Abstract # 3463014

ctos®

Virtual Annual Meeting
November 18–21, 2020

Session 10 - Advances in Angiosarcoma, PEComa, and Clear Cell Sarcoma
November 21, 9:00 AM to 10:00 AM

LONG-TERM FOLLOW-UP FROM AMPECT, an OPEN-LABEL PHASE 2 REGISTRATION TRIAL of *nab*-SIROLIMUS for PATIENTS with ADVANCED MALIGNANT PERIVASCULAR EPITHELIOID CELL TUMORS (PEComa)

Andrew J. Wagner, MD, PhD[1] Vinod Ravi, MD,[2] Richard F. Riedel, MD,[3] Kristen N. Ganjoo, MD,[4] Brian A. Van Tine, MD, PhD,[5] Rashmi Chugh, MD,[6] Lee D. Cranmer, MD, PhD,[7] E. Maria Gordon, MD,[8] Jason L. Hornick, MD, PhD,[9] Heng Du, MD,[9] Berta Grigorian,[10] Anita N. Schmid, PhD,[10] Shihe Hou, PhD,[10] Katherine Harris, DrPH,[10] David J. Kwiatkowski, MD, PhD,[9] Neil P. Desai, PhD,[10] Mark A. Dickson, MD,[11]

1. Dana-Farber Cancer Institute, Boston, MA
2. MD Anderson Cancer Center, Houston, TX
3. Duke Cancer Institute, Durham, NC
4. Stanford University, Stanford, CA
5. Washington University in Saint Louis, St. Louis, MO
6. University of Michigan, Ann Arbor, MI
7. Univ Washington/Fred Hutchinson Cancer Res Ctr, Seattle, WA
8. Sarcoma Oncology Center, Santa Monica, CA
9. Brigham and Women's Hospital, Boston, MA
10. Aadi Bioscience, Pacific Palisades, CA
11. Memorial Sloan Kettering Cancer Center, New York, NY

Disclosures

- **Research Funding: Aadi Bioscience,**

- **This study (NCT02494570) was sponsored by Aadi Bioscience**
- **This study was funded in part by FDA Office of Orphan Products Development (OOPD) Grant R01FD005749**

Abstract # 3463014

ctos® Virtual Annual Meeting November 18–21, 2020

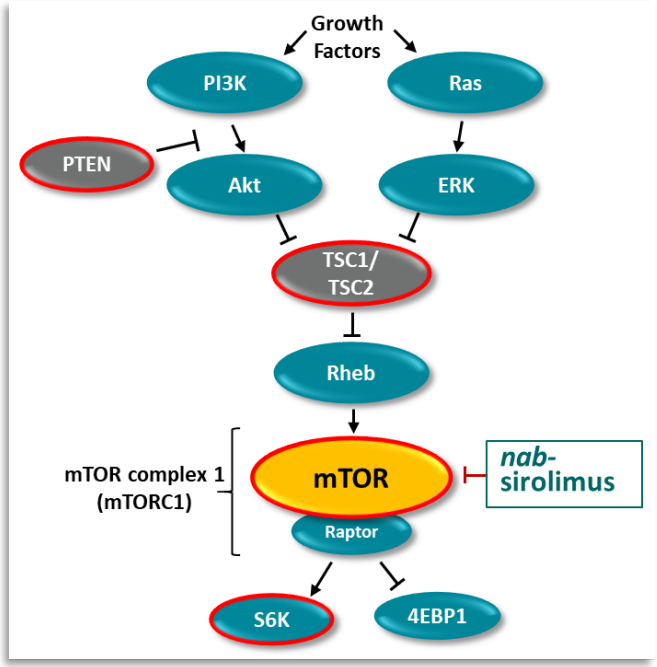
Rationale for *nab*-Sirolimus (ABI-009) for Patients with Advanced Malignant Perivascular Epithelioid Cell tumor (PEComa)

