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nab-SIROLIMUS IN PATIENTS WITH MALIGNANT PEComa PREVIOUSLY TREATED WITH mTOR INHIBITORS: EMERGING EXPERIENCE FROM AN EXPANDED ACCESS PROGRAM

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DISCLOSURES

- My Institution receives funding from Eli-Lilly and Aadi Bioscience Inc.
- I have no other potential conflicts of interest

Background and Rationale

- In the AMPECT study, patients with malignant PEComa naïve to mTOR inhibitors (mTORi) had an independent radiology review best overall response rate of 39%, and 50% of patients had a DOR exceeding 36+ months (median not reached, 5.6 — 55.5+) on long term follow up [1]
- Preclinical models suggest that increased activity of *nab*-sirolimus over other mTOR inhibitors is related to the higher intratumoral concentrations and more complete target suppression achievable [2]
- To clinically test that hypothesis, we sought to evaluate clinical benefit of *nab*-sirolimus in patients with malignant PEComa who previously failed treatment with a prior mTOR inhibitor
- Patients were treated in an Expanded Access Program (NCT03817515) with *nab*-sirolimus at 100 mg/m^2 given on D1 and D8 of a 21-day cycle

1. Wagner et al., CTOS 2021, Abst 1080747; Hou et al., AACR Molecular Targets 2021, Abst P138

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Methods

- **Protocol Design: Multi-institutional Expanded Access for an Intermediate-size Population**

  Key Eligibility:

  - **Patients must have advanced metastatic perivascular epithelioid cell tumors (PEComa) or a malignancy with relevant genetic mutations or mTOR pathway activation**
  - **≥18 years old**
  - **ECOG Performance Status 0–2**

- **Current Analysis:**

  Patients

  - **Histologically confirmed malignant PEComa**
  - **Prior Treatment with an mTORi, except for *nab*-sirolimus**

  Data collection

  - **Mutational profile by next generation sequencing, when available**
  - **Post-hoc Response Analysis RECIST v1.1**
  - **Prior treatment history and outcome, when available**
  - **Adverse Events, when available**

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Disposition and Prior mTOR Treatment History

- Sixteen (16) patients with malignant PEComa who previously failed treatment with an mTORi were enrolled in the EAP between July 2019 and July 2021

Variable	Prior mTORi Treated Patients n = 16
Patients with Prior mTORi Rx	
1 prior mTORi	**12**
≥ 2 prior mTORi	4
Prior mTORi list : sirolimus, everolimus, temsirolimus, sapanisertib	
Patients with other therapies in addition to mTORi	**5**
Other Prior Rx list: axitinib + pembrolizumab, letrozole, gemcitabine, nivolumab + ipilimumab, bempegaldesleukin + nivolumab, pazopanib, sunitinib, gemcitabine + docetaxel	
Patients with mTORi as last therapy prior to *nab*-sirolimus	**13**
Lines of Prior Therapy, Median (Range)	**1 (1 – 6)**

- History of Treatment Failure and Prior Response History
  - 14/16 patients progressed on prior mTORi; 1/16 had intolerable toxicities; 1/16 had surgery following tumor shrinkage

- Prior Response History

Best Overall Response*	All patients n = 16	≥ 2 prior mTORi n = 4
PR	**4 (25%)**	**0**
SD	**3 (19%)**	**2 (50%)**
PD	**8 (50%)**	**2 (50%)**
NE tox	**1 (6%)**	**-**

*for pts receiving >1 prior mTORi, response is provided for last mTORi preceding *nab*-sirolimus
NE tox = pt came off for toxicity prior to any evaluation

