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WEEKLY *nab*-SIROLIMUS IN PATIENTS WITH ADVANCED MALIGNANT PERIVASCULAR EPITHELIOID CELL TUMORS (PECOMA): RESULTS FROM AMPECT, AN OPEN-LABEL PHASE 2 REGISTRATION TRIAL WITH INDEPENDENT RADIOLOGY REVIEW

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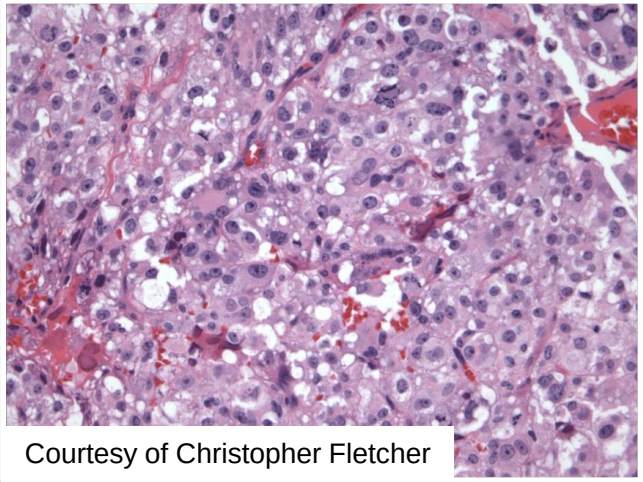
Rationale for *nab*-Sirolimus (ABI-009) for Patients with Advanced Malignant Perivascular Epithelioid Cell tumor (PEComa)

Rare sarcoma subtype with an undefined cell of origin

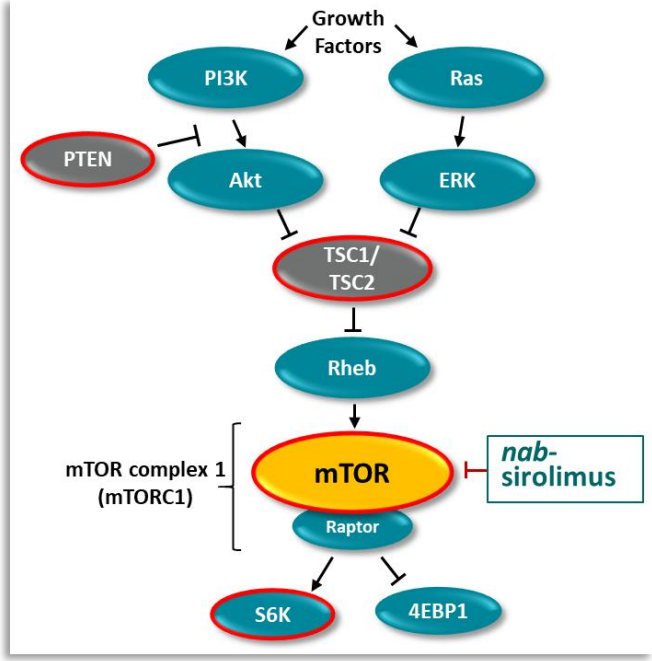
- Distinctive cells that show a focal association with blood-vessel walls [1]
- Usually express both melanocytic and smooth muscle markers [1]
- High risk of metastases [1]
- Cytotoxic chemotherapy shows minimal benefit [2]
- No drugs specifically approved for treatment of advanced PEComa



Courtesy of Christopher Fletcher

mTOR pathway activation is common in PEComa

- Case reports and retrospective reports of mTOR inhibitor treatment show substantial clinical benefit [2-6]
- PEComas can be associated with mutations (inactivation or deletions) of *TSC1* or *TSC2*, which encode negative regulators of the mTOR signaling pathway [7]

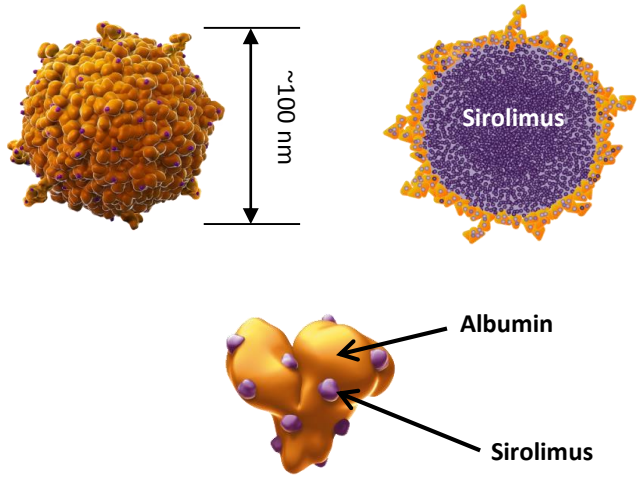


[1] Ben-Ami et al., Expert Opinion on Orphan Drugs 2018; [2] Bleeker et al., Sarcoma 2012; [3] Wagner et al., JCO 2010; [4] Dickson et al., Int J Cancer 2013; [5] Sanfilippo et al., Clin Cancer Res 2019; [6] Martignoni et al., Virchows Arch 2008; [7] Gao et al., Signal Transduction 2015

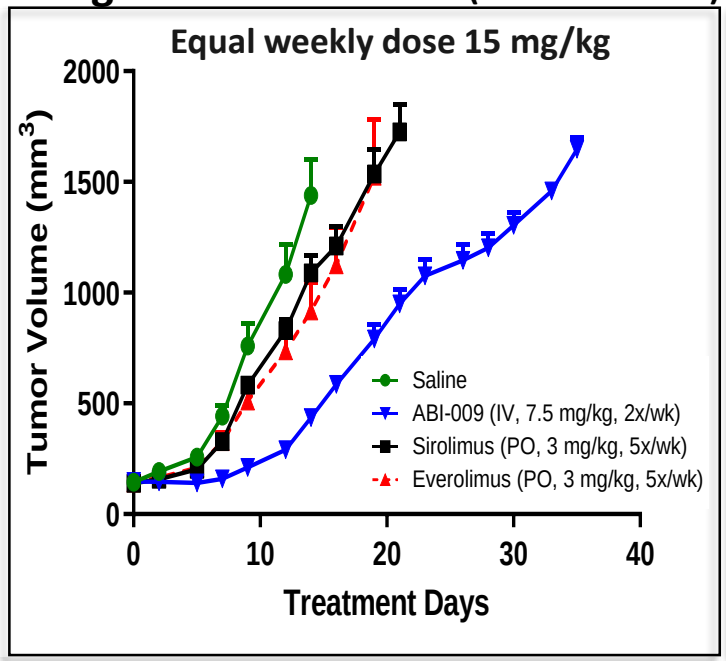
Why *nab*-Sirolimus (ABI-009)?