Rare sarcoma subtype with an undefined cell of origin

- High risk of metastases [1]
- Cytotoxic chemotherapy shows minimal benefit [2]
- No drugs approved for treatment of malignant PEComa

mTOR pathway activation is common in PEComa

- Case reports and retrospective reports of mTOR inhibitor treatment suggest evidence of 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

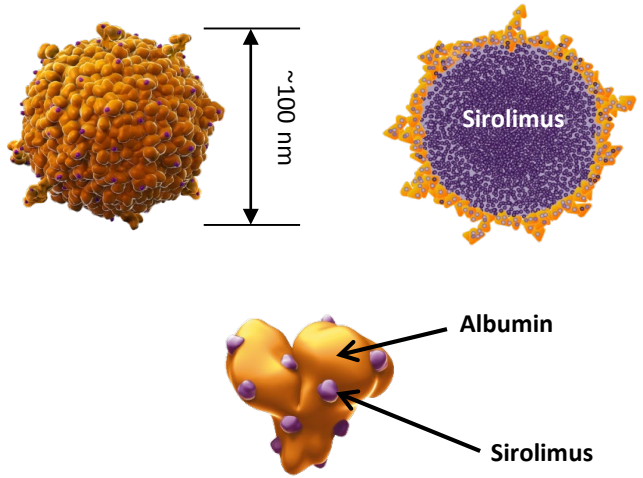
Abstract # 3463014

ctos® Virtual Annual Meeting November 18–21, 2020

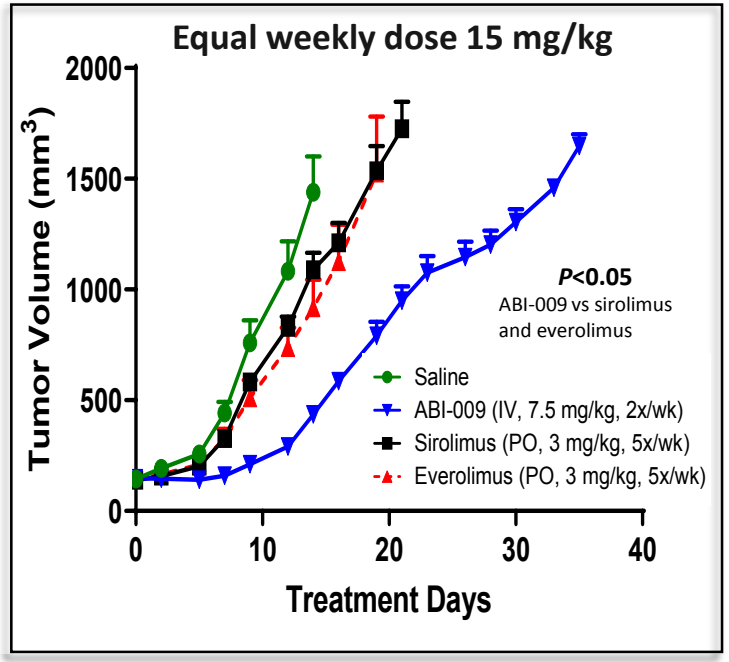
Why *nab*-Sirolimus (ABI-009)?

- ***nab*-Sirolimus (nanoparticle albumin-bound sirolimus; ABI-009) is an investigational 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 vitro and in vivo* [1-3]**

