ABI-009 (*nab*-sirolimus) in Advanced Malignant Perivascular Epithelioid Cell Tumors (PEComa): Preliminary Efficacy, Safety, and Mutational Status from AMPECT, an Open-label Phase 2 Registration Trial

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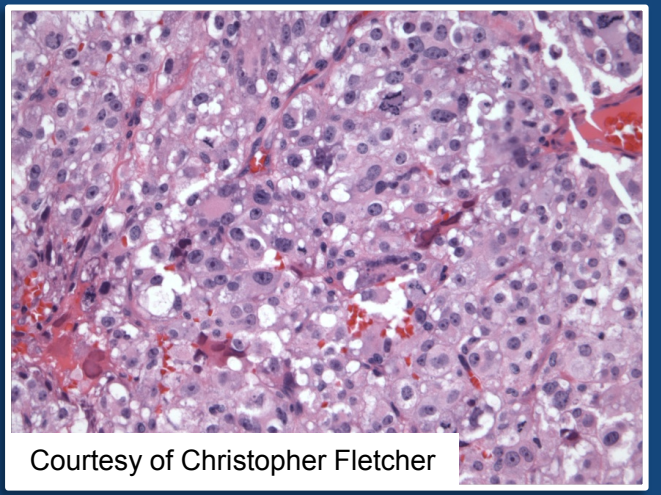
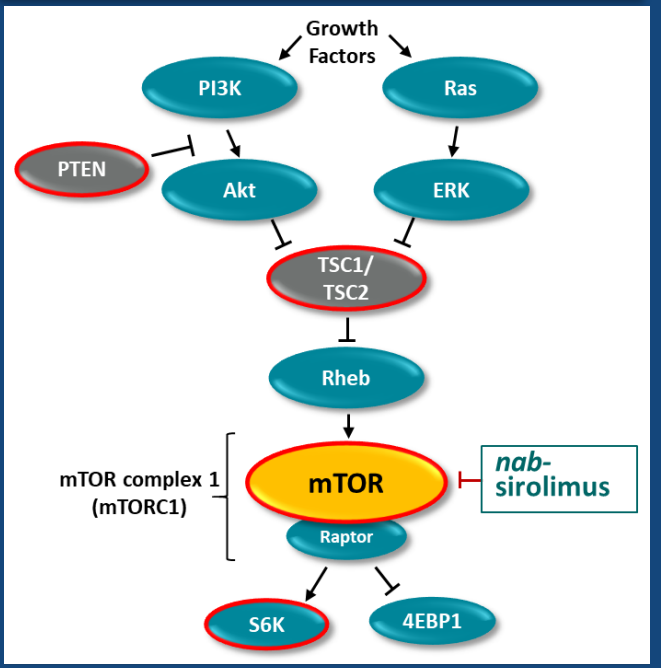
Malignant Perivascular Epithelioid Cell tumor (PEComa)

- 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]
  - Historically, cytotoxic chemotherapy shows minimal benefit[2]
  - No drugs specifically approved for treatment of advanced PEComa
- mTOR pathway activation is common[2, 3]
  - Case reports of mTOR inhibitor treatment show substantial clinical benefit[3, 4]
  - PEComas can be associated with mutations (inactivation or deletions) of *TSC1* or *TSC2*, which encode negative regulators of the mTOR signaling pathway[5,6]


Courtesy of Christopher Fletcher



[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] Martignoni et al., Virchows Arch 2008; [6] Gao et al., Signal Transduction 2015

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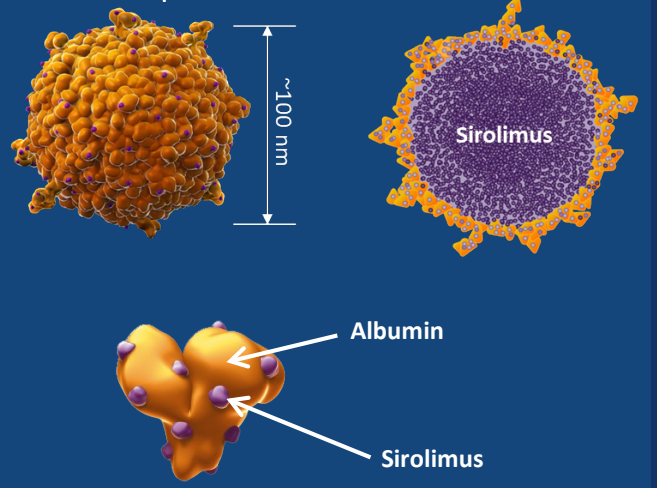
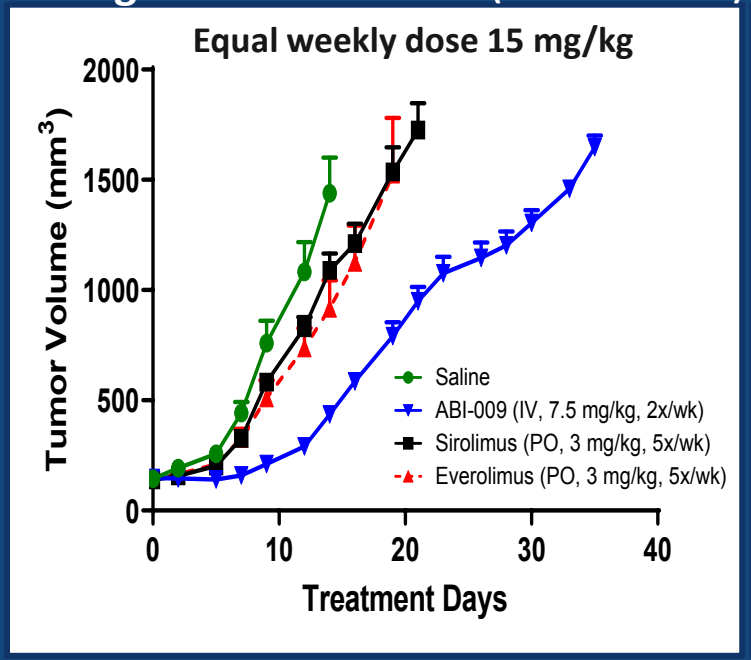
ABI-009 (*nab*-Sirolimus)

