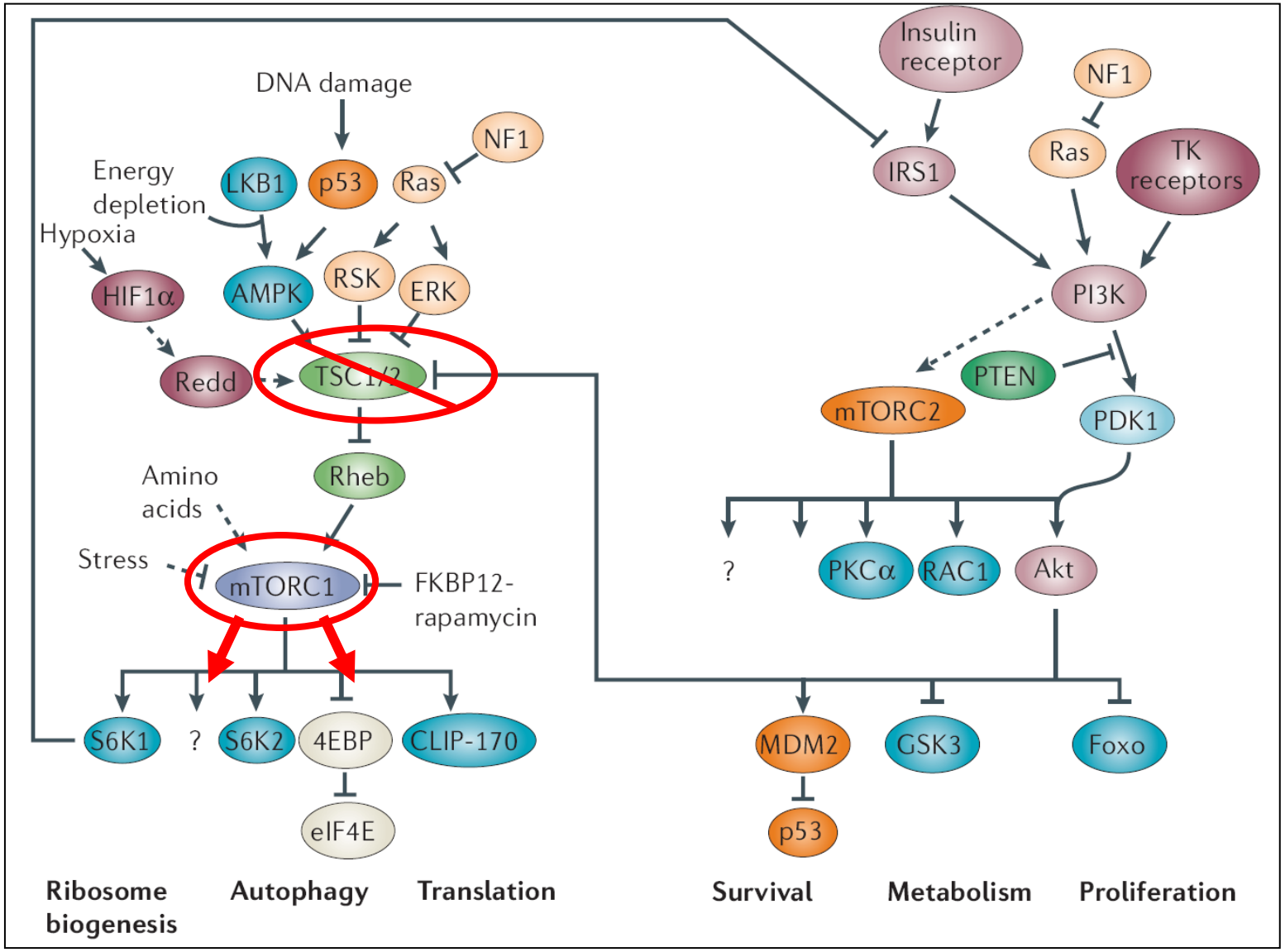


mTOR signaling pathway



Sabatini (2006) Nature Reviews Cancer 6:729