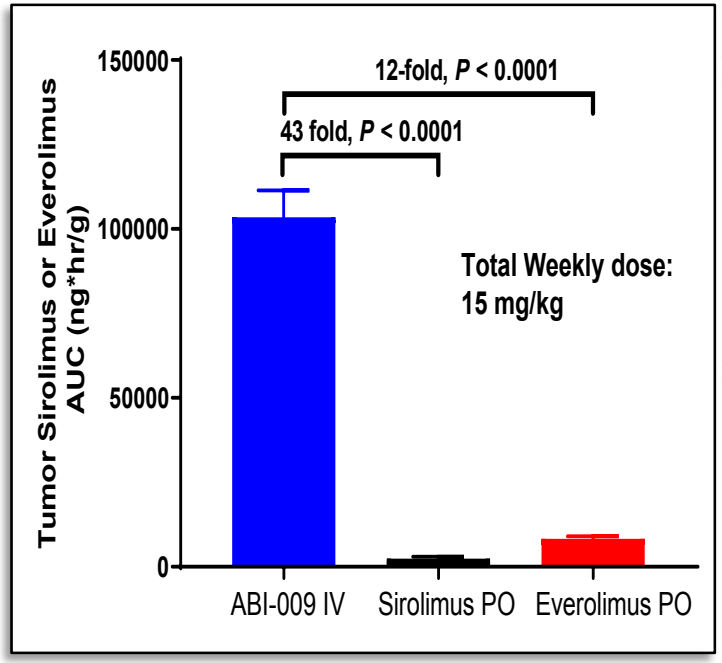
***nab*-Sirolimus Nanoparticle Schematic Cross Section**



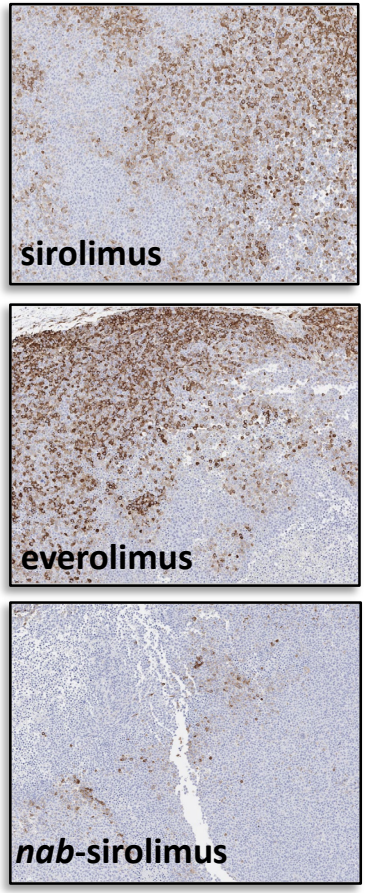
Xenograft tumor model (bladder cancer)



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] Hou, J Pharmacol Exper Ther, submitted Oct 2020

Abstract # 3463014

ctos® Virtual Annual Meeting November 18–21, 2020

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

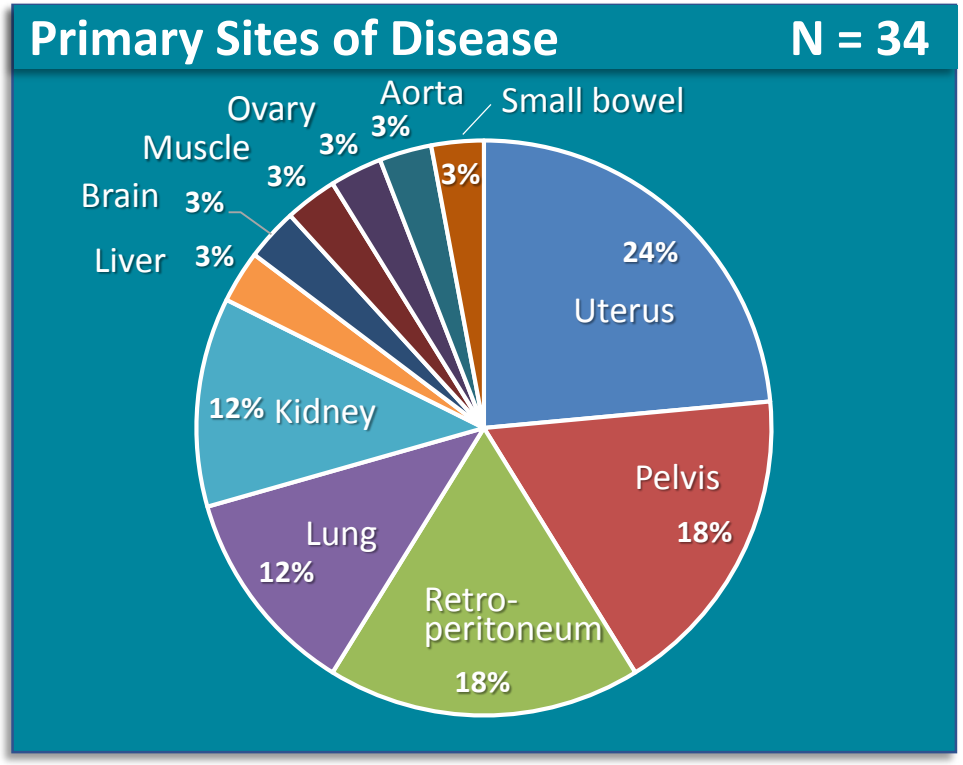
- **Primary Endpoint – ORR by Independent Radiology Review**
  - CT/MRI (RECIST v1.1) every 6 weeks
- **Secondary Endpoints**
  - DOR, PFS at 6 months, median PFS, median OS
  - Safety
- **Key Exploratory Endpoints**
  - Investigator response assessment
  - Biomarkers: mutational analysis (NGS, IHC,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