- Oral mTOR inhibitors have poor and variable absorption, often require therapeutic monitoring, and have incomplete target suppression
- *nab*-Sirolimus (nanoparticle albumin-bound sirolimus; ABI-009) is a novel IV 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 [1-3]

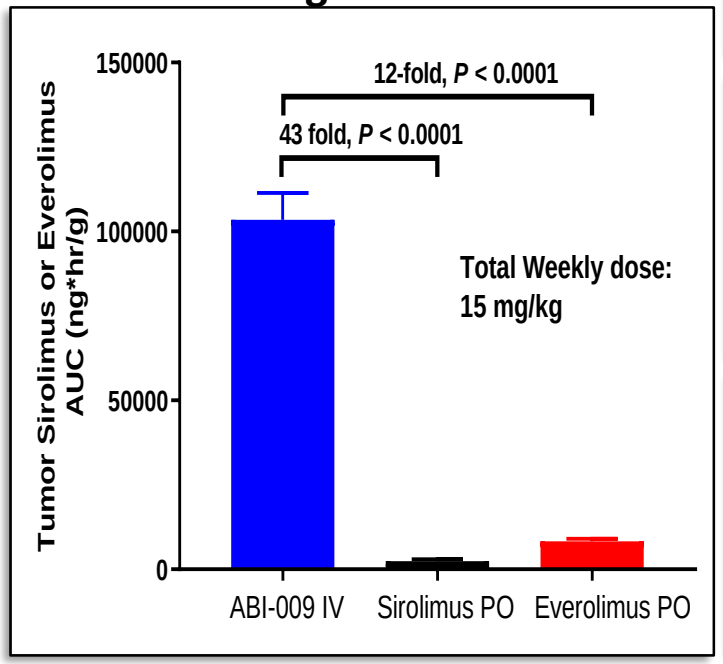
nab-Sirolimus Nanoparticle Schematic Cross Section



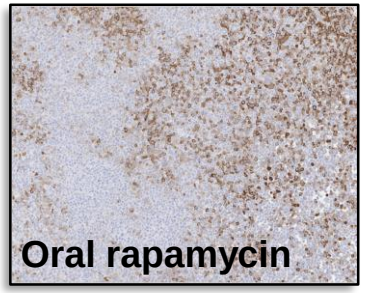
Xenograft tumor model (bladder cancer)

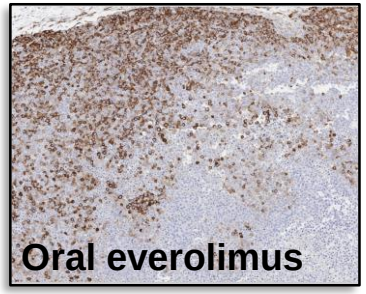


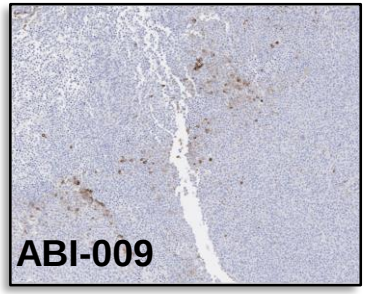
Tumor drug accumulation



Tumor IHC pS6 suppression: D7 post dose (15 mg/kg/wk)







[1] Hou et al., AACR 2019, #348
[2] Hou et al., AACR 2019, #3896
[3] Aadi Bioscience internal data

AMPECT: *nab*-Sirolimus in Advanced Malignant PEComa
Phase 2 Registrational Open-label Multicenter Study Design

Key Eligibility
- ≥18 years old
- ECOG PS 0, 1
- Histologically confirmed malignant PEComa
- Locally advanced inoperable or metastatic disease
- No prior mTOR inhibitors

ClinicalTrials.gov: NCT02494570

Treatment Phase
nab-Sirolimus 100 mg/m^2 IV D1, 8 q 21d until progression or unacceptable toxicity

Quarterly Follow-up for survival

Sample Size: ORR of ~30% in 30 evaluable patients to exclude the lower bound of the 95% CI of 14.7%

Efficacy Evaluable Patients: Must receive ≥1 dose of *nab*-sirolimus; must have centrally confirmed PEComa

- **Primary Endpoint – ORR by Independent Radiology Review**
  - CT/MRI (RECIST v1.1) every 6 weeks
- **Secondary Endpoints**
  - DOR, PFS at 6 months, median PFS, median OS
  - Safety
- **Key Exploratory Endpoints**
  - Investigator response assessment
  - Biomarkers: mutational analysis (*TSC1*/*TSC2*), pS6 (IHC)

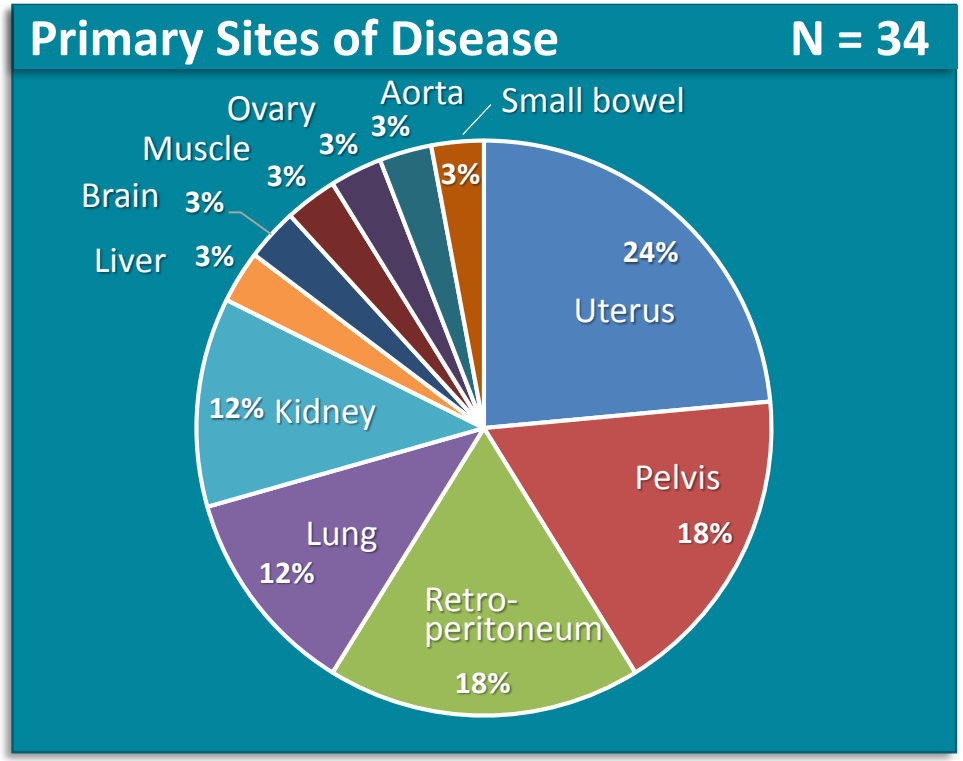
Primary analysis was prespecified to occur when all patients have had a chance to be treated for ≥6 months => Data cut on May 22, 2019