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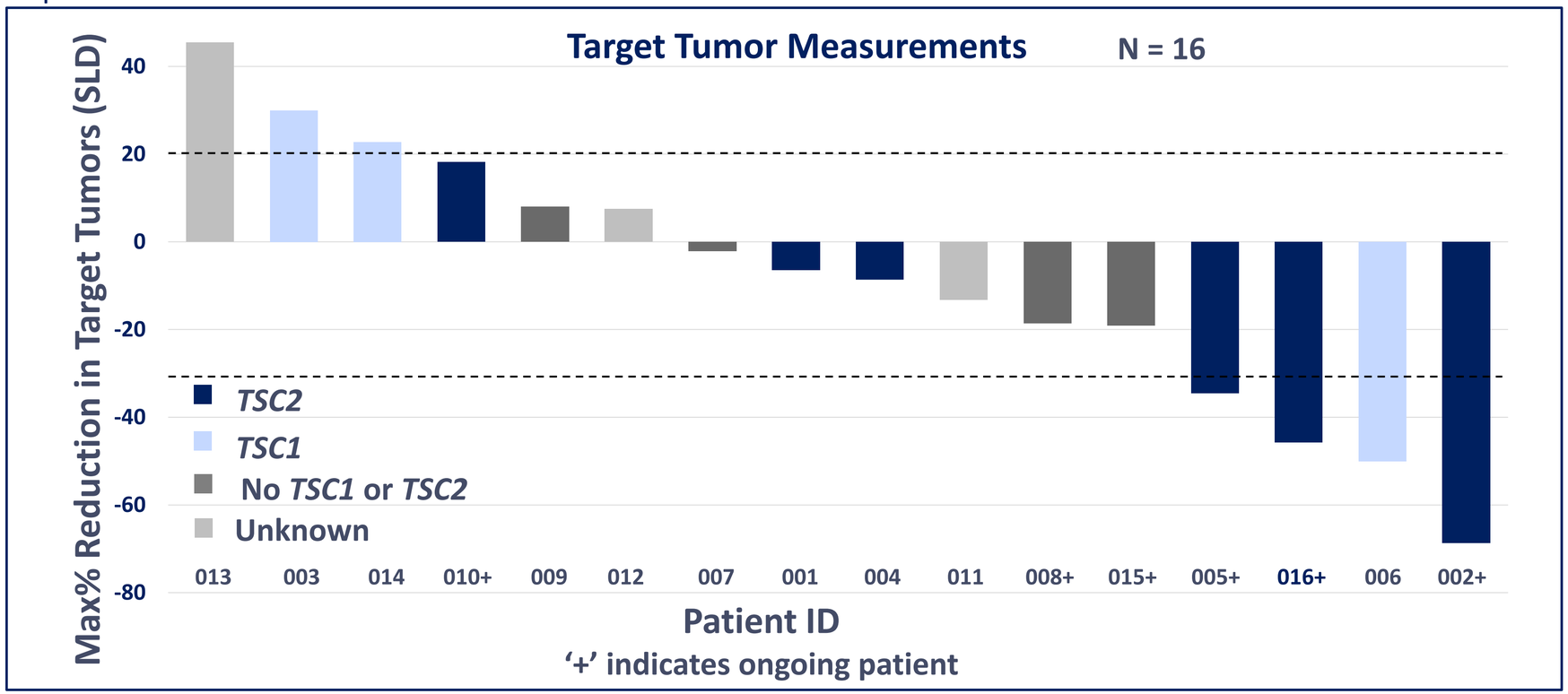
Efficacy of *nab*-Sirolimus in prior mTORi Treated Patients (N=16)

Best Overall Responses	All Patients
	N = 16
Partial Response	**4/16 (25%)**
Stable Disease	**8/16 (50%)**
Stable Disease ≥12 weeks	6/16 (38%)
Progressive Disease	**4/16 (25%)**

Best Overall Responses Patients with NGS* (N=13)	*TSC1*	*TSC2*	*Non TSC1/TSC2*
	n = 3	n = 6	n = 4
Partial Response	**1/3 (33%)**	**3/6 (50%)**	**0**
Stable Disease	**0**	**3/6 (50%)**	**3/4 (75%)**
Stable Disease ≥12 weeks	**0**	2/6 (33%)	3/4 (75%)
Progressive Disease	**2/3 (66%)**	**0**	**1/4 (25%)**

- 10/16 (63%) patients had Disease Control (CR or PR or SD ≥3 months)
- 4 *nab*-sirolimus responders:
  - BOR on prior mTORi: 1/4 SD, 2/4 PD, 1/4 NE due to toxicity
  - 2/4 had 3 prior lines of Rx