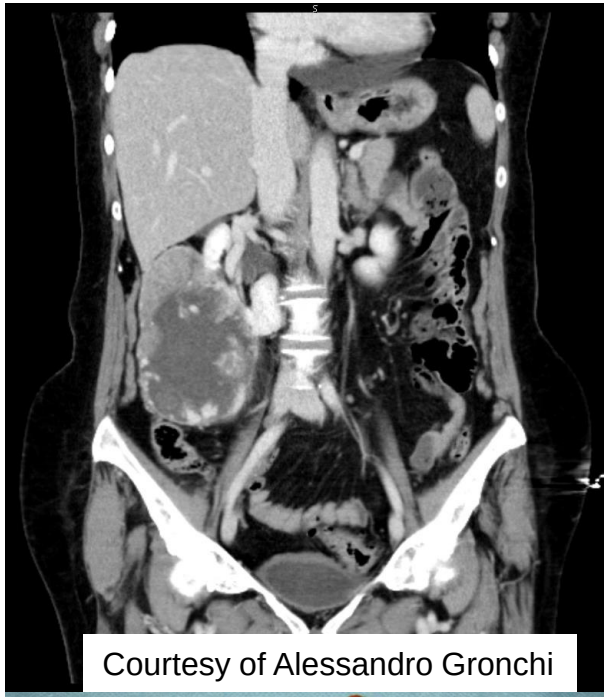
mTOR signaling pathway



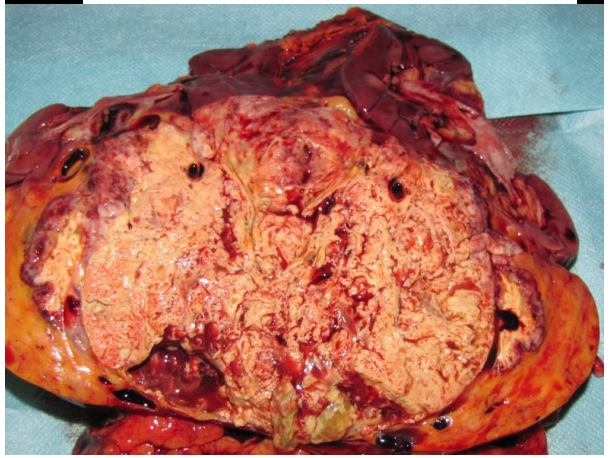
Sabatini (2006) Nature Reviews Cancer 6:729