AMPECT Baseline Demographics and Characteristics

Enrollment is closed, study ongoing: 10 patients on treatment at the data cutoff of May 22, 2019

Variable	All Patients (N = 34)
Age, median (range), years	60 (27, 78)
≥65 years, n (%)	15 (44)
Female, n (%)	28 (82)
Race, n (%)	
White	24 (71)
Black	3 (9)
Asian	3 (9)
Pacific Islander/Hawaiian	1 (3)
Other/Unknown	3 (9)
ECOG 0, n (%)	26 (76)
ECOG 1, n (%)	8 (24)
Metastatic, n (%)	29 (85)
Locally Advanced, inoperable, n (%)	5 (15)
Prior Systemic Rx for Advanced PEComa,* n (%)	4 (12)

* *docetaxel, doxorubicin, gemcitabine, ifosfamide, olaratumab*



Most Common Metastatic Sites	N = 29
Lung	21 (72%)
Liver	6 (21%)
Abdomen *	8 (28%)
Pelvis	5 (17%)

* *Includes abdomen, colon, omentum, perigastric area, mesenteric root, peritoneum, serosa*

AMPECT Safety Summary, Treatment-related Adverse Events (TR AEs)

TR AEs	Any Grade >25% n (%)	Grade 3** n (%)
Patients with Any TR AEs	34 (100)	
Hematologic TRAEs		
Anemia *	16 (47)	4 (12)
Thrombocytopenia *	11 (32)	1 (3)
Nonhematologic TRAEs		
Stomatitis/Mucositis *	27 (79)	6 (18)
Rash *	19 (56)	--
Fatigue	20 (59)	1 (3)
Nausea	16 (47)	--
Diarrhea	13 (38)	--
Weight Decreased	13 (38)	--
Hyperglycemia *	12 (35)	3 (9)
Hypertriglyceridemia *	11 (32)	1 (3)
Hypercholesterolemia *	11 (32)	--
Decreased Appetite	11 (32)	--
Dermatitis*	10 (29)	--
Dysgeusia	10 (29)	--
Headache	10 (29)	--
Peripheral Edema	9 (26)	--

*Indicate Adverse Events of Special Interest and related preferred terms are grouped.
** Additional G3 TRAEs were 6% hypokalemia, and 3% each of AST/ALT, amylase ↑, hypophosphatemia, insomnia, lipase ↑, lymphocyte ↓, skin infection, vomiting .

TR Serious AEs	n (%)
Patients with Any TR SAE	**8 (24)**
Dehydration (G3)	2 (6)
Abdominal pain (G2)	1 (3)
Diarrhea (G2)	1 (3)
Edema (3)	1 (3)
Enteritis (G3)	1 (3)
Pancytopenia (G3)	1 (3)
Acute Coronary Syndrome (G3)	1 (3)
Acute Kidney Injury (G3)	1 (3)

- No grade 4 or 5 TR AEs
- No unexpected AEs
- Pneumonitis 6/34 (18%), G1/G2 only
- Discontinuation due to AE: 2/34 (6%) patients (grade 2 anemia and grade 1 cystitis)

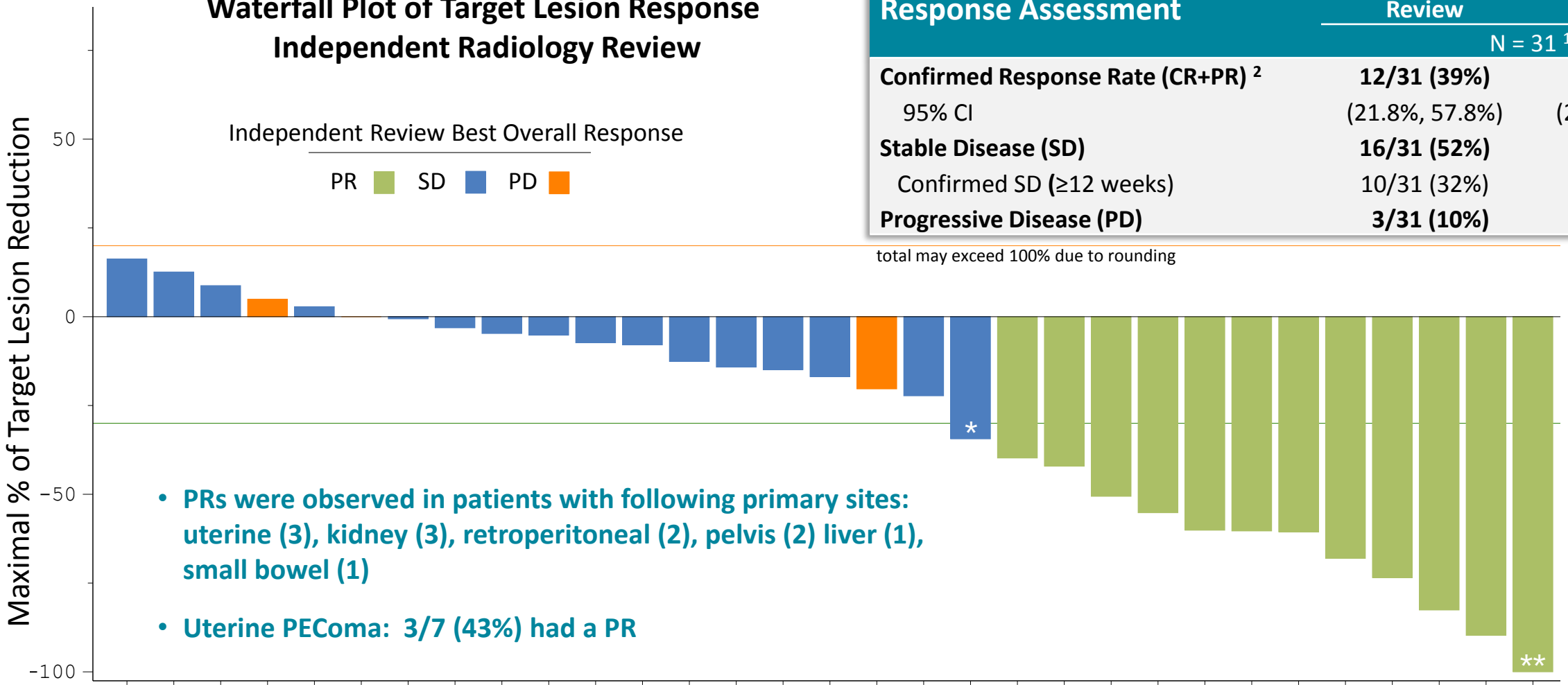
AMPECT ABI-009 Treatment Exposure

Enrollment closed in November 2018, 10/34 (30%) patients on treatment as of the data cutoff on May 22, 2019