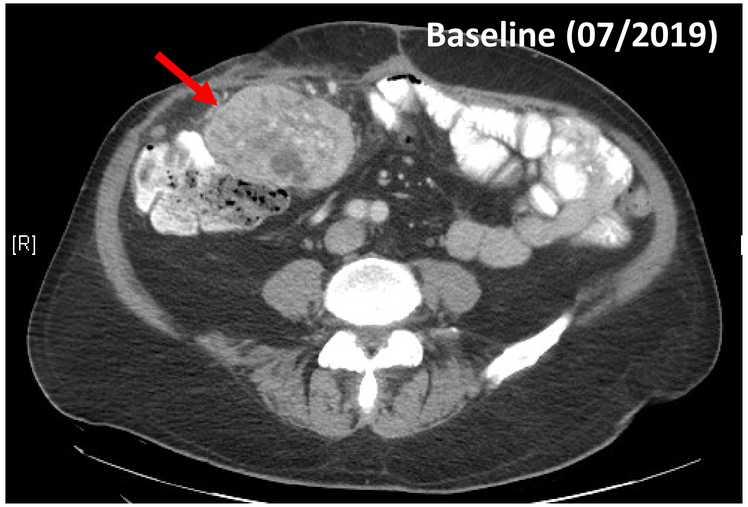
- 13 patients had available NGS reports
- Responders: 4/9 (44%) pts with *TSC1*/*TSC2* vs 0/4 with no *TSC1*/*TSC2* alterations

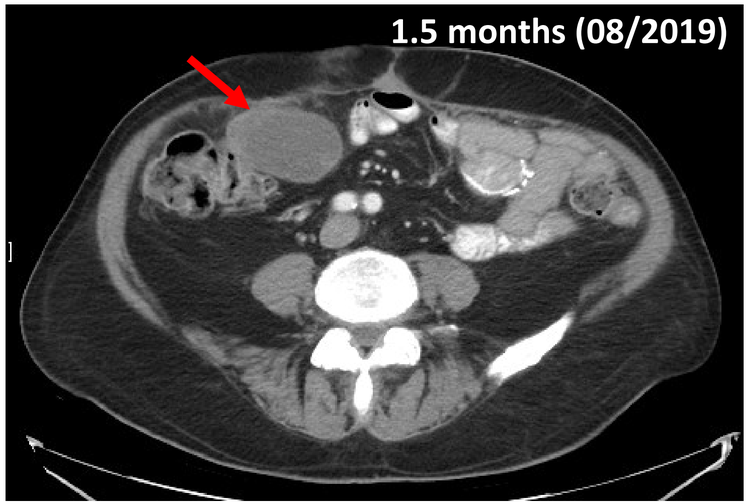


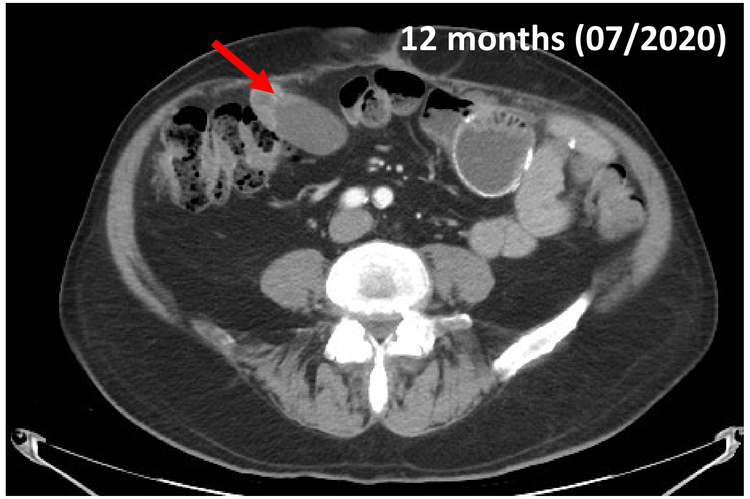
* 3 patients had Unknown mutational status; NGS reports included MSK-IMPACT, MDA Molecular Diagnostic Lab, Foundation One, Oncopanel

