Biomarker Analysis From AMPECT Correlating Response to *nab*-Sirolimus in PEComa With *TSC1* and *TSC2* Inactivating Alterations

#LB288

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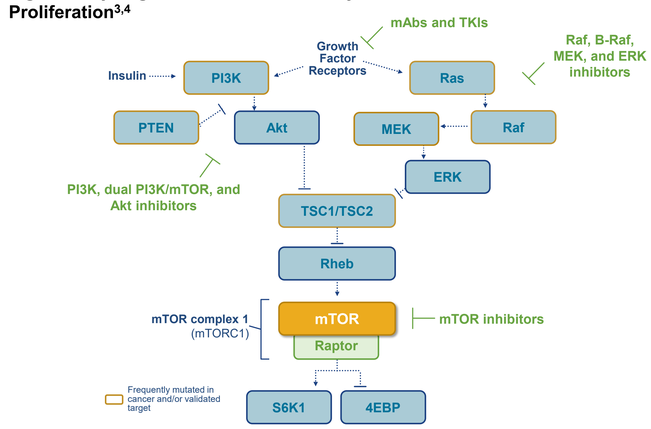
INTRODUCTION

- *nab*-Sirolimus is an mTOR inhibitor (mTORi) approved in the United States for the treatment of adult patients with locally advanced, unresectable, or metastatic malignant perivascular epithelioid cell tumor (PEComa), regardless of mutation status, based on clinical efficacy and safety data from the phase 2, multicenter, open-label AMPECT trial (ClinicalTrials.gov: NCT02494570)[1]
- Tuberous sclerosis complex subunit 1 or 2 (*TSC1* and *TSC2*) are tumor suppressor genes and key upstream regulators of mTOR complex 1 (mTORC1)
  - Inactivating alterations (loss-of-function mutations or deletions) in these genes lead to mTORC1 hyperactivation, which may contribute to tumor formation and proliferation (**Figure 1**)[1,2]
    - Pro- and anti-oncogenic signals converge on the *TSC1*-*TSC2* complex, which inhibit aberrant cell growth by negatively regulating mTORC1 activity[3-5]
      - The *TSC1*-*TSC2* complex functions as a GTPase-activating protein to revert Rheb to an inactive guanosine diphosphate-bound state[3,4,6]
      - Functional inactivation of *TSC1* and *TSC2* activates Rheb and downstream effectors of mTOR signaling, such as S6K[6]

Figure 1. Dysregulation of mTOR Activity Results in Uncontrolled Cell Growth and Proliferation[3,4]



4EBP, eIF4E binding protein; Akt, Akt serine/threonine kinase; B-Raf, B-Rad serine/threonine kinase; ERK, extracellular signal-regulated kinases; i, inhibitor; mAb, monoclonal antibody; MEK, mitogen-activated protein kinase; mTOR, mechanistic target of rapamycin; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; Raf, rapidly accelerated fibrosarcoma protein; Raptor, regulatory-associated protein of mTOR; Ras, rat sarcoma virus homolog; Rheb, Ras homolog enriched in brain; S6K1, p70S6 kinase 1; TKI, tyrosine kinase inhibitor; *TSC1/TSC2*, tuberous sclerosis complex subunit 1 or 2.

- Inactivating alterations in *TSC1* and/or *TSC2* have been observed in several types of cancer, but there are currently no approved treatment options for these patients
- Phosphorylation of S6 ribosomal protein (pS6) is a reliable surrogate for mTORC1 activity[1]
- Here we present the results of an exploratory biomarker analysis performed on tissue samples from patients enrolled in the AMPECT study (data cutoff: April 29, 2022)

METHODS

- Targeted exome next-generation sequencing (NGS) using a 500-gene OncoPanel test (Center for Advanced Molecular Diagnostics, Brigham and Women's Hospital, Boston, MA) assessed mutations, copy number changes, and translocation events
- pS6 expression was assessed by immunohistochemistry (IHC)