Variable	*nab*-Sirolimus N = 34
Median Follow-up, median months (min, max)	**11.5 (1, 37+)**
Number of Treatment Cycles, median (Min, max)	**8.5 (1, 46+)**
Patients with a dose reduction, n (%) 1 dose reduction 2 dose reductions	**13 (38)** 11 (32) 2 (6)
Patients with a dose delay, n (%)	**24 (71)**
% of Protocol Dose, median mg/m^2 (min, max)	**92 (45, 100)**
Average Dose Intensity, median mg/m^2/week (min, max)*	**62 (30, 67)**

* Note, 2/3qw cycle, max dose intensity is 66.7 mg/m^2/wk

AMPECT: Response Assessment



Response Assessment	Independent Review	Investigator Review
	N = 31 [1]	
Confirmed Response Rate (CR+PR) [2]	**12/31 (39%)**	**13/31 (42%)**
95% CI	(21.8%, 57.8%)	(24.5%, 60.9%)
Stable Disease (SD)	**16/31 (52%)**	**15/31 (48%)**
Confirmed SD (≥12 weeks)	10/31 (32%)	10/31 (32)
Progressive Disease (PD)	**3/31 (10%)**	**3/31 (10%)**

total may exceed 100% due to rounding

- **PRs were observed in patients with following primary sites: uterine (3), kidney (3), retroperitoneal (2), pelvis (2) liver (1), small bowel (1)**
- **Uterine PEComa: 3/7 (43%) had a PR**

[1] 3/34 treated patients were not evaluable - 2 pts confirmed as 'not PEComa' (misdiagnosis), 1 pt had no tissue for central confirmation of PEComa

[2] All confirmed responses are PR

* 1 patient had an unconfirmed PR and thus best response is an SD as per RECIST v1.1

** Patient with CR in target lesion had a nonCR/nonPD nontarget lesion, thus overall assessment is a PR as per RECIST v1.1

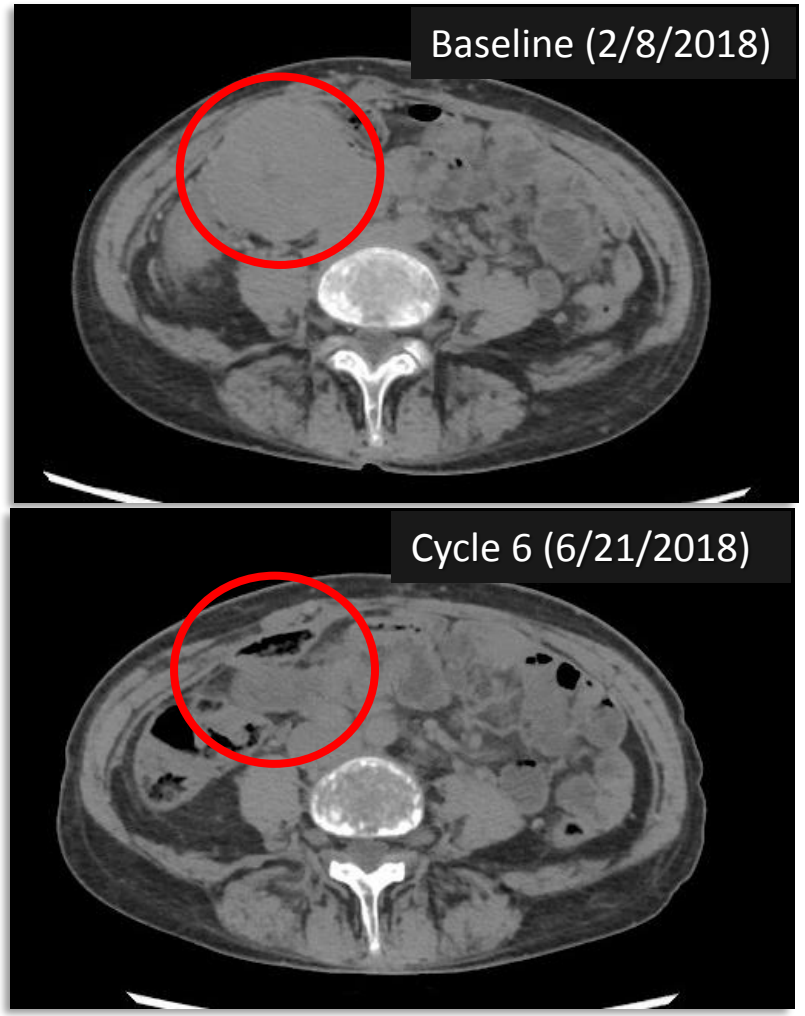
Primary Data cut on May 22, 2019

Response to *nab*-Sirolimus

Rapid and durable responses in metastatic uterine primary PEComa, a hard to treat subtype [1]