- Oral mTOR inhibitors have poor and variable absorption, often require therapeutic monitoring, and have incomplete target suppression
- *nab*-Sirolimus (nanoparticles of albumin-bound sirolimus; ABI-009) is a novel IV mTOR inhibitor with **significantly higher anti-tumor activity, intratumoral drug accumulation, and mTOR target (pS6) suppression at equal dose** vs oral mTOR inhibitors in preclinical models[1,2,3]

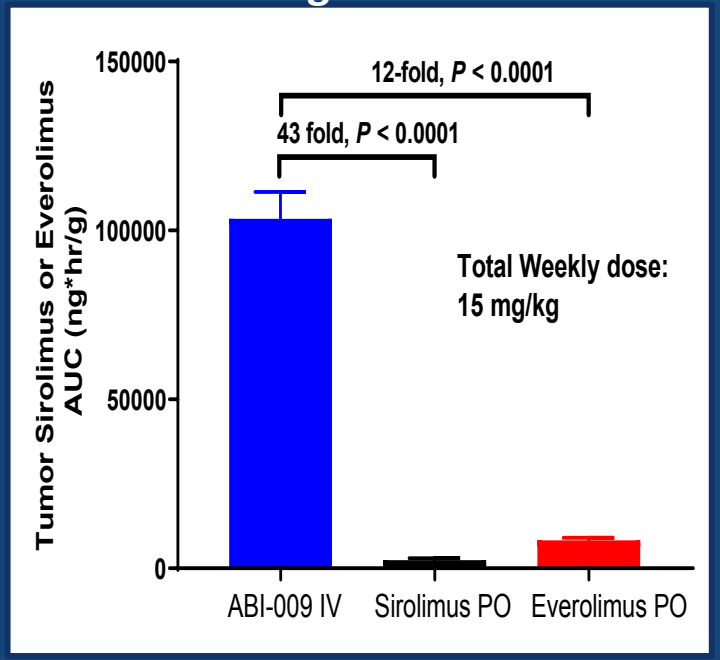
nab-Sirolimus Nanoparticle Schematic



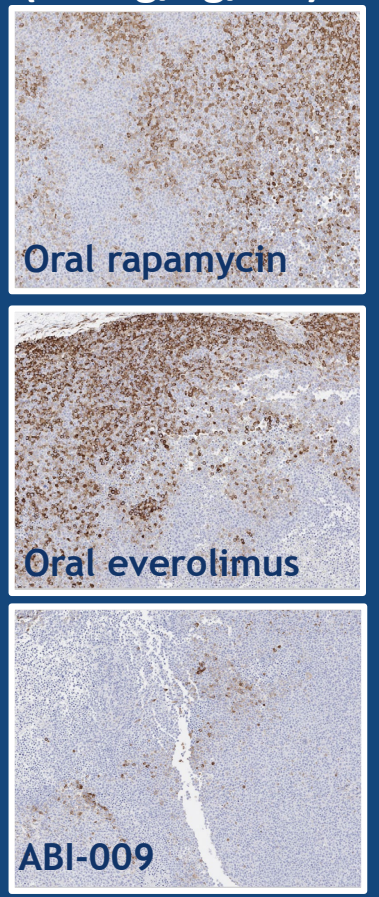
Xenograft tumor model (bladder cancer)



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

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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

Treatment Phase

nab-Sirolimus 100 mg/m² 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 assessment
  - CT/MRI (RECIST v1.1) every 6 weeks
- **Secondary Endpoints**
  - DOR, PFS at 6 months, median PFS, median OS
  - Safety
- **Key Exploratory Endpoints – *Data Presented***
  - Investigator response assessment
  - Biomarkers: mutational analysis (*TSC1*/*TSC2*), pS6 (IHC)

ClinicalTrials.gov: NCT02494570

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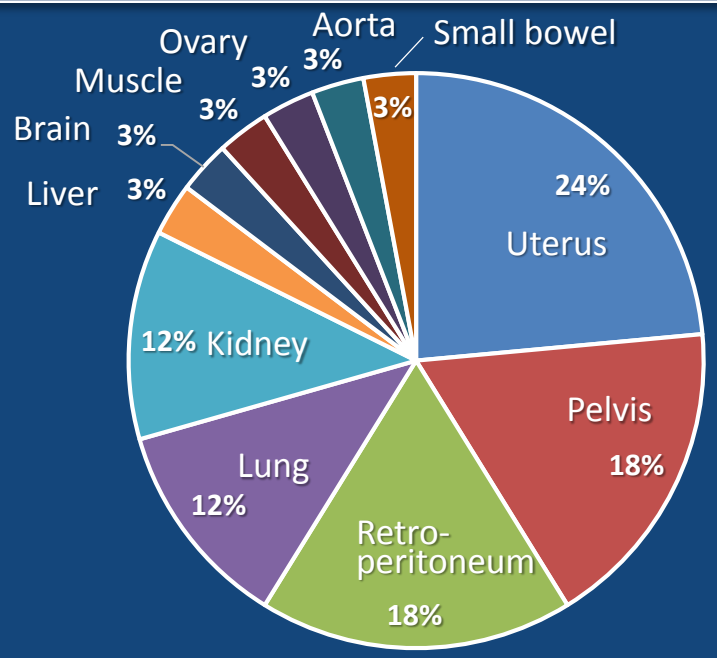
Baseline Demographics and Characteristics