Tumor Response to *nab*-Sirolimus in prior mTORi Progressed Patients

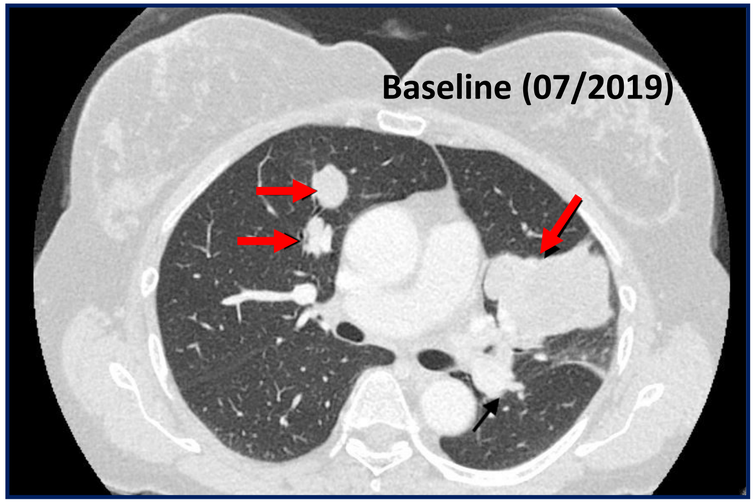
Patient #2+ *TSC2*, 68 yr old male; Primary site small bowel, metastatic to peritoneum. Progressed on 3 prior Rx (sirolimus, bempegaldesleukin + nivolumab, pazopanib). Images courtesy of Mark Dickson, MD. (Memorial Sloan Kettering Cancer Center)

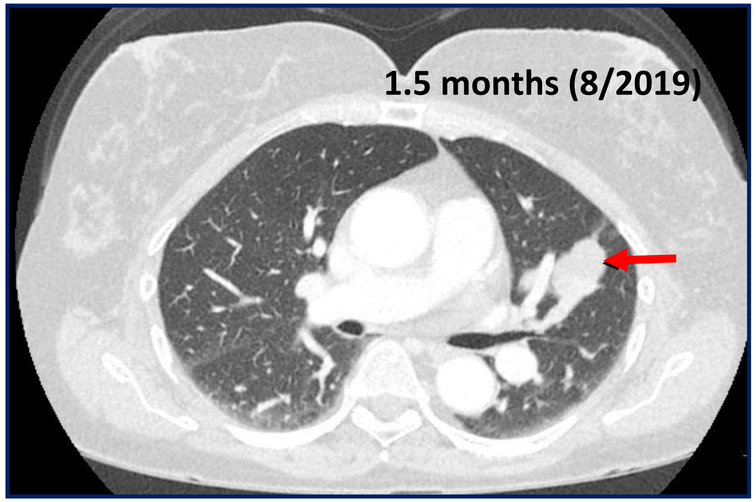






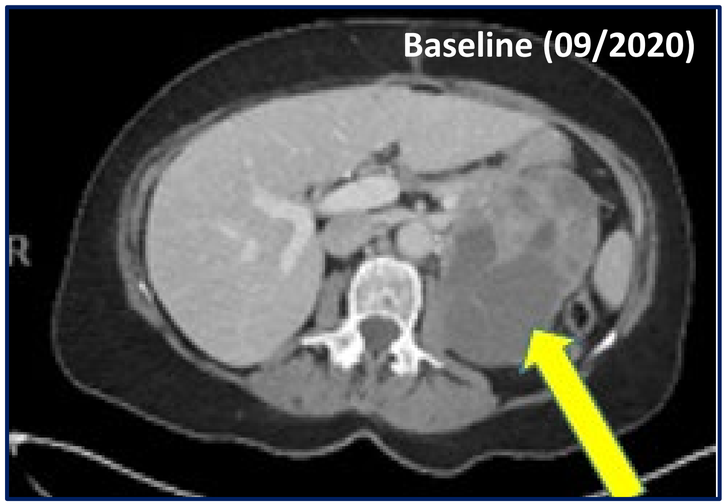
Patient #6 *TSC1*, 58 yr old female; Primary site lungs, metastatic to bilateral pulmonary nodules; Progressed on everolimus (BOR was PD)
Images courtesy of Martina Murphy, MD. (U of Florida)