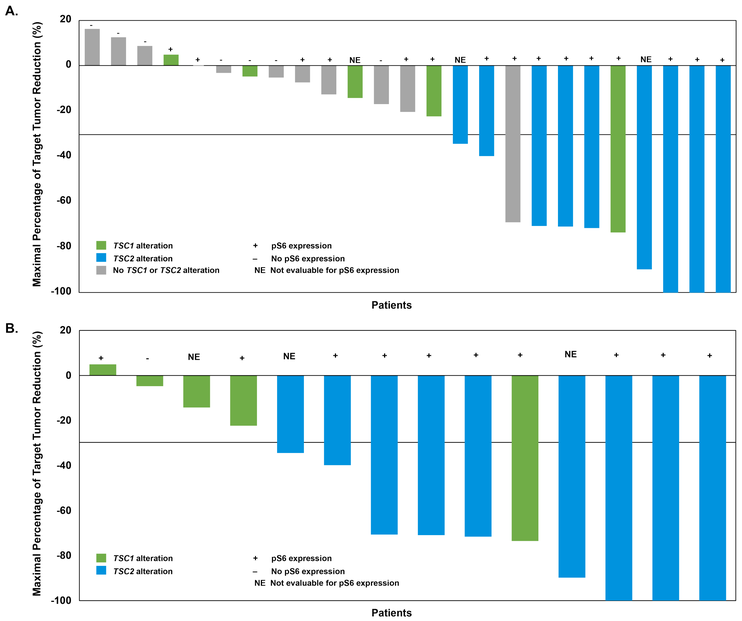
RESULTS

- Twenty-five patients had tissue sufficient for NGS, 56% (14/25) had either *TSC1* (n=5, 20%) or *TSC2* (n=9, 36%) mutations or copy number events: *TSC1*, 1 frameshift, 3 splice site, and 1 nonsense mutation; *TSC2*, 1 nonsense and 7 frameshift mutations, and 1 homozygous deletion (**Figure 2**)
- In this dataset, *TSC1* and *TSC2* inactivating alterations were mutually exclusive
- Patients with *TSC1* or *TSC2* inactivating alterations achieved a clinically meaningful benefit (**Figure 3**, **Figure 4**, and **Table 1**)
  - 64.3% (9/14) confirmed objective overall responses (including complete and partial responses) (**Table 1**)
  - Median (95% CI) duration of response (DOR) of 45.7 (5.6, not reached [NR]) months, progression-free survival (PFS) of 41.2 (5.5, NR) months (**Figure 4**)
  - Overall survival (OS) of NR (31.6, NR) months

Figure 2. Correlation Between Mutation Status and Response

CR, complete response; IHC, immunohistochemistry; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 3. Target Lesion Changes (A) in All Patients With NGS Results (n=25) and (B) in Subgroup of Patients With *TSC1* or *TSC2* Alteration (n=14)



Target tumor reduction may not match best overall response assessment, which takes into consideration nontarget lesions and observations of new lesions per RECIST v1.1.

Figure 4. Rapid and Durable Responses in Patients With *TSC1* or *TSC2* Alteration (n=14)

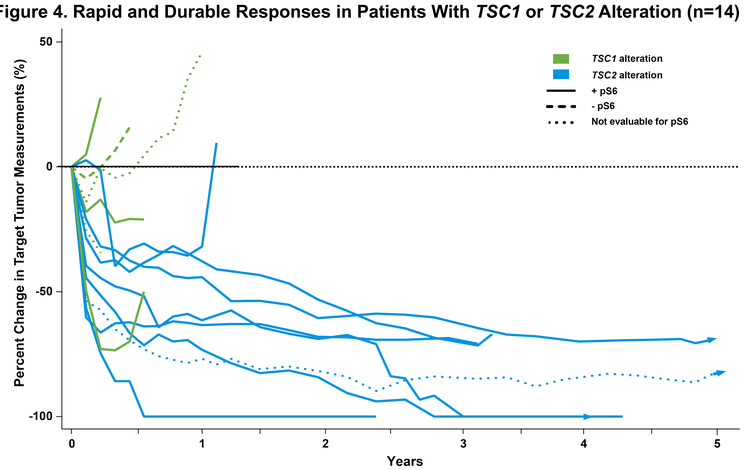


Table 1. Summary of Overall Response, DOR, PFS, and OS in All Patients With NGS Results