The primary analysis to evaluate all primary and secondary objectives was preplanned when all patients had the opportunity to be treated for 6 months, which occurred on May 22, 2019.

AMPECT Baseline Demographics and Characteristics

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*



Treatment-related Adverse Events (TRAEs)

TRAEs	Any Grade >25% n (%)	Grade 3** n (%)
Patients with Any TRAEs	34 (100)	
Hematologic TRAEs		
Anemia *	16 (47)	4 (12)
Thrombocytopenia *	11 (32)	1 (3)
Nonhematologic TRAEs		
Stomatitis/Mucositis *	27 (79)	6 (18)
Fatigue	20 (59)	1 (3)
Rash *	19 (56)	--
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)	--

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

*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 .

Primary Data cut on May 22, 2019

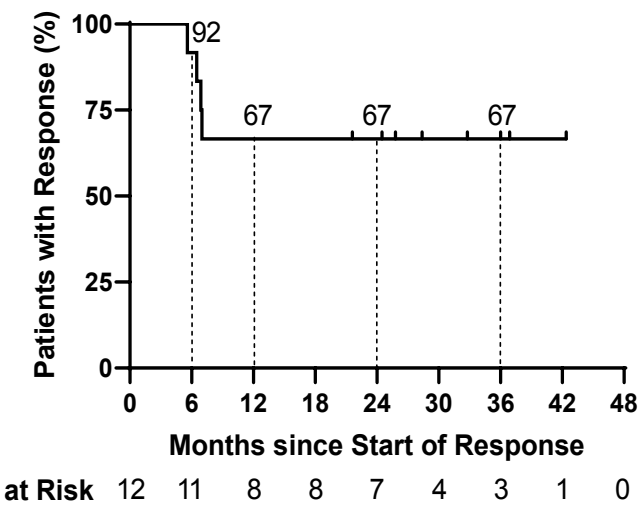
Best Responses and Duration of Response – 1-yr Follow-up after the Primary Analysis

Variable	Independent Review	Investigator Review
Best Response	**N = 31** [1]	**N = 31** [1]
Confirmed Response Rate (CR + PR)	**39% (12/31, 95%CI: 22, 58)**	**42% (13/31, 95%CI: 25, 61)**
Complete Response	3% (1/31, 95%CI: 0, 17)	0
Partial Response	36% (11/31, 95%CI: 19, 55)	42% (13/31, 95%CI: 25, 61)
Stable Disease	**52% (16/31, 95%CI: 33, 70)**	**48% (15/31, 95%CI: 30, 67)**
Progressive Disease	**10% (3/31, 95%CI: 2, 26)**	**10% (3/31, 95%CI: 2, 26)**
Disease Control Rate [2]	**71% (22/31, 95%CI: 52, 86)**	**74% (23/31, 95%CI: 56, 88)**
Duration of Response	**n = 12**	**n = 13**
Range: min - max, months [3]	**5.6 — 42.4+**	**1.5 – 42.4+**
Median DOR	**Not Reached**	**Not Reached**
DOR rate at 6 months	**92% (11/12)**	**85% (11/13)**
DOR rate at 12 months	**67% (8/12)**	**67% (8/13)**
DOR rate at 18 months	**67% (8/12)**	**54% (7/13)**