Enrollment is closed, study is ongoing

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)
Other or unknown	4 (12)
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 (%)	
None	30 (88)
Any*	4 (12)

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

Primary Site of Disease N = 34



Most Common Metastatic Sites	N = 29
Lung	21 (72%)
Liver	6 (21%)
Abdomen	5 (17%)
Pelvis	5 (17%)
Peritoneum	3 (10%)

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Safety Summary, Treatment-related Adverse Events

TRAEs, N = 34	Any Grade >25%	Grade 3
Hematologic TRAEs	n (%)	
Anemia	16 (47)	4 (12)
Thrombocytopenia	11 (32)	1 (3)
Nonhematologic TRAEs		
Stomatitis/Mucositis	25 (74)	6 (18)
Dermatitis/Rash	22 (65)	--
Fatigue	20 (59)	1 (3)
Nausea	16 (47)	--
Diarrhea	13 (38)	--
Weight Decreased	12 (35)	--
Hyperglycemia	12 (35)	3 (9)
Hypertriglyceridemia	11 (32)	1 (3)
Hypercholesterolemia	11 (32)	--
Decreased Appetite	11 (32)	--
Dysgeusia	10 (29)	--
Headache	10 (29)	--
Peripheral Edema	9 (26)	--

Additional G3 TRAEs were:

- **6%: hypokalemia**
- **3% ea: AST/ALT, amylase ↑, hypophosphatemia, insomnia, lipase ↑, lymphocyte ↓, skin infection, vomiting**

SAEs in N=34	n (%)
Dehydration (G3)	2 (6)
Abdominal pain (G2)	1 (3)
Diarrhea (G2)	1 (3)
Enteritis (G3)	1 (3)
Pancytopenia (G3)	1 (3)
Acute Coronary Syndrome (G3)	1 (3)
Acute Kidney Injury (G3)	1 (3)

- **Pneumonitis 6/34 (18%), G1/G2 only**
- **No unexpected AEs**
- **No grade 4 events**
- **7/34 (21%) patients had a SAE related to treatment**
- **12/34 (35%) patients had a dose reduction for an AE**
- **2/34 (6%) patients had an AEs that resulted in discontinuation**

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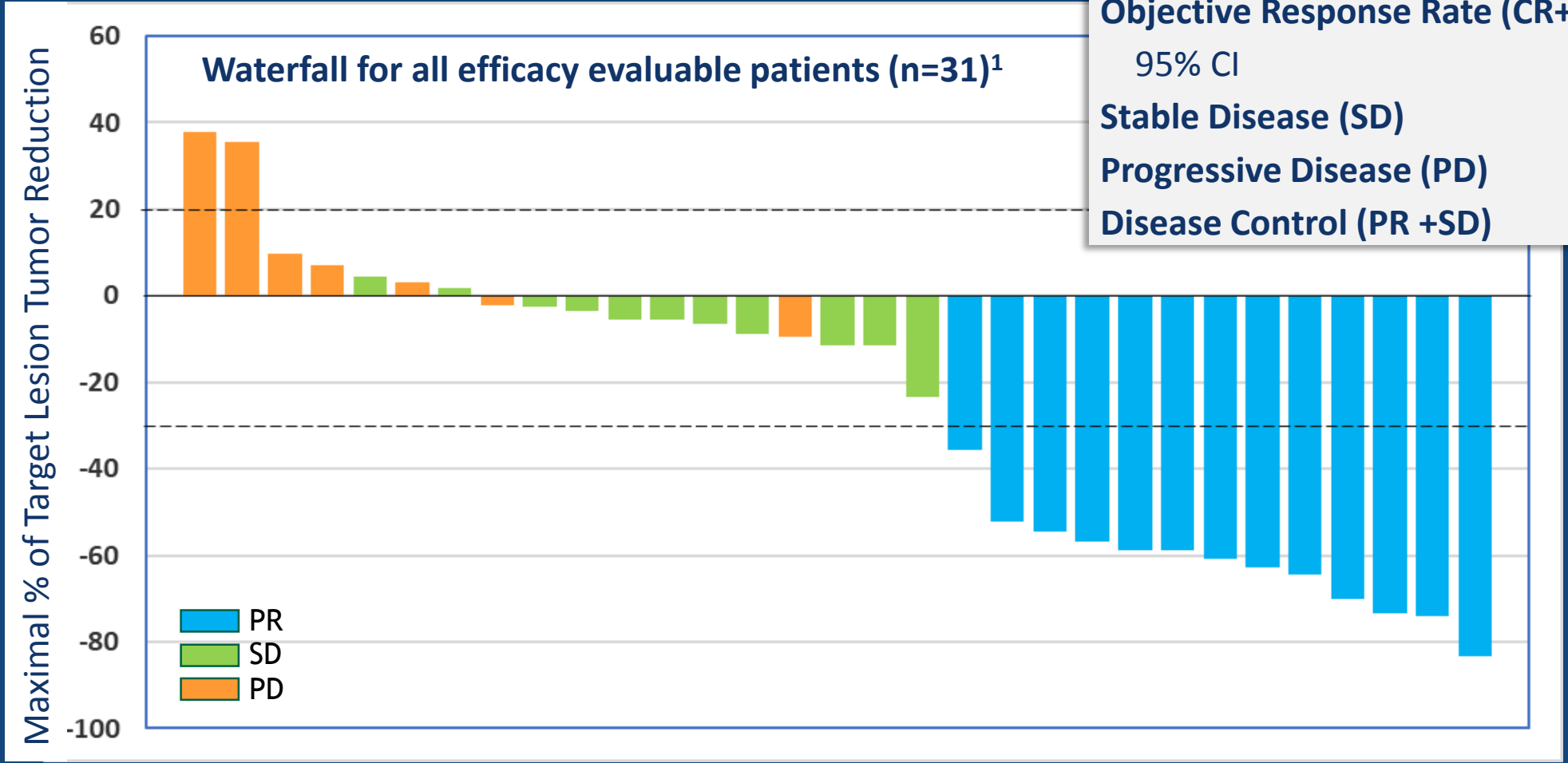
Efficacy Summary, Investigator Assessed Responses

