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Mutational analysis and safety/efficacy in a phase 2 multi-center investigation of ABI-009 (*nab*-rapamycin) in patients with advanced malignant perivascular epithelioid cell tumors (PEComa)

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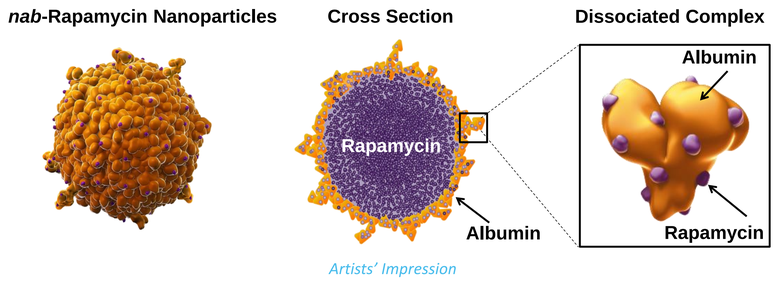
BACKGROUND

- The PEComa family is comprised of rare mesenchymal tumors that can occur in any parts of the body, most commonly in the uterus, kidney, and abdominal cavity. The most common types of PEComas are angiomyolipoma (AML), lymphangioleiomyomatosis (LAM), and benign and malignant PEComa.
- The prognosis of malignant PEComa is poor, with a median survival estimated at 12-17 months and without therapies approved for this indication.[1]
- PEComas are often associated with the loss of tumor suppressor genes *TSC1* or *TSC2* [2-3] leading to hyperactivation of the mTOR pathway, making it a promising target for treatment.[1] In a few clinical case reports, mTOR inhibitors showed evidence of activity in malignant PEComa.[4]
- This clinical study evaluating ABI-009 is the first clinical trial for patients with advanced malignant PEComa.

ABI-009



Artists' Impression

- ABI-009 is a novel albumin-bound rapamycin nanoparticle with a mean particle size of 88 nm, freely dispersible in saline.
  - Investigational agent for the treatment of a variety of diseases, in which mTOR inhibition is indicated, including oncology, hematology, and cardiovascular, metabolic, and central nervous system diseases
  - Linear pharmacokinetics (PK) over a clinically relevant dose range = predictable drug exposure with dose modification

METHODS

Study Design

Planned N = 30 evaluable patients

Patients with histologically confirmed malignant PEComa

→

Treatment Phase

ABI-009 100 mg/m^2 IV weekly for 2 weeks followed by a week of rest

Treatment until progression or unacceptable toxicity

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Quarterly Follow-up for survival and initiation of new therapy

For the Full List of Eligibility Criteria, refer to ClinicalTrials.gov: NCT02494570

Key Inclusion Criteria

- Pathologically confirmed malignant PEComa
- Metastatic or locally advanced measurable disease
- Surgery is not an option
- ≥18 yrs old
- naïve to mTORs
- ECOG PS 0,1
- Adequate biological parameters

Key Exclusion Criteria

- Lymphangioleiomyomatosis (LAM)
- Active uncontrolled CNS metastasis
- Active gastrointestinal bleeding
- Uncontrolled medical illness
- HIV, HBV, HCV
- Use of inhibitors / inducers of CYP3A4 <14 days

- **Primary Endpoint:** ORR by independent assessment, via RECIST v1.1
- **Secondary Endpoints:**
  - DOR, PFS at 6 months, median PFS, median OS:
    - Analyzed separately for those with metastatic and locally advanced disease
  - Safety
- **Exploratory Endpoints:**
  - Investigator ORR
  - PK / PD correlative analyses for safety / efficacy
  - Tumor biomarkers:
    - Blood samples: cell-free plasma DNA analysis using next-generation seq
    - Pretreatment tumor biopsy mutation analysis to assess resistance mechanism
- **Study Status** as of May 24, 2018:
  - 11 activated sites across the US
  - Of 31 screened patients, 26 enrolled, and 25 patents have been treated:
    - The main reason for ineligibility has been pathology not confirming PEComa
- **Enrollment Timeline:** FPI Apr 2016, and anticipated LPI by EO 2018
- **Evaluations, Assessments:**
  - Tumor response are assessed by CT or MRI
    - CT/MRI at baseline, then at every 6 weeks after C1D1 for the first year, then every 12 weeks thereafter
  - Safety: AEs are graded using the NCI CTCAE V4.03
  - Posttreatment follow-up for survival, new therapy initiation
- An **independent data monitoring committee** is in place for this trial
  - First DMC meeting in Apr 2017 with 14 pts enrolled revealed no concerns

OBJECTIVES

- The primary objective of this open-label, prospective, multi-center study is to investigate the efficacy of intravenous (IV) ABI-009 100 mg/m^2 given weekly for 2 of 3 weeks in advanced malignant PEComa.
- The secondary objectives are safety and to further investigate the efficacy.
- Key exploratory objectives are to evaluate tumor biomarkers and mutational status.

Statistical Considerations

- A sample size of 30 evaluable patients, assuming an observed ORR of 30%, will be sufficient to exclude an inactive regimen (<15% ORR) with 95% confidence.

Dose Modifications

Dose Level[a]	ABI-009, mg/m^2
Starting dose	100
−1	75
−2	56

- Max 2 dose reductions allowed. If an AE resolves to ≤G1, and no AEs are seen in the next cycle, the dose may be increased to the previous level.

ANTICIPATED CONCLUSIONS

- The present study, PEC-001, will determine whether ABI-009 is efficacious and safe for the treatment of malignant PEComa.
- This study may identify an effective treatment for this ultra-rare disease and add to the scant armamentarium of treatment options.
- This study may identify biomarkers that are predictive of response or resistance to therapy with ABI-009.

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