[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
Note, total may exceed 100% due to rounding
[2] Stable Disease was defined as complete or partial responses and stable disease ≥12 weeks
[3] "+" indicate ongoing value

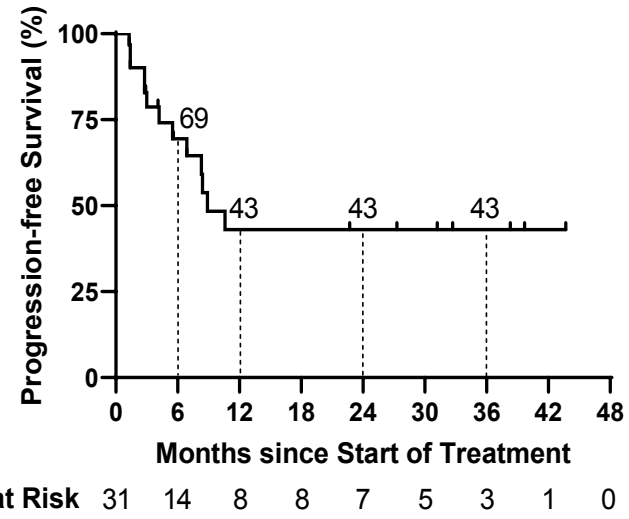
Durable Responses and PFS and OS

DOR among Pts with Response



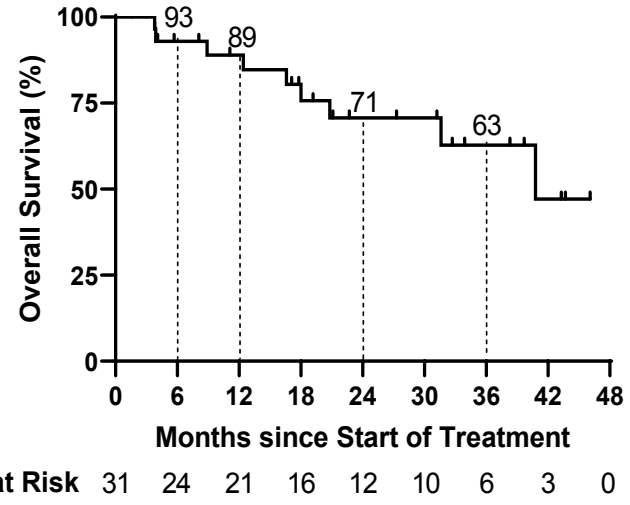
Median DOR: not reached

PFS for all Pts



Median PFS: 8.9 mo

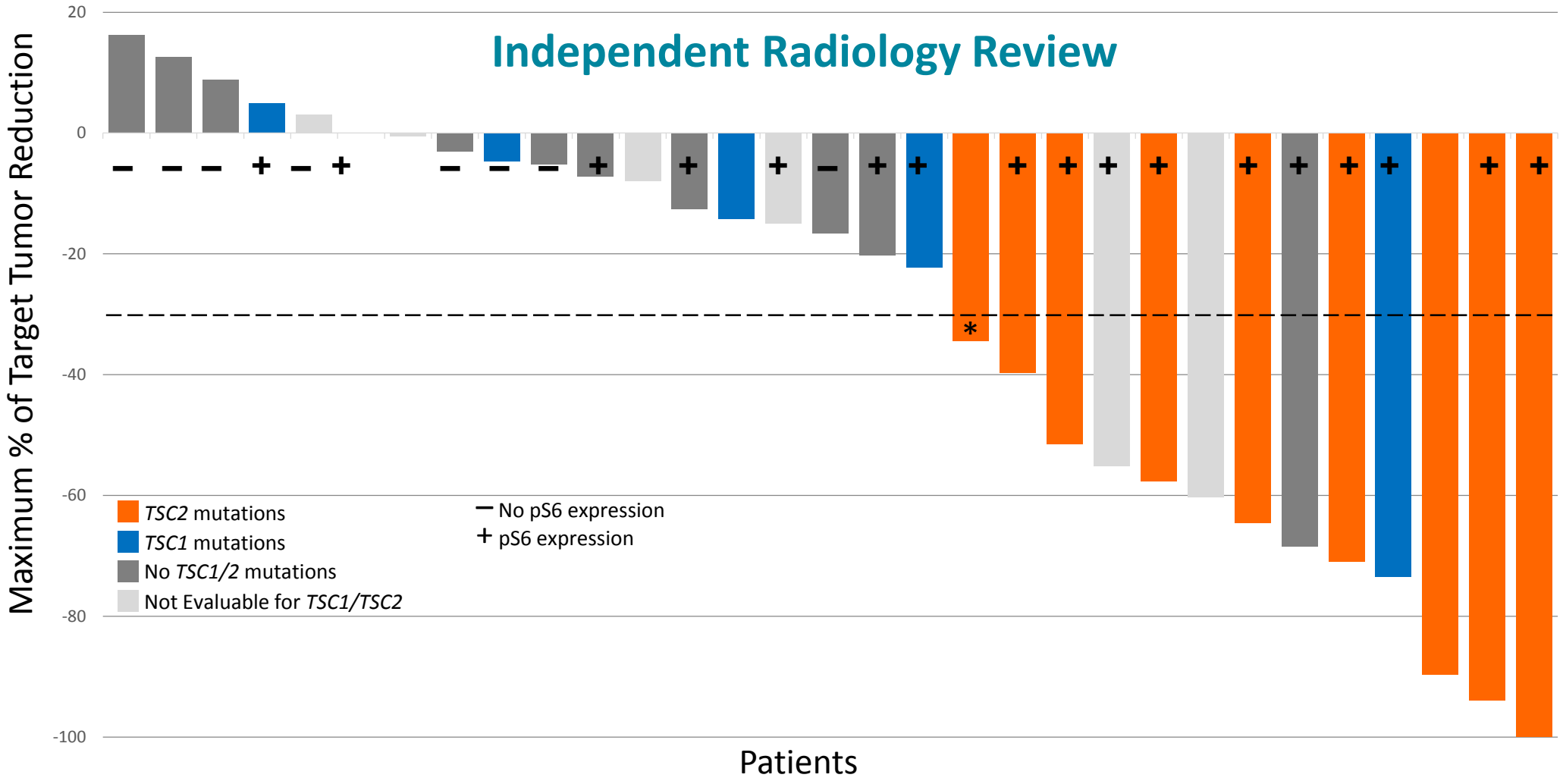
OS for all pts



Median OS: 40.8 mo