Malignant PEComa

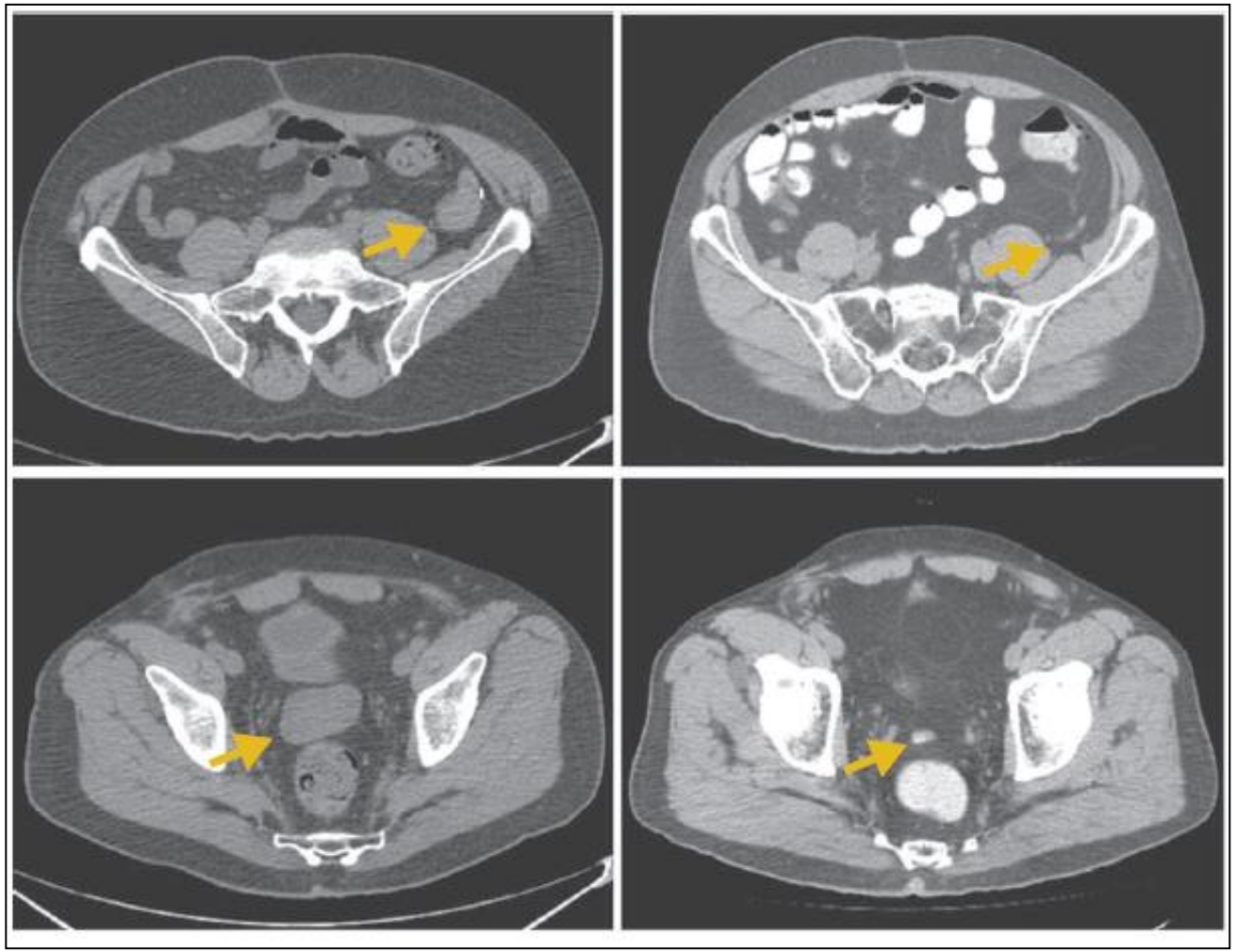
- Ultra-rare sarcoma with yearly incidence of <1/1,000,000
- 4:1 female:male distribution
- Can arise anywhere; uterus and kidney are most common primary sites
- Poorly responsive to standard cytotoxic chemotherapy
- Because of similarities to LAM/AML and reported activation of mTOR pathway, off-label use of mTOR inhibitors offered to patients with advanced disease



Courtesy of Alessandro Gronchi



Metastatic PEComa treated with mTOR inhibitor sirolimus



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JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Clinical Activity of mTOR Inhibition With Sirolimus in Malignant Perivascular Epithelioid Cell Tumors: Targeting the Pathogenic Activation of mTORC1 in Tumors

Andrew J. Wagner, Izabela Malinowska-Kolodziej, Jeffrey A. Morgan, Wei Qin, Christopher D.M. Fletcher, Natalie Vena, Azra H. Ligon, Cristina R. Antonescu, Nikhil H. Ramaiya, George D. Demetri, David J. Kwiatkowski, and Robert G. Maki

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Presented in part at the 14th Annual Meeting of the Connective Tissue Oncologic Society, November 13-15, 2008, London, United Kingdom.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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A B S T R A C T

Purpose
Perivascular epithelioid cell tumors (PEComas) represent a family of mesenchymal neoplasms, mechanistically linked through activation of the mTOR signaling pathway. There is no known effective therapy for PEComa, and the molecular pathophysiology of aberrant mTOR signaling provided us with a scientific rationale to target this pathway therapeutically. On this mechanistic basis, we treated three consecutive patients with metastatic PEComa with an oral mTOR inhibitor, sirolimus.