Response Assessment	All patients [1] (N = 31)
Objective Response Rate (CR+PR)[2]	13/31 (42%)
95% CI	(24.5%, 60.9%)
Stable Disease (SD)	11/31 (35%)
Progressive Disease (PD)	7/31 (23%)
Disease Control (PR +SD)	24/31 (77%)



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

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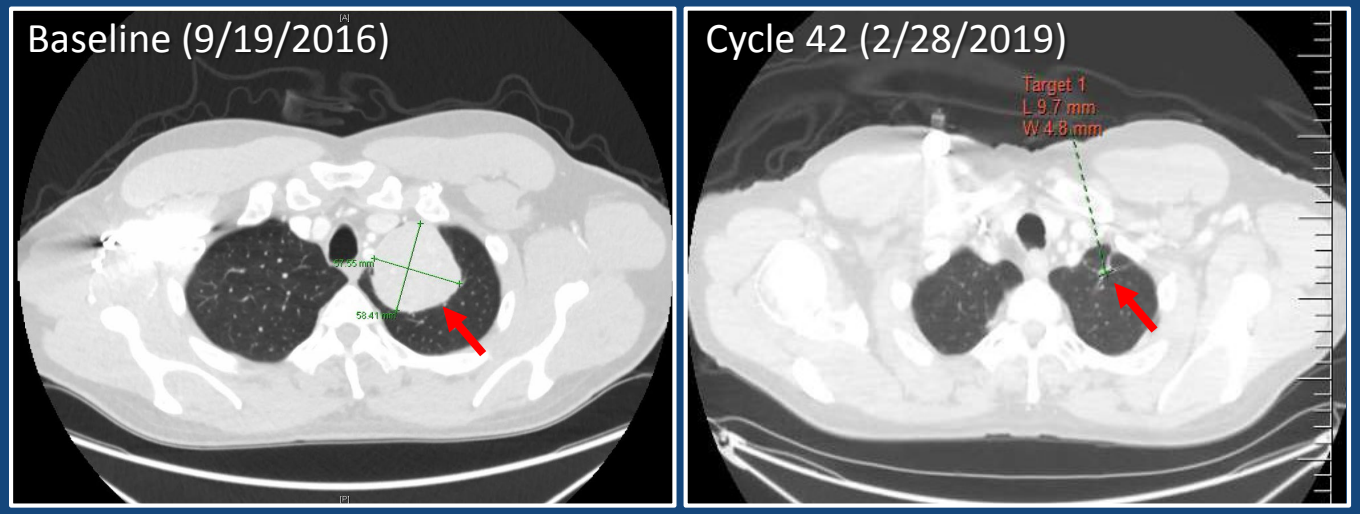
Response to *nab*-Sirolimus

55 yr old man

Primary site: Retroperitoneum, metastatic to lung

PR occurred at 1st restaging (6 weeks)

Pt currently on treatment (>2 yr on therapy)