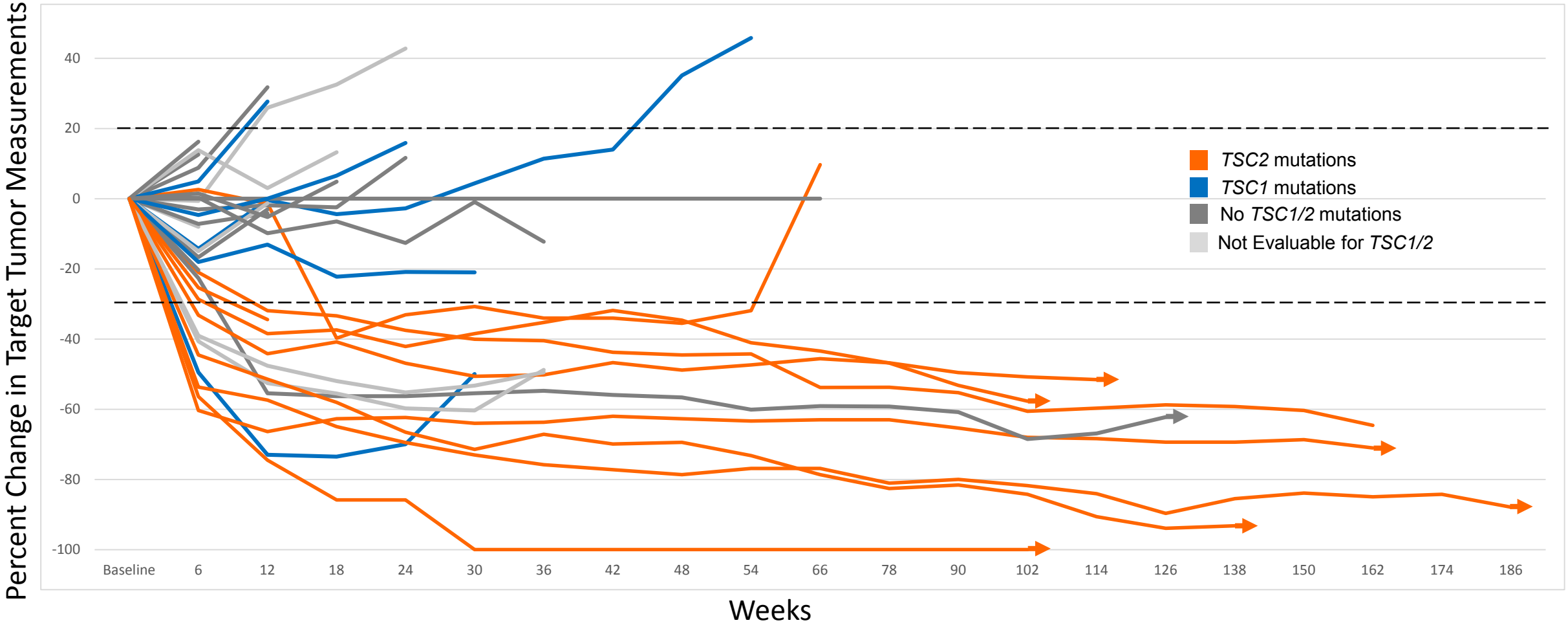
- Median DOR has not been reached, 50% of patients had a DOR of 25.2+ months (range 5.6, 42.4+ months)
  - For patients with *TSC2* mutations 50% of patients had a DOR of 28.6+ months (range: 6.5 to 42.4+ months)