67-year old woman

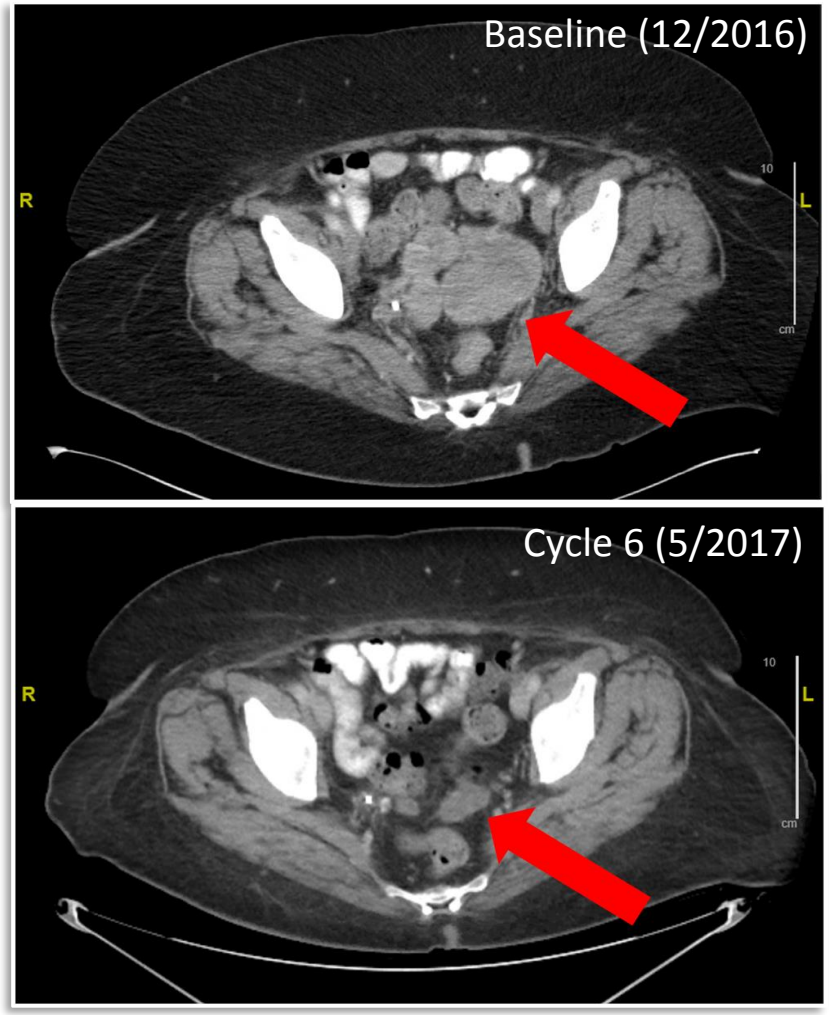
- **Primary site: Uterus; metastatic to spleen, colon, perigastric, pulmonary area**
- **PR occurred at 1st restaging (6 weeks)**
- **Patient currently on treatment (>1.5 years on therapy)**



Images courtesy of Kristen Ganjoo, MD (Stanford University)

67-year old woman

- **Primary site: Uterus, metastatic to pelvis and lung**
- **PR occurred at 1st restaging (6 weeks)**
- **Patient received 10 cycles of treatment**



Images courtesy of Andrew Wagner, MD, PhD (Dana Farber)

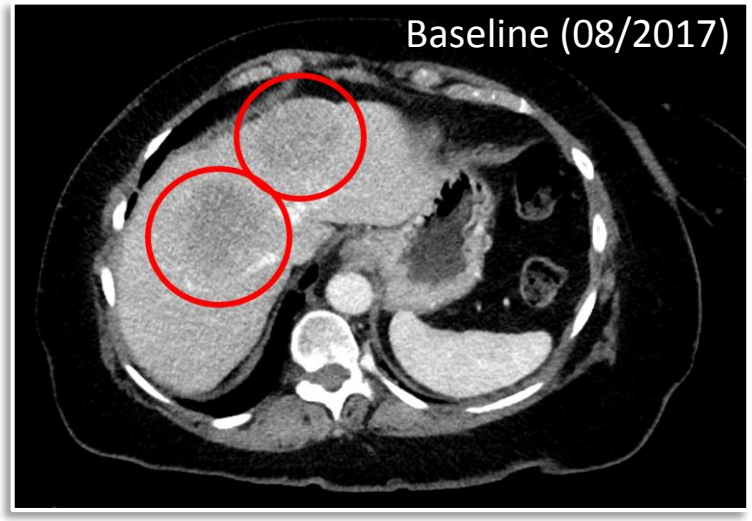
[1] Sanfilippo, 2019

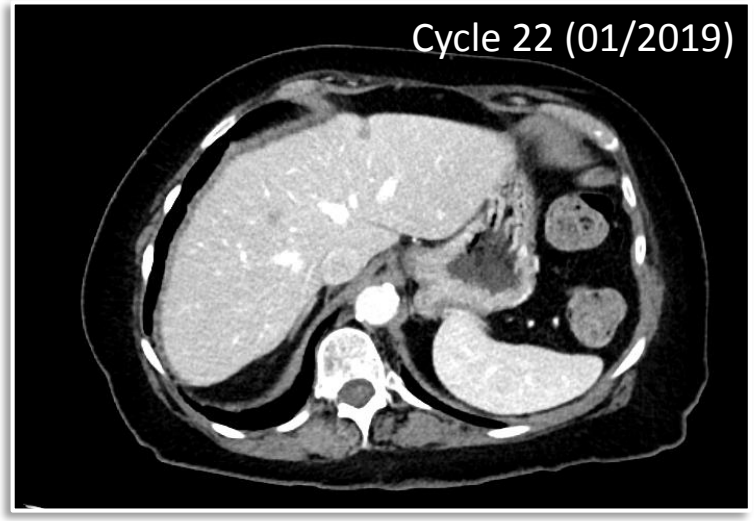
Response to *nab*-Sirolimus

Rapid and durable responses in metastatic retroperitoneal primary PEComa

70-year old woman

- **Primary site: Retroperitoneum, metastatic to lung and liver**
- **PR occurred at 1st restaging (6 weeks)**
- **Patient currently on treatment (>2 years on therapy)**