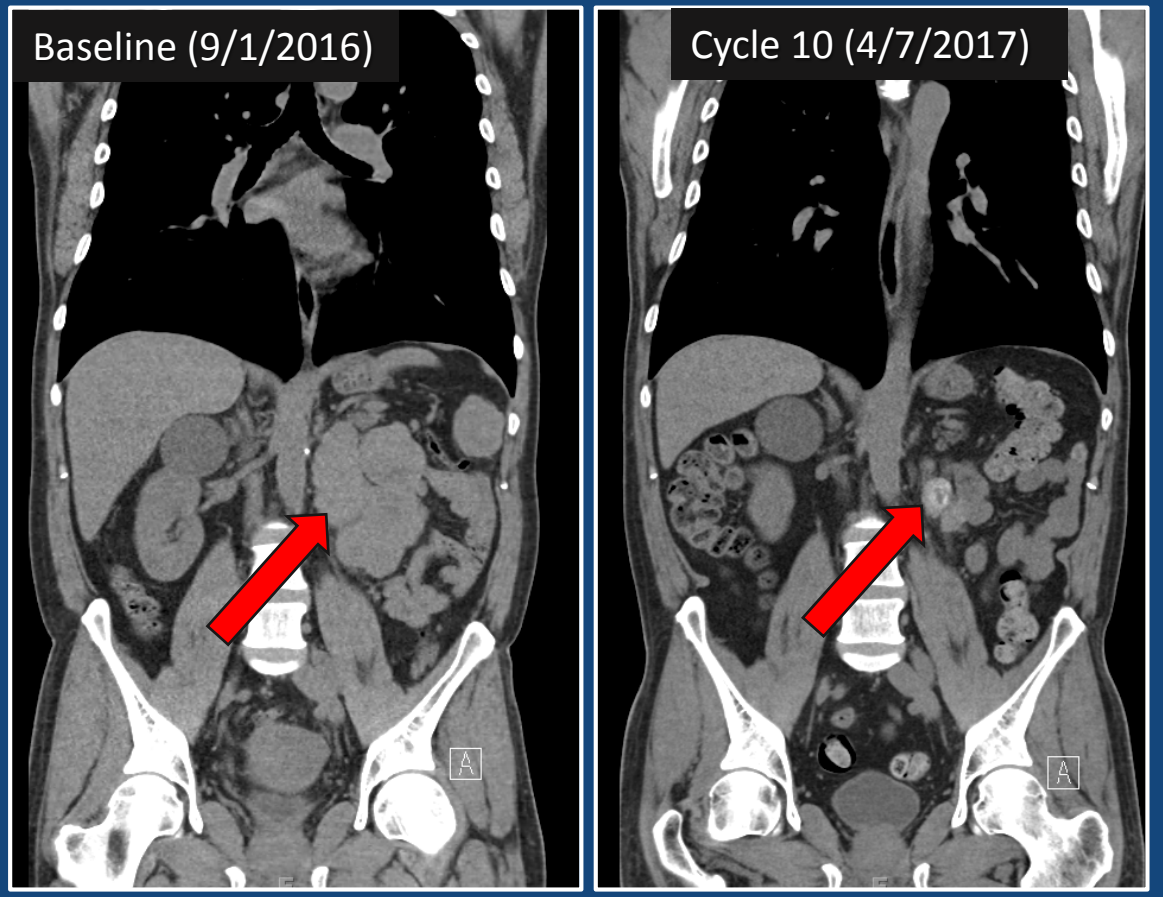


Images courtesy of Lee Cranmer, MD (Univ of Washington)

47 yr old man

Primary site: kidney, metastatic to kidney and pelvis

PR occurred at 1st restaging (6 weeks)



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

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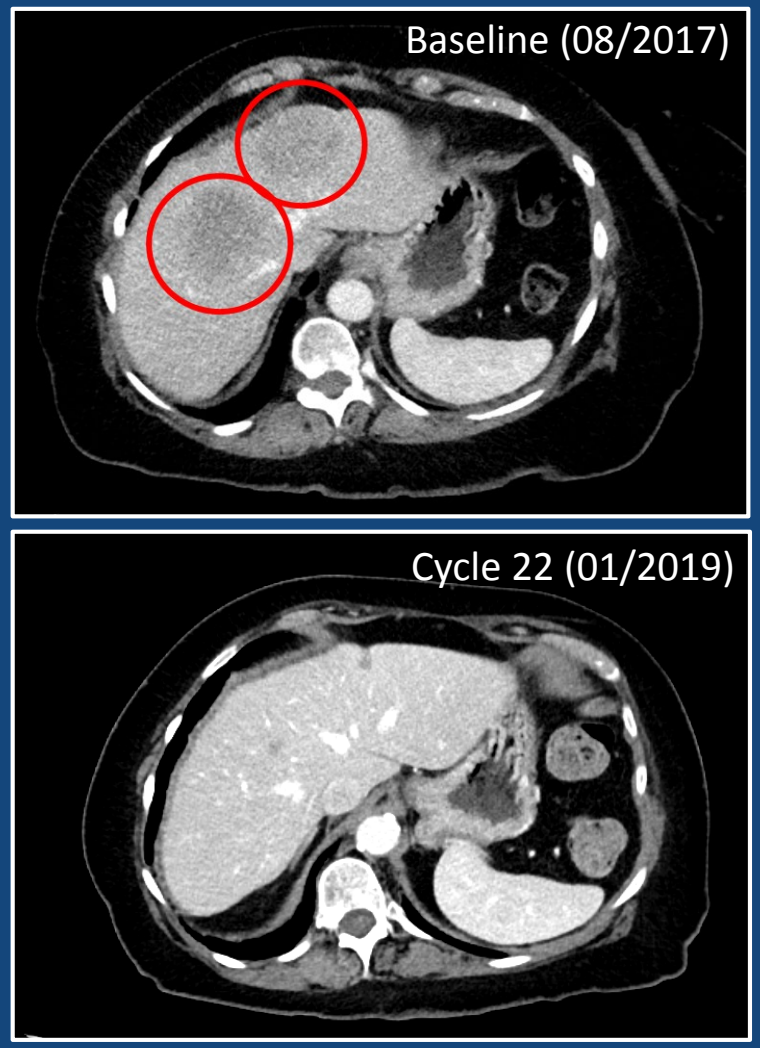
Response to *nab*-Sirolimus