Patients and Methods
Patients with advanced PEComa were treated with sirolimus and consented to retrospective collection of data from their medical records and analysis of archival tumor specimens. Tumor response was determined by computed tomography scans obtained at the clinical discretion of the treating physicians. Tumors were assessed for immunohistochemical evidence of mTORC1 activation and genetic evidence of alterations in *TSC1* and *TSC2*.

Results
Radiographic responses to sirolimus were observed in all patients. PEComas demonstrated loss of TSC2 protein expression and evidence of baseline mTORC1 activation. Homozygous loss of *TSC1* was identified in one PEComa.

Conclusion
Inhibition of mTORC1, pathologically activated by loss of the TSC1/TSC2 tumor suppressor complex, is a rational mechanistic target for therapy in PEComas. The clinical activity of sirolimus in PEComa additionally strengthens the pathobiologic similarities linking PEComas to other neoplasms related to the tuberous sclerosis complex.

J Clin Oncol 28:835-840. © 2010 by American Society of Clinical Oncology

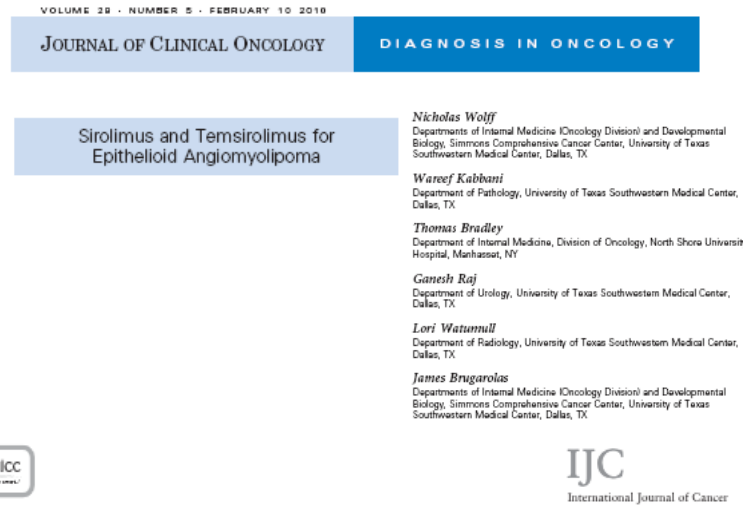
INTRODUCTION

Sarcomas are a heterogeneous collection of tumors sharing a common mesenchymal origin. Historically, treatment studies of pooled subtypes of sarcoma have shown overall poor responses to conventional chemotherapeutic agents.[1] However, in recent years, identification of molecular subtypes of sarcoma has led to the application of effective targeted therapies, such as imatinib mesylate for the treatment of gastrointestinal stromal tumors that usually harbor activating mutations in the *KIT* receptor tyrosine kinase. Identification of molecular alterations in other sarcoma subtypes may lead to more effective therapies for this otherwise difficult-to-treat group of diseases.

The perivascular epithelioid cell tumor (PEComa) family of tumors consists of related mesenchymal neoplasms that exhibit myomelanocytic differentiation and share a distinctive cell type, the perivascular epithelioid cell, or PEC.[2-4] The major members of this family include lymphangioleiomyomatosis (LAM), a disease predominantly presenting as numerous nodular and interstitial pulmonary lesions in premenopausal women; angiomyolipoma (AML), commonly identified as an asymptomatic renal lesion with evidence of vascular, muscle, and adipocytic differentiation; and PEComa, an epithelioid malignancy with clear-to-granular eosinophilic cytoplasm typically arising in the gastrointestinal tract, retroperitoneum, uterus, or somatic soft tissues, composed of nests and sheets

Wagner et al. *J Clin Oncol* (2010);28:835

Additional Case Reports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JOURNAL OF CLINICAL ONCOLOGY DIAGNOSIS IN ONCOLOGY

Sirolimus and Temsirolimus for Epithelioid Angiomyolipoma

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IJC
International Journal of Cancer