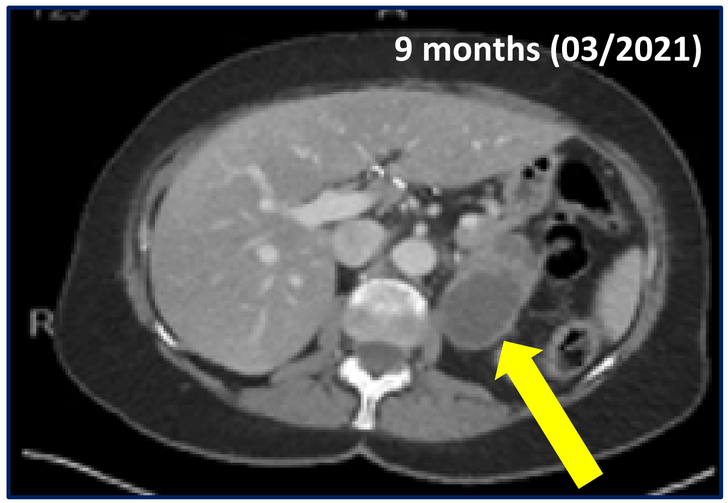




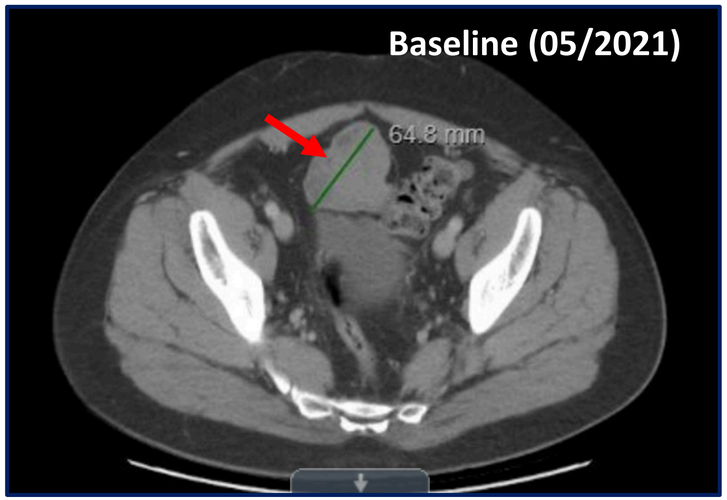
Tumor Response to *nab*-Sirolimus in prior mTORi Progressed Patients

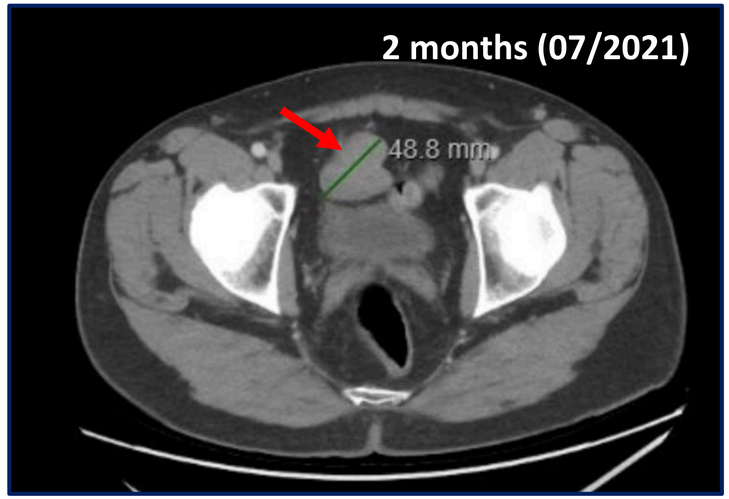
Patient #16+, *TSC2* , 67 yr old female; Primary site kidney, metastatic to abdomen. Progressed on 3 prior Treatments (sirolimus, everolimus, sirolimus)
Images courtesy of Christopher Thomas, MD. (Wake Forest School of Medicine)





Patient #8+, No *TSC1/TSC2*, 43 yr old man; Primary site pelvis, metastatic to intestines. Progressed on 3 prior Rx (evero, nivo+ipi, axitinib + pembro, sunitinib)
Images courtesy of Rashmi Chugh, MD. (U of Michigan)