70 yr old woman

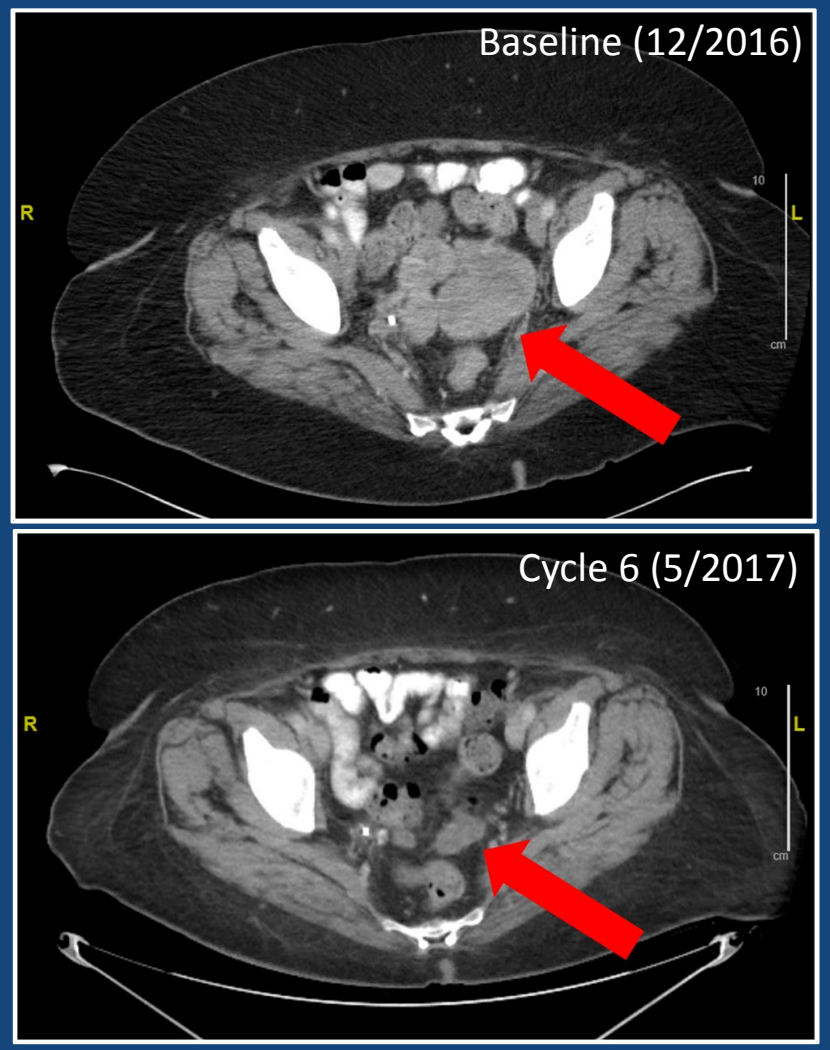
Primary site: Retroperitoneum, metastatic to lung and liver

PR occurred at 1st restaging (6 weeks)

Pt currently on treatment (>1 yr on therapy)



Images courtesy of Richard Riedel, MD (Duke Univ)



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

67 yr old woman

Primary site: Uterus, metastatic to pelvis and lung

PR occurred at 1st restaging (6 weeks)

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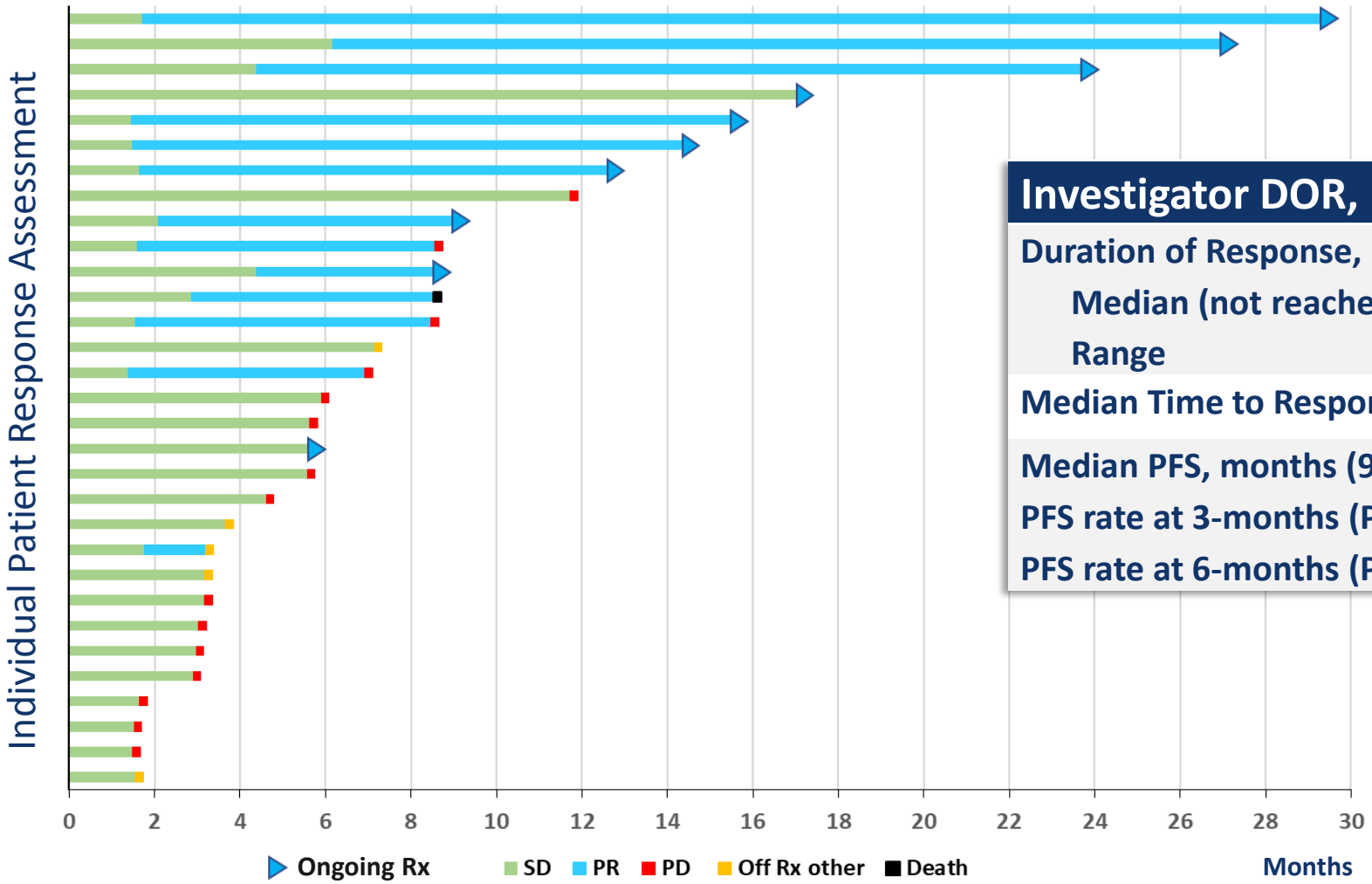
Duration of Response, Time to Response, Progression-free Survival