Target Lesion Changes Per Mutational Status, 1-year Follow-up



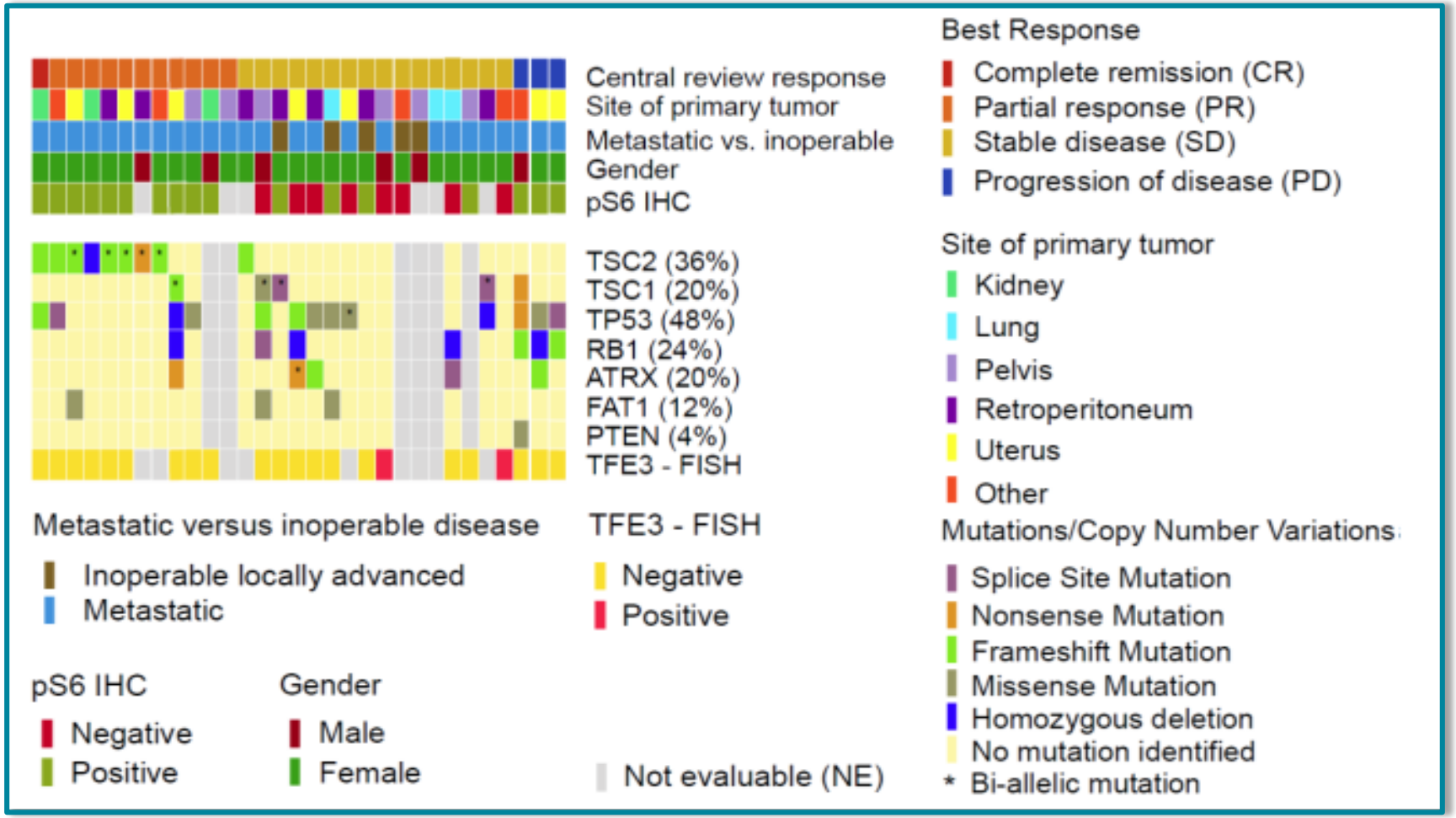
* 1 patient had an unconfirmed PR and thus best response is an SD as per RECIST v1.1

Rapid and Durable Responses Observed, Particularly in Patients with *TSC2* Mutations



Co-mut Plot of Individual Patient Response to *nab*-Sirolimus and Mutational / Biomarker Status

- Responses were significantly correlated with TSC2 mutations
- Lack of expression of pS6 was a negative predictor of response
- Responses occurred irrespective of primary anatomical sites



Long-term follow up from AMPECT: *nab*-Sirolimus in Advanced Malignant PEComa

- ***This registrational trial met its primary endpoint; the independently assessed ORR was 39% (95% CI 22% - 58%), including a CR, with durable responses and acceptable safety profile***
  - Median DOR has not been reached, 50% of patients had a duration of response of 25.2+ months, (range 5.6, 42.4+ months)
  - Disease control (PR + SD ≥12 weeks) was achieved in 71% of patients
  - 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
- ***Mutational Analysis vs Response*:**
  - *TSC2* mutations: 89% (8/9 pts) confirmed ORR by independent review (1/9 pts had an unconfirmed response)
  - The median DOR has not been reached for patients with *TSC2* mutations
  - Responses also occurred in some patients with *TSC1* or no *TSC1 / TSC2* or unknown mutational status
- ***This first prospective study in advanced malignant PEComa suggests that nab-sirolimus is active in a rare and aggressive sarcoma for which there are no approved therapies***
- ***A TSC1 / TSC2 mutant tumor-agnostic study is planned***

Abstract # 3463014

ctos®

Virtual Annual Meeting
November 18–21, 2020

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