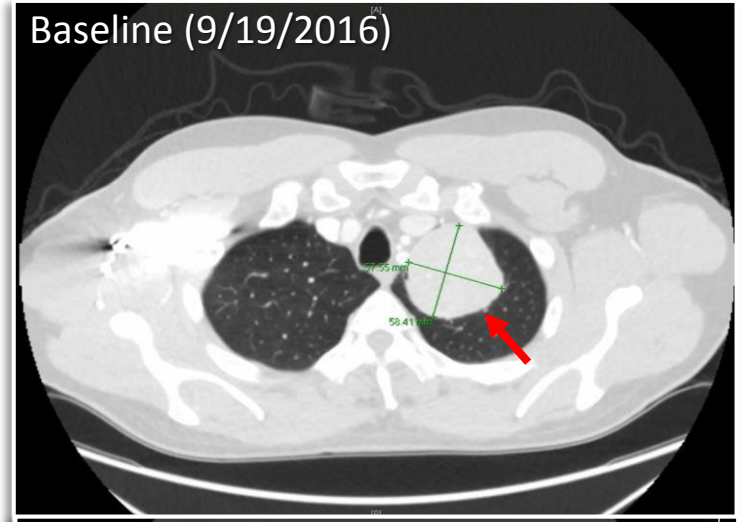


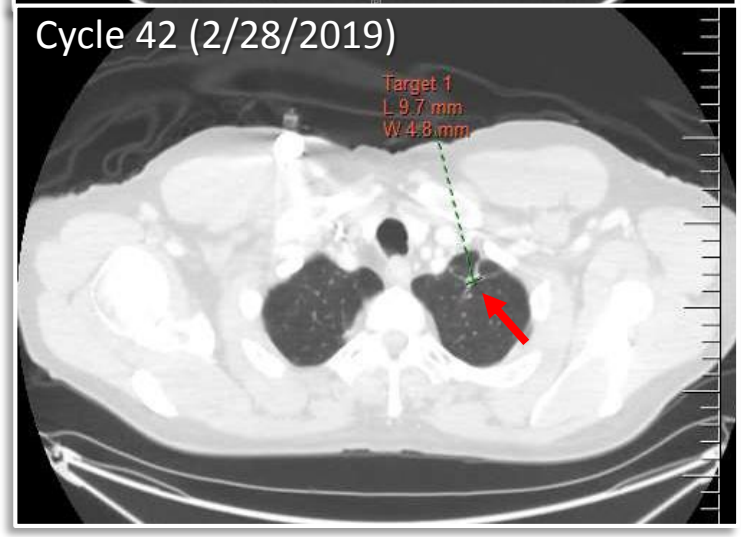


Images courtesy of Richard Riedel, MD (Duke Univ)

55-year old man

- **Primary site: Retroperitoneum, metastatic to lung**
- **PR occurred at 1st restaging (6 weeks)**
- **Patient currently on treatment (>2.5 years on therapy)**





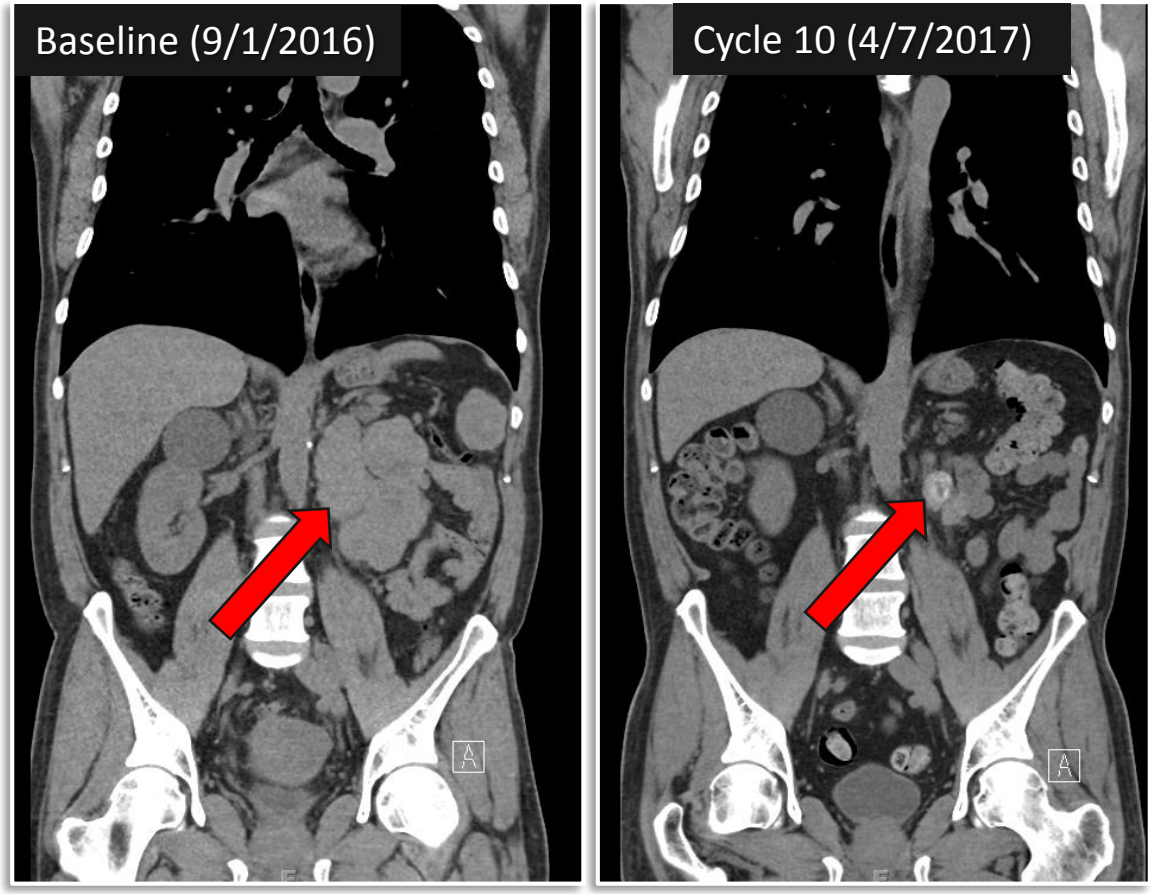
Images courtesy of Lee Cranmer, MD (Univ of Washington)