Investigator DOR, PFS, and TTR	N = 31
Duration of Response, months (95% CI)	
Median (not reached)	-- (6.2, --)
Range	1.5, 27.7+
Median Time to Response (TTR), months (95% CI)	1.4 (1.3, 2.7)
Median PFS, months (95% CI)	8.4 (5.5, --)
PFS rate at 3-months (PFS3), rate (95%CI)	80% (60.4%, 90.4%)
PFS rate at 6-months (PFS6), rate (95% CI)	61% (40.6%, 76.4%)

- 8/13 (62%) PR still ongoing
  - 3 pts ongoing tx >1yr and 3 pts >2 yrs
- 2/7 SD >11 months on therapy

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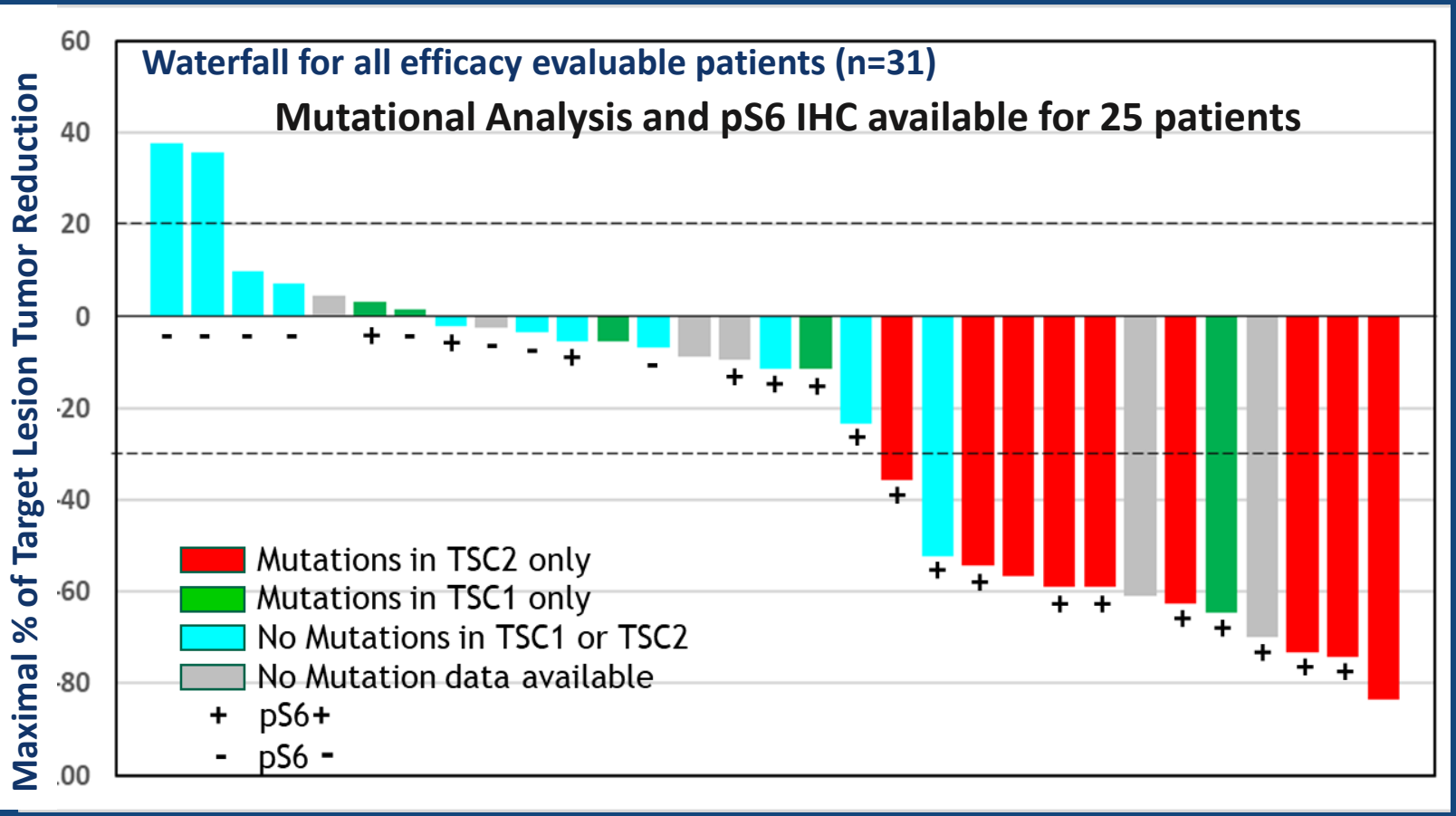
Mutational Analysis and Biomarkers

