Abstract #339405

# Institutional experience with *nab*-sirolimus in patients with malignancies harboring *TSC1* or *TSC2* mutations

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## Background

- *TSC1* and *TSC2* genes encode tumor suppressors in the mTOR pathway; mutated at low frequency across tumor types (~1–2%)
  - Retrospective analyses did not show association between mutation status for *TSC1*/*TSC2*/*mTOR* and everolimus, an mTOR inhibitor (mTORi)[1]
  - In a Phase 2 study, patients with *TSC1* or *TSC2* mutations in advanced solid tumors treated with everolimus had a 7% (2/30) response rate[2]
  - In a xenograft model, *nab*-sirolimus showed significantly higher tumor accumulation, target suppression (pS6), and antitumor activity versus everolimus or sirolimus[3]
- In the AMPECT study, patients with advanced PEComa were treated with a novel mTORi, *nab*-sirolimus; the subset of patients with *TSC1* or *TSC2* mutations had a response rate of 64% (9/14)[4,5]
- Herein we report outcomes in patients with malignancies and neoplasms other than malignant PEComa bearing *TSC1* or *TSC2* mutations, treated in an Expanded Access Program (NCT03817515) with *nab*-sirolimus at 100 mg/m$^2$ given D1, D8 of a 21-day cycle

## Methods

- **Study Design:** Multi-institutional Expanded Access for an Intermediate-size Population
- **Key Eligibility:**
  - ≥18 years old, with ECOG Performance Status 0–2
  - Histologically confirmed malignant PEComa OR any other malignancy with mutation in mTOR pathway genes
- **Response Analysis:** RECIST v1.1

## Results

- Eight (8) patients with neoplasms other than malignant PEComa bearing *TSC1* or *TSC2* mutations were enrolled between Aug 2019 and Nov 2020.
- Median lines of prior therapy = 3.5

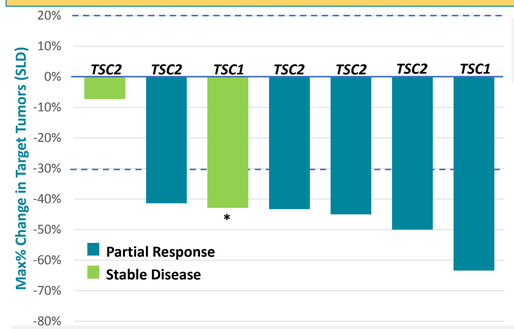
### Safety:

- Treatment-emergent AEs (≥30%) included edema, infections, mucositis, and pain (71% each), nail changes and vomiting (57% each), and hypertension and nausea (43% each). Majority of events were G1/G2
- Treatment-related SAEs were reported in 2 patients and included hyperglycemia and infection (Pt#4) and acute kidney injury (Pt#7) possibly secondary to administration of contrast
- Dose reductions occurred in 3/8 patients (38%) from 100 mg/m$^2$ to 75 mg/m$^2$

## Results *(continued)*

**Patients with various malignancies bearing *TSC1* or *TSC2* mutations, most with progression on multiple prior therapies, showed evidence of response and manageable toxicities with *nab*-sirolimus**

- **8 patients were treated, 6 were mTOR-naïve and 2 were previously treated with an mTORi; 7/8 were evaluable for response analysis:**
  - **5 patients had confirmed PR – all of them were mTOR-naïve**
  - **5 patients are still on therapy as of the data cutoff (March 2021)**

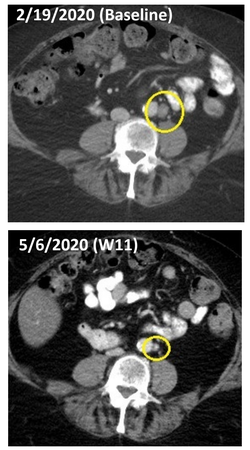



| Patient # | 5 | 1 | 4 | 7 | 8 | 6 | 2 |
|---|---|---|---|---|---|---|---|
| Disease | Endometrial Cancer | Endometrial Stromal Sarcoma | Angio-sarcoma | High-grade Sarcoma | Leiomyo-sarcoma | Lymphangio-leiomyoma | Ovarian Cancer |
| Prior mTORi | Yes § | No | No | No | No | No | No |
| Prior lines Rx | 3 | 3 | 2 | 5 | 4 | 0 | 4 |