Response to *nab*-Sirolimus

Rapid and durable response in metastatic kidney primary PEComa

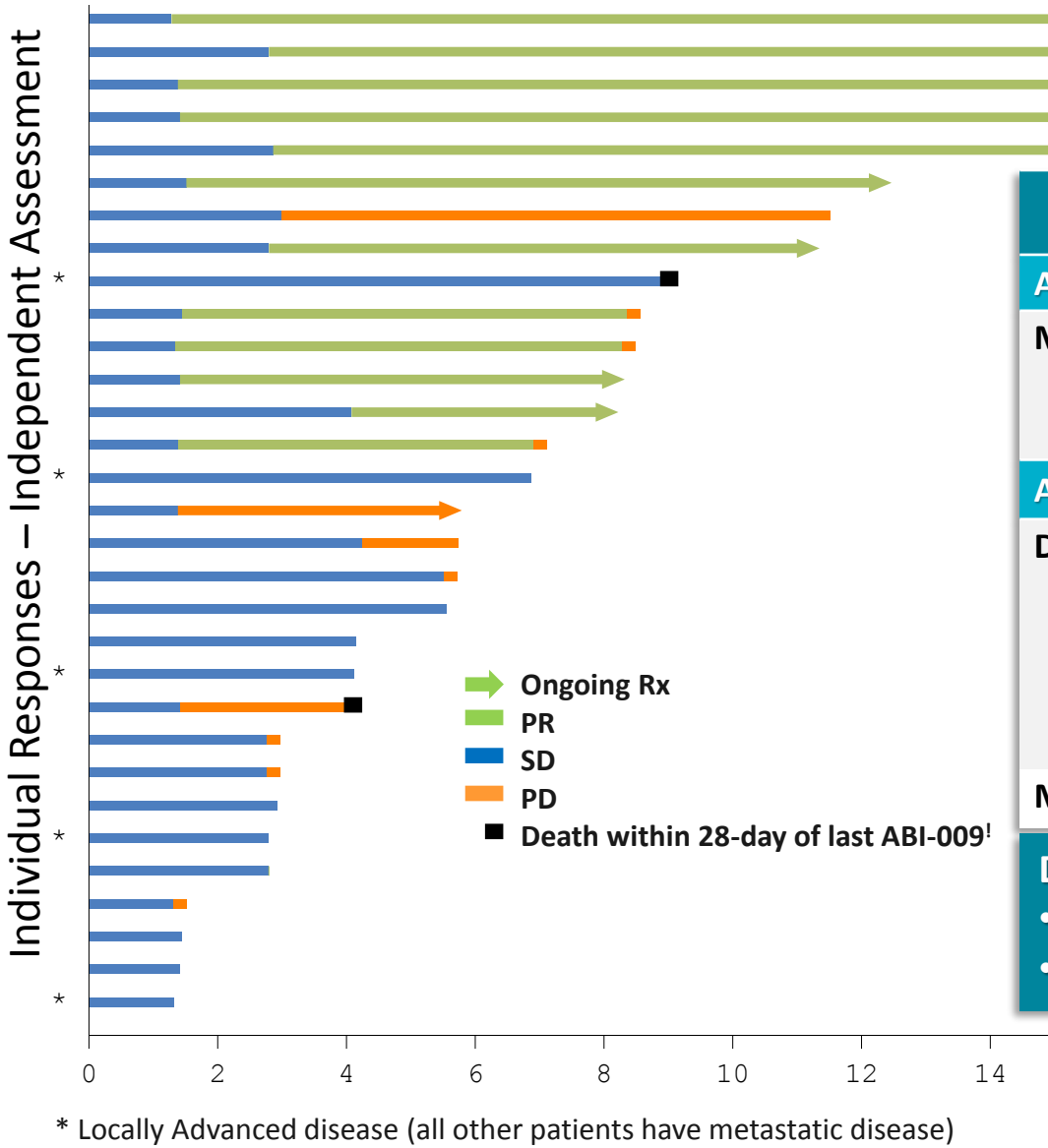
47-year old man

- **Primary site: kidney, metastatic to kidney and pelvis**
- **PR occurred at 1st restaging (6 weeks)**
- **Patient received 12 cycles of treatment**



Images courtesy of Brian Van Tine, MD (Washington University)

AMPECT: Duration of Response, Progression-free Survival, Time-to-Response, Duration of Treatment



	Independent Review	Investigator Review
All Efficacy Evaluable Patients	N = 31	
Median PFS, mo (95% CI)	**8.9 (5.5, --)**	**8.4 (5.5, --)**
PFS rate at 3-mo (PFS3)	79%	80%
PFS rate at 6-mo (PFS6)	70%	61%
All Responders	n = 12	n = 13
Duration of Response median (not reached), mo**	**15.3+**	**13.8+**
Range, mo	**(5.6, 33.2+)**	**(1.5, 33.2+)**
% with duration ≥ 6-mo	92	85
% with duration ≥ 9-mo	75	62
% with duration ≥ 12-mo	67	54
Median Time to Response (TTR), mo (range)	**1.4 (1.3, 4.1)**	**1.4 (1.3, 5.6)**

Duration of Treatment of Responders as of Nov 6, 2019

- **9/12 (75%) >1 year on treatment; 5/12 (42%) >2 years**
- **8/12 (67%) still ongoing treatment**

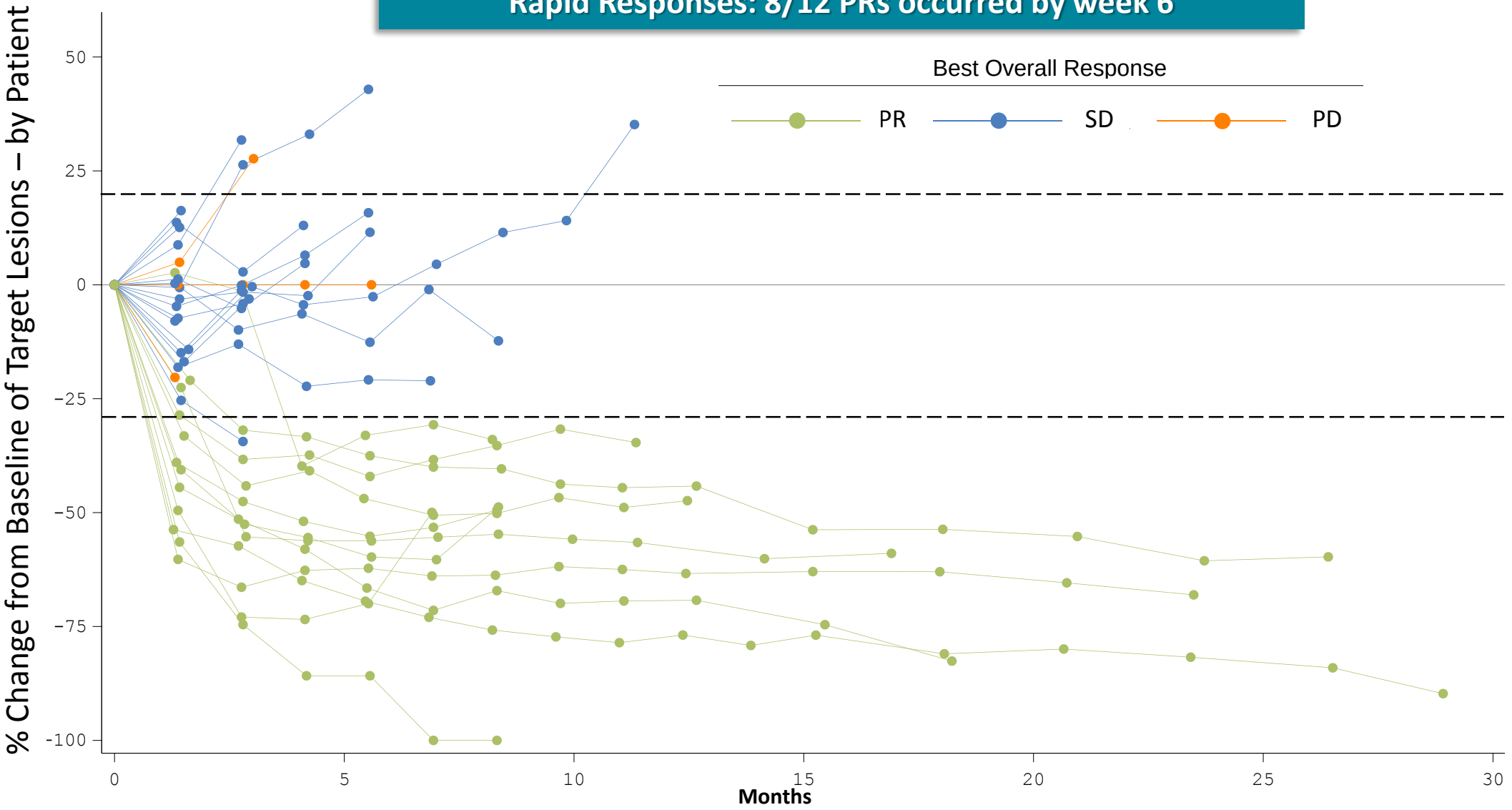
* Locally Advanced disease (all other patients have metastatic disease)