Efficacy vs *TSC1/TSC2* mutations/deletions by NGS and pS6 by IHC



TSC1/TSC2 Mutational Analysis N = 25	Responders (PR) n = 11	Non-responders (SD+PD) n = 14
TSC2 (n=9)	9/9 (100%)	0
TSC1 (n=5)	1/5 (20%)	4/5 (80%)
No *TSC1* or *2* (n=11)	1/11 (9%)	10/11 (91%)
		P < 0.0001 (2x3 Fisher)
Unknown status (n=6)	2/6 (33%)	4/6 (66%)

pS6 IHC N = 25	Responders (PR) n = 10	Non-responders (SD+PD) n = 15
pS6 + (n=17)	10/17 (59%)	7/17 (41%)
pS6 - (n=8)	0	8/8 (100%)
		P = 0.0077 (2x2 Fisher)
Unknown status (n=6)	3/6 (50%)	3/6 (50%)

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

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Preliminary Results of Registrational trial: AMPECT *nab*-Sirolimus in Advanced Malignant PEComa

Conclusions

- Preliminary data suggest that *nab*-sirolimus is highly active with an ORR of 42%, durable responses, and acceptable safety profile
- No new safety signals observed despite relatively high doses of *nab*-sirolimus compared to other mTOR inhibitors
- Disease control (PR + SD) was achieved in 77% of patients
- All (9/9) patients with *TSC2* mutations responded
- Responses were also seen in patients with *TSC1* mutations (1/5) or no *TSC1/2* mutations (1/11)
  - Responses also occurred in patients with unknown mutational status (2/6)
- 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

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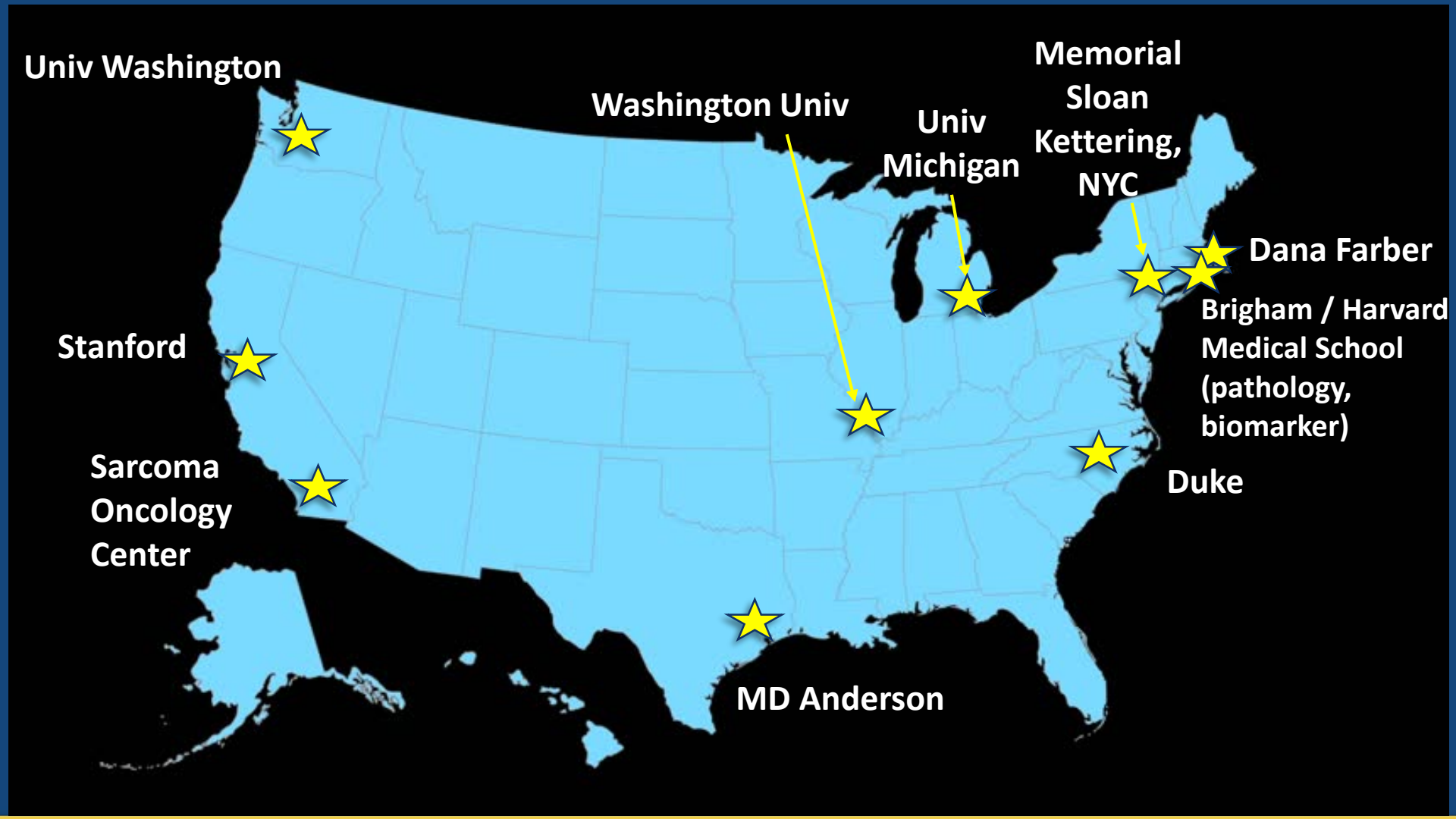
Thank you to the patients and families, and to the study teams!



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