	TSC1 (n=5)	*TSC2* (n=9)	Combined: *TSC1* or *TSC2* (n=14)	Combined: Neither *TSC1* nor *TSC2* (n=11)	pS6: Positive (n=17)	pS6: Negative (n=8)	pS6: Total (N=25)
Complete/partial response, n (%)	1 (20)	8 (88.9)	9 (64.3)	1 (9.1)	10 (58.9)	0	10 (40)
Stable disease, n (%)	3 (60)	1 (11.1)	4 (28.6)	10 (90.9)	4 (23.5)	8 (100)	12 (48)
Progressive disease, n (%)	1 (20)	0	1 (7.1)	0	3 (17.6)	0	3 (12)
mDOR, months (95%CI)[a]	5.6 (NE, NE)	51.7 (6.5, NR)	45.7 (5.6, NR)	36.2 (NE, NE)	39.7 (5.6, NR)	NE	39.7 (5.6, NE)
mPFS, months (95%CI)[a]	5.5 (1.4, NR)	53.1 (10.6, NR)	41.2 (5.5, NR)	8.9 (1.4, NR)	24.4 (2.8, 53.1)	5.5 (2.8, NR)	24.4 (5.5, 53.1)
mOS, months (95% CI)[a]	31.6 (3.8, NR)	NR (53.1, NR)	NR (31.6, NR)	30.3 (8.9, NR)	53.1 (18.0, NR)	37.0 (16.6, NR)	53.1 (20.8, NR)

Assessments based on RECIST v1.1. [a]Median estimates are obtained from Kaplan-Meier survival curves. CR, complete response; DOR, duration of response; m, median; NE, not evaluable; NR, not reached; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

- At the time of final analysis, 6 patients with *TSC2* alteration and 1 patient with *TSC1* alteration achieved a partial response; 2 patients with *TSC2* alteration achieved a complete response
- Responses also occurred in 1 patient with no *TSC1* or *TSC2* alterations and a positive pS6 IHC
- Mutations in *TP53*, *RB1*, and *ATRX* were also common (48%, 24%, and 20%, respectively)
- Of tissue samples evaluable for IHC (N=25), responses occurred in 58.8% (10 of 17) of patients with pS6 positive tumors versus 0% (0 of 8) with pS6 negative tumors; pS6 expression was positively associated with response to *nab*-sirolimus (*P*=0.008, Fisher exact; **Table 1**)
- Median (95 %CI) DOR for pS6-positive responders was 39.7 (5.6, NR) months (**Table 1**)
- In pS6-positive vs pS6-negative patients, the median (95 %CI) PFS was 24.4 (2.8, 53.1) vs 5.5 (2.8, NR) months, and OS was 53.1 (18.0, NR) vs 37.0 (16.6, NR) months (**Table 1**)

CONCLUSIONS

- A variety of pathogenic inactivating alterations were observed in *TSC1* and *TSC2* genes, though *TSC2* alterations were most commonly frameshift mutations; *TSC1* and *TSC2* alterations were mutually exclusive
- These observations suggest that loss of function alterations in *TSC1* or *TSC2* were a strong predictive factor for response to *nab*-sirolimus in these patients, and warrants further studies for the role of *nab*-sirolimus in other tumors with *TSC1* or *TSC2* inactivating alterations
- pS6 expression was a positive predictor of response to *nab*-sirolimus and was frequently found in patients with *TSC1* or *TSC2* alterations; the absence of pS6 expression was a negative predictor of response to *nab*-sirolimus
- A tumor-agnostic study (PRECISION I, ClinicalTrials.gov: NCT05103358) is now recruiting patients with pathogenic inactivating *TSC1* or *TSC2* alterations to further examine these biomarker findings

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