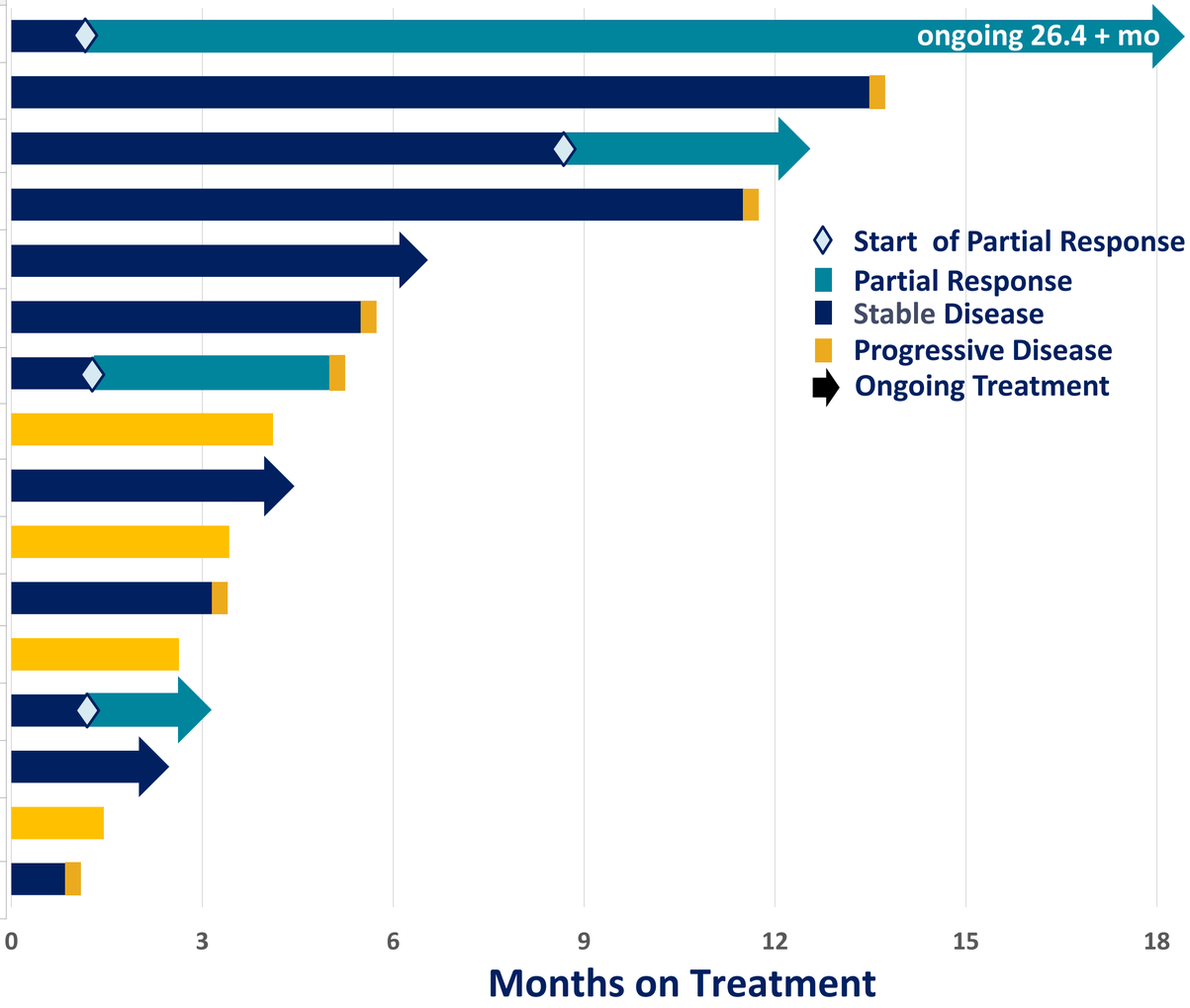




Efficacy of *nab*-Sirolimus in prior mTORi Treated Patients (N=16)

- **3/4 responding patients are still ongoing, range 2.6+ - 26.4+ months**
  - **Best response to prior mTOR : 1/4 SD, 2/4 PD, and 1/4 NE**
- **4/16 patients had >11 months of therapy with *nab*-sirolimus**
  - **Best Response to prior mTOR: 1/4 had SD and 3/4 had PD**