** DOR is based on additional 5.5 months follow-up (Nov 6, 2019) after the primary analysis date of ORR; ! Deaths unrelated to *nab*-sirolimus

Primary Data cut on May 22, 2019

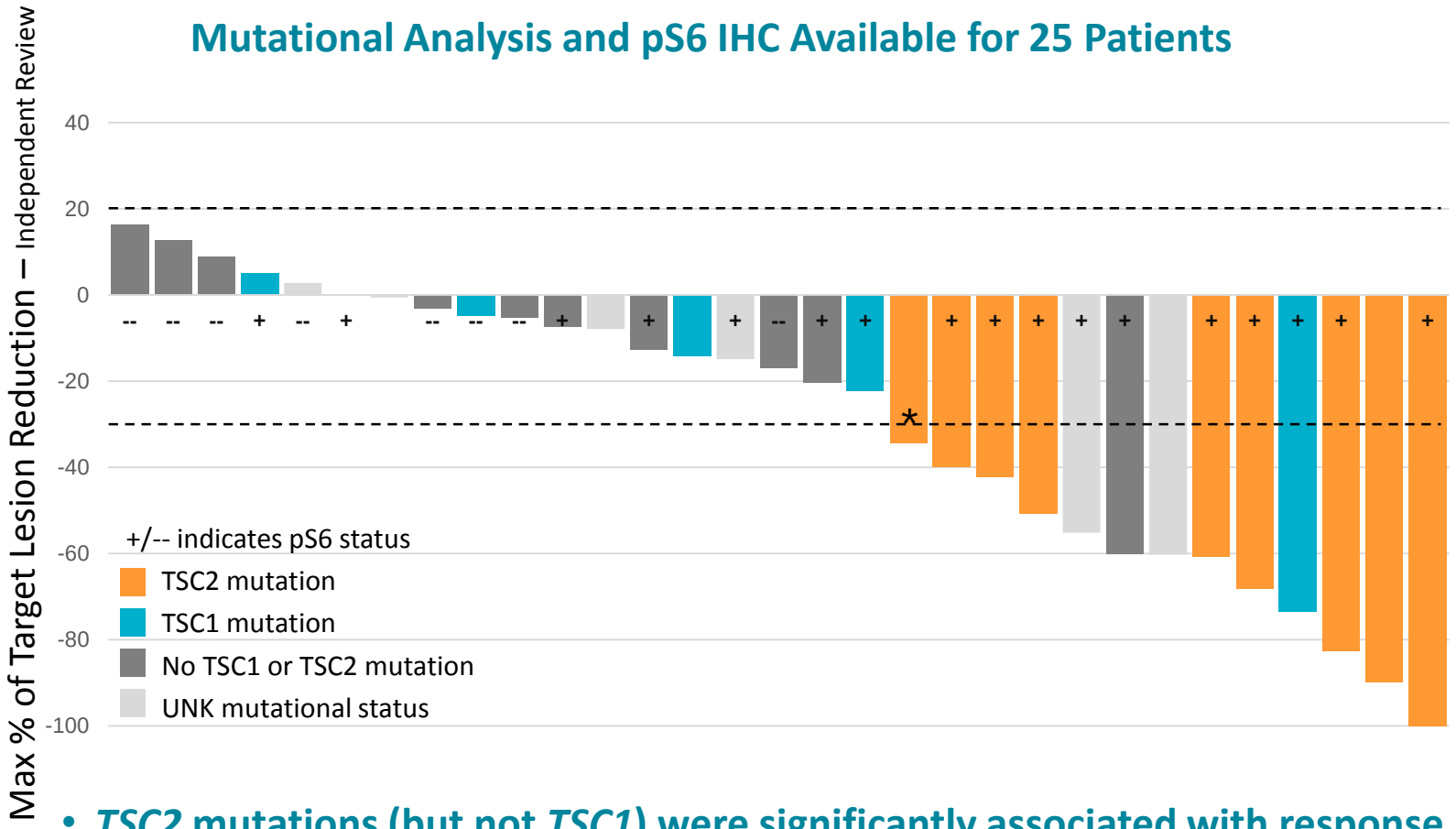
AMPECT: Independent Radiology Review Longitudinal Tumor Size

Rapid Responses: 8/12 PRs occurred by week 6



Primary Data cut on May 22, 2019

Mutational Analysis and Biomarkers
Efficacy vs TSC1/TSC2 mutations by NGS and pS6 by IHC



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%)

- ***TSC2*** **mutations (but not *TSC1*) were significantly associated with response**
- **pS6 activation was significantly associated with response; while non-activation was associated with non-response**
- **Majority (10/11, 91%) of patients with *TSC1* or *TSC2* mutations showed activation (phosphorylation) of S6**

Biomarker lab: David Kwiatkowski, MD, PhD; Brigham and Women's Hospital/Harvard Medical School

AMPECT Conclusions from the Registrational Trial: *nab*-Sirolimus in Advanced Malignant PEComa

- ***This registrational trial met its primary endpoint; the independently assessed ORR was 39% (95% CI 22% - 58%) with durable responses (50% with ongoing response duration >15.3 months) and acceptable safety profile***
- High degree of concordance between investigator and independent review of response
- No new safety signals observed despite relatively high doses of *nab*-sirolimus compared to other mTOR inhibitors
- 90% (28/31) patients had a best response PR or SD
  - Disease control (PR + SD ≥12 weeks) was achieved in 71% of patients
- High response rate (43%) in patients with primary uterine PEComa, a hard to treat subset[1]
- ***Mutational Analysis vs Response*:**
  - *TSC2* mutations: 89% (8/9 pts) confirmed ORR by independent review (1/9 pts had an unconfirmed response)
  - Lower response rate in *TSC1* mutations [(20%) 1/5 pts] or no *TSC1/2* mutations [(9%) 1/11 pts]
  - Responses also occurred in patients with unknown mutational status [(33%) 2/6 pts]
- ***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***

1. Sanfilippo et al., Clin Cancer Res 2019

Thank you to the patients and families, and to the study teams!