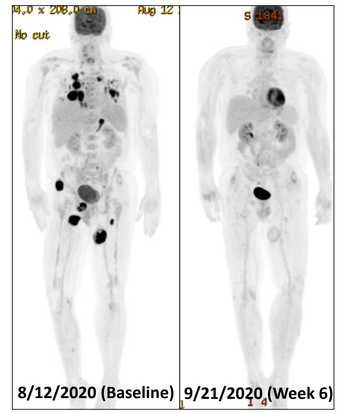
| Disease | # Prior Rx | Prior mTORi | List of Prior RX | Mut | Pt # |
|---|---|---|---|---|---|
| Endometrial Stromal Sarcoma | 3 | No | EXE, LET, FUL | *TSC2* | 1 |
| Ovarian Cancer | 4 | No | CIS+PAC, BEV, PAR, CAR, LDX+GEM | *TSC1* | 2 |
| Angiosarcoma | 2 | No | DOX+IFO+MES, PAC | *TSC1* | 4 * |
| Leiomyosarcoma | 4 | No | DOX+OLA, TRA, GEM+DOC, ERI+PEM | *TSC2* | 8 |
| Lymphangioleio-myoma ¥ | 0 | No | none | *TSC2* | 6 |
| Endometrial Cancer | 3 | Yes | ANA, LEU, SIR | *TSC2* | 5 § |
| High-grade Sarcoma | 5 | No | DOX+IFO, GEM+DOC, GEM, PAZ, PEM+DEN | *TSC2* | 7 |
| Ovarian Cancer | 6 | Yes | LDX, CAR, BEV, GEM, ENZ, MLN-0128 | *TSC2* | 3 § |

Drug Abbreviations: ANA = anastrazole; BEV = bevacizumab; CAR = carboplatin; CIS = cisplatin; DEN = denosumab; DOC = docetaxel; DOX = doxorubicin; ENZ = enzalutamide; ERI = eribulin; EXE = exemestane; FUL = fulvestrant; GEM = gemcitabine; IFO = ifosfamide; l = liposomal; LET = letrozole; LEU = leuprolide; MLN-0128 = sapanisertib (mTORi); OLA = olaratumab; PAC = paclitaxel; PAZ = pazopanib; PEM = pembrolizumab; SIR = sirolimus (mTORi); TRA = trabectidine;

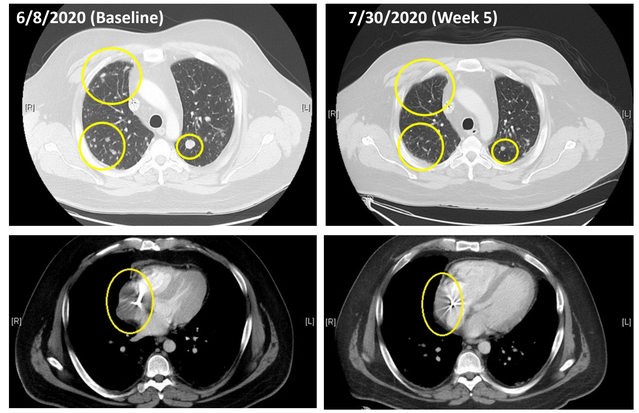
Pt #2: Ovarian Cancer with *TSC1 mutation* (4 prior lines Rx). Retroperitoneal and pelvic metastases

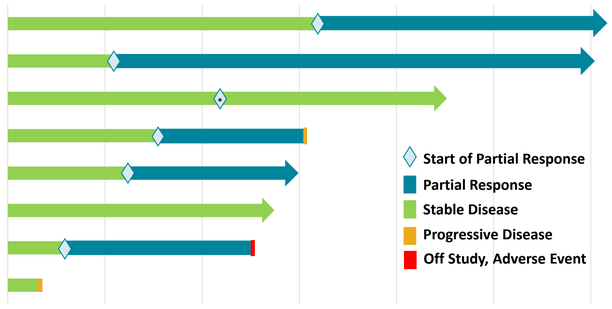



Pt #7: High Grade Sarcoma with *TSC2 mutation* (5 prior lines Rx). Metastasis to lung, bone, and soft tissue; Li-Fraumeni syndrome




Pt #4: Angiosarcoma with *TSC1 mutation* (2 prior lines Rx) involving right atrium, pericardium and with pulmonary metastasis




* After initial SD, Pt# 4 had treatment break due to infection/surgery/healing, totaling ~ 2.5 months. Subsequent imaging showed PR in target lesions along with new lesions. The patient resumed therapy with ongoing benefit

§ Progressed on mTORi prior to receiving ABI-009

¥ Pt #6 had a progressive retroperitoneal mass

## Conclusions and Future Directions

- Encouraging preliminary results in patients with *TSC1* or *TSC2* mutations
- A tumor-agnostic study of *nab*-sirolimus in MTOR-naïve patients with *TSC1* or *TSC2* mutant malignancies is planned

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**References:**

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