# Prior Rx	List of Prior Rx and Best Overall Response (BOR) for Each Line	BOR on prior mTOR*	*TSC1 / TSC2*	Patient ID
3	sirolimus (SD), bempegaldesleukin + nivolumab (tox NE), pazopanib (PD)	SD	*TSC2*	002+
4	Everolimus (PD), nivo + Ipi (PD), axitinib + pembro (PD), sunitinib (PD)	PD	*None*	007
3	Sirolimus (PR), everolimus (tox NE), sirolimus (PD)	PD	*TSC2*	016+
3	Everolimus (PD), letrozole + everolimus (PD), pazopanib (SD)	PD	*TSC2*	001
1	Everolimus (PR)	PR	*None*	015+
4	Sirolimus (tox NE), gemcitabine (NE), nivo + ipilimumab (SD), temsirolimus (SD)	SD	*TSC2*	004
1	Everolimus (PD)	PD	*TSC1*	006
1	Everolimus (PD)	PR	*TSC1*	014
1	Sirolimus (PD)	PD	*None*	008+
1	Everolimus (PR)	PR	UNK	013
1	Everolimus (PD)	PD	UNK	011
1	Everolimus (PD)	PD	*None*	009
1	sirolimus (tox NE)	NE tox	*TSC2*	005+
1	Everolimus (PD)	PD	*TSC2*	010+
3	Sirolimus (SD), ipi/nivo (PD), sapanisertib (PD), gemcitabine+docetaxel (PD), pazopanib (SD), pazopanib + sirolimus (SD)	SD	*TSC1*	003
1	Everolimus (PR)	PR	UNK	012



NE tox = pt came off for toxicity prior to any evaluation; NE = Not Evaluable; '+' indicates ongoing patient
***BOR on last mTOR if patient had >1 prior mTOR ; All patients came off of prior mTORi due to PD, except patient 005+ who had intolerable toxicities and patient 015+ who had a surgery, after which the patient had a recurrence**

Safety of *nab*-Sirolimus in prior mTORi Treated Patients (N=16)

Adverse Events in ≥10% Patients	All Grades N = 16	Grades 1-2	Grade 3
Hematologic Adverse Events			
Anemia	8 (50%)	6 (38%)	2 (13%)
Thrombocytopenia	4 (25%)	3 (19%)	1 (6%)
Nonhematologic Adverse Events			
Fatigue	5 (31%)	5 (31%)	
Rash	5 (31%)	4 (25%)	1 (6%)
Mucositis	3 (19%)	3 (19%)	
Creatinine increase	3 (19%)	3 (19%)	
Edema	3 (19%)	3 (19%)	
ALT	2 (13%)	1 (6%)	1 (6%)
Alkaline phosphate incr	2 (13%)	1 (6%)	1 (6%)
AST	2 (13%)	1 (6%)	1 (6%)
Diarrhea	2 (13%)	2 (13%)	
Hypercholesterolemia	2 (13%)	2 (13%)	
Hypertension	2 (13%)	2 (13%)	
Hypertriglyceridemia	2 (13%)	2 (13%)	
Hypokalemia	2 (13%)	2 (13%)	
Nausea	2 (13%)	2 (13%)	

Treatment-related Adverse Events (TR AE) by Frequency

- The most common (>20%) TR AEs:
  - anemia (50%)
  - rash and fatigue (31% each)
  - thrombocytopenia (25%)

- No Grade ≥4 TR AEs occurred

Treatment-related Serious Adverse Events (TR SAE) by Patient

- 5/16 (31) patients had at least 1 TR SAE: anemia, colitis, mucositis, rash, thrombocytopenia

Dose Reductions

- 4/16 (25%) patients had dose reductions including 2 patients with a PR, who maintained response
  - 3/4 were dose reduced to 75 mg/m^2
  - 1/4 was dose reduced to 30 mg/m^2

nab-Sirolimus in Patients with Malignant PEComa Previously Failing Treatment with an mTOR Inhibitor

- *nab*-Sirolimus showed encouraging clinical benefit including Partial Responses in patients previously failing other mTOR inhibitors as well as other targeted therapies in an Expanded Access Program
- Safety profile of *nab*-sirolimus appears to be acceptable and allowed ongoing treatment for approximately 1 year or more in several patients
- Partial Response occurred in 25% of patients
- Disease Control Rate (CR/PR + SD≥3 months) was 63%
- Consistent with results from AMPECT, *TSC1* or *TSC2* alterations were associated with response (4/9, 44%) despite prior progression on mTOR and/or multiple lines of prior therapy
- A tumor-agnostic study is planned for patients with pathogenic inactivating *TSC1* or *TSC2* alterations

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