Extrarenal perivascular epithelioid cell tumors (PEComas) respond to mTOR inhibition: Clinical and molecular correlates

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Int. J. Cancer: **132**, 1711–1717 (2013) © 2012 UICC

Treatment with the mTOR inhibitor temsirolimus in patients with malignant PEComa

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Annals of Oncology May 2010

Precision Medicine and Imaging
Clinical Cancer Research

Role of Chemotherapy, VEGFR Inhibitors, and mTOR Inhibitors in Advanced Perivascular Epithelioid Cell Tumors (PEComas)

Roberta Sanfilippo[1], Robin L. Jones[2], Jean-Yves Blay[3], Axel Le Cesne[4], Salvatore Provenzano[1], Georgios Antoniou[2], Olivier Mir[4], Giovanni Fucà[1], Elena Fumagalli[1], Rossella Bertulli[1], Silvia Stacchiotti[1], Mehdi Brahmi[3], Federica Grosso[5], Armelle Dufresne[3], Nadia Hindi[6,7], Marta Sbaraglia[8], Alessandro Gronchi[9], Paola Collini[10], Angelo P. Dei Tos[8,11], and Paolo G. Casali[1,12]

Clin Cancer Res 2019;25:5295–300

ANTICANCER RESEARCH *34*: 3663-3668 (2014)

A Retrospective Study of Patients with Malignant PEComa Receiving Treatment with Sirolimus or Temsirolimus: The Royal Marsden Hospital Experience

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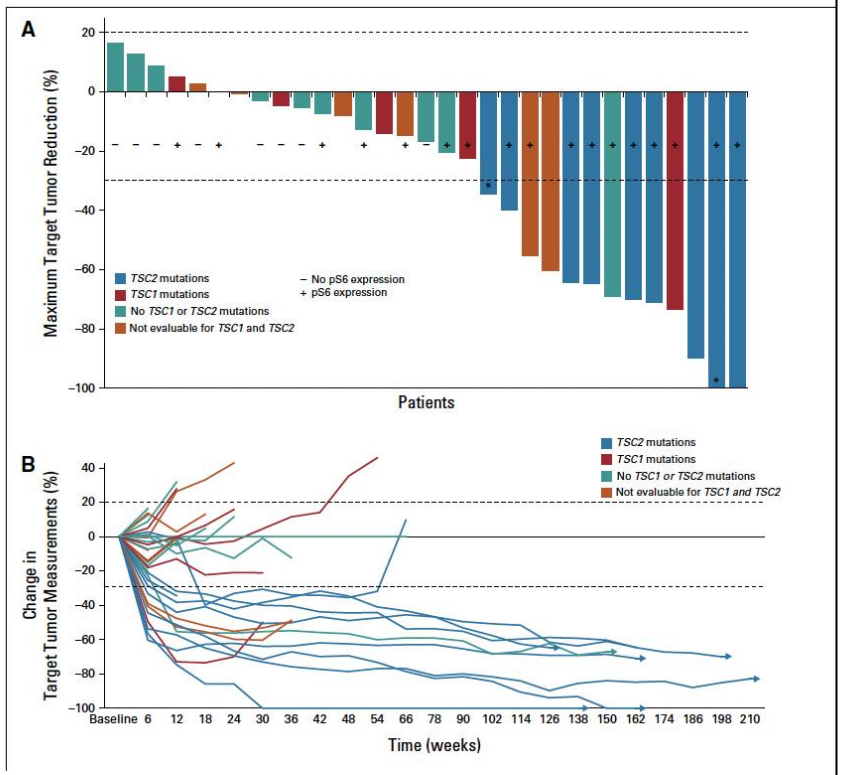
mTOR inhibitors adopted as standard approach, but no drugs registered for this purpose

Prospective study: *nab*-sirolimus in malignant PEComa

- 31 evaluable patients with advanced malignant PEComa (no prior mTORi)
- 9 sites in the US, April 2016-November 2018
- *nab*-sirolimus 100 mg/m2 d1,8 in 21d cycles
- Confirmed responses in 12/31 (39%) patients
- mPFS 10.6 mo
- mOS 40.8 mo
- mDOR not reached



Safety profile similar to oral mTORi

rapid communications abstract

nab-Sirolimus for Patients With Malignant Perivascular Epithelioid Cell Tumors

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

PURPOSE Malignant perivascular epithelioid cell tumor (PEComa) is a rare aggressive sarcoma, with no approved treatment. To our knowledge, this phase II, single-arm, registration trial is the first prospective clinical trial in this disease, investigating the safety and efficacy of the mammalian target of rapamycin inhibitor *nab*-sirolimus (AMPECT, NCT02494570).

PATIENTS AND METHODS Patients with malignant PEComa were treated with *nab*-sirolimus 100 mg/m^2 intravenously once weekly for 2 weeks in 3-week cycles. The primary end point was objective response rate evaluated by independent radiology review. Key secondary end points included duration of response, progression-free survival, and safety. A key exploratory end point was tumor biomarker analysis.

RESULTS Thirty-four patients were treated (safety evaluable), and 31 were evaluable for efficacy. The overall response rate was 39% (12 of 31; 95% CI, 22 to 58) with one complete and 11 partial responses, 52% (16 of 31) of patients had stable disease, and 10% (3 of 31) had progressive disease. Responses were of rapid onset (67% by week 6) and durable. Median duration of response was not reached after a median follow-up for response of 2.5 years, with 7 of 12 responders with treatment ongoing (range, 5.6-47.2+ months). Twenty-five of 31 patients had tumor mutation profiling: 8 of 9 (89%) patients with a *TSC2* mutation achieved a confirmed response versus 2 of 16 (13%) without *TSC2* mutation ($P < .001$). The median progression-free survival was 10.6 months (95% CI, 5.5 months to not reached), and the median overall survival was 40.8 months (95% CI, 22.2 months to not reached). Most treatment-related adverse events were grade 1 or 2 and were manageable for long-term treatment. No grade ≥ 4 treatment-related events occurred.

CONCLUSION *nab*-Sirolimus is active in patients with malignant PEComa. The response rate, durability of response, disease control rate, and safety profile support that *nab*-sirolimus represents an important new treatment option for this disease.

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ASSOCIATED CONTENT
Protocol
Author affiliations and support information (if applicable) appear at the end of this article.
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INTRODUCTION

Perivascular epithelioid cell tumors (PEComas) are mesenchymal neoplasms, composed of histologically and immunohistochemically distinctive epithelioid cells.[1,2] Most PEComas are clinically benign and do not metastasize, but malignant PEComas demonstrate local invasion and/or metastatic spread. Malignant PEComas are classified as an ultrarare soft tissue sarcoma (STS) with an estimated annual incidence of ≤ 1/1,000,000 population,[3] arise most commonly at visceral sites (especially renal, uterine, and gastrointestinal), and have a female predominance.

Malignant PEComa has no approved treatment. Although often treated with cytotoxic chemotherapy regimens, these have shown modest benefit.[4] Some patients with PEComas benefited from treatment with mTORC1 inhibitors (including sirolimus, everolimus, and temsirolimus), as described in case reports and retrospective analyses.[4-9] PEComas commonly have loss-of-function mutations in or deletions of *TSC1* or *TSC2*.[10] In addition, PEComas often show evidence of mTORC1 activation with phosphorylation of p70S6K and ribosomal protein S6 by immunohistochemistry (IHC).[11] Aberrant mTORC1 signaling is a key driver of cell proliferation and tumor formation,[12] suggesting

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Why was this approach successful?

Commonly altered pathway
+ effective/tolerable drug

Activity demonstrated by
significant tumor shrinkage

Biotech/pharma willing to conduct
study in ultra-rare disease

Question for Discussion:

In this example, reduction in size of tumors was a marker for drug activity. How do we demonstrate efficacy when tumors are controlled (but do not shrink) and when randomization is not feasible?

Thank you!

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