Inactivating Alterations in *TSC1* and *TSC2*, Co-Mutations, and Genomic Instability in Advanced Cancers: Analysis of a Real-World Patient Population Using the Foundation Medicine Genomic Database

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Objective

- **To characterize *TSC1* and *TSC2* alterations across a large real-world patient population with advanced cancer using data from tumor tissue biopsies**

KEY FINDINGS

- **In a large real-world database of patients with advanced cancer, known/likely inactivating alterations in *TSC1* or *TSC2* occurred across common tumor types at rates as high as 9.6% (urinary bladder tumors), and in 1.9% of patients overall**
- **Most known/likely inactivating alterations in *TSC1* and *TSC2* occurred in the context of low tumor mutational burden and/or microsatellite stable status, suggesting that these are unlikely to be passenger mutations and instead may potentially serve as driver mutations**
- **Low frequencies of co-occurring targetable oncogenic drivers also suggest that therapeutic targeting of *TSC1* and *TSC2* inactivating alterations may be a potentially effective treatment approach in this patient population. This hypothesis is being tested in the currently enrolling PRECISION 1 study (NCT05103358)**

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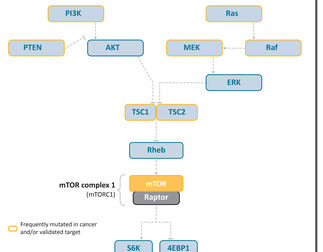
BACKGROUND

- The tumor suppressor genes *TSC1* and *TSC2* are critical negative regulators of mTOR activity whose inactivation can lead to tumor cell growth[1–4] (**Figure 1**)

Figure 1. Dysregulation of the PI3K-AKT-mTOR pathway via inactivation of the TSC1-TSC2 complex can lead to overactivation and tumorigenesis



4EBP, eukaryotic translation initiation factor 4E (eIF4E)-binding protein; **AKT**, protein kinase B; **ERK**, extracellular signal-regulated kinase; **MEK**, mitogen-activated protein kinase kinase; **mTOR**, mammalian/mechanistic target of rapamycin; **mTORC1**, mTOR complex 1; **PI3K**, phosphatidylinositol 3-kinase; **PTEN**, phosphatase and tensin homolog; **Raf**, rapidly accelerated fibrosarcoma; **Raptor**, regulatory-associated protein of mTOR; **Ras**, rat sarcoma virus homolog; **Rheb**, Ras homolog enriched in brain; **S6K**, ribosomal S6 kinase; **TSC1/TSC2**, tuberous sclerosis complex subunit 1 or 2.

- *nab*-Sirolimus, a nanoparticle albumin-bound, IV administered mTOR inhibitor, is approved in the United States for treatment of adult patients with advanced malignant PEComa[5] based on the safety and efficacy demonstrated in the AMPECT trial (NCT02494570)[6]
- Of patients with known inactivating alterations in *TSC1* or *TSC2*, 9 of 14 (64.3%) with malignant PEComa in AMPECT[6] and 5 of 7 (71.4%) in the pan-tumor Expanded Access Program (NCT03817515)[7] had confirmed responses to the mTOR inhibitor *nab*-sirolimus and manageable toxicities
- PRECISION 1 (NCT05103358), a currently enrolling tumor-agnostic study, is assessing the clinical benefit of *nab*-sirolimus in patients with malignant solid tumors harboring inactivating alterations in *TSC1* and/or *TSC2*
- *TSC1* and/or *TSC2* mutational data from a real-world genomic database were analyzed to characterize and enumerate the frequency of these alterations across tumor types

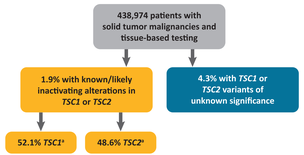
METHODS

- Next-generation sequencing (NGS) data (from 2010 to 2022) from the Foundation Medicine genomic database of patients primarily with advanced cancer, exclusive of hematological malignancies, were analyzed using the FoundationInsights™ web-based platform
- *TSC1* and *TSC2* variants were categorized according to likelihood of inactivation—"known", "likely", "ambiguous", or "unknown"—based on Foundation Medicine's assessments for identification. Assessment included listing in the Catalogue of Somatic Mutations in Cancer, existing relevant literature to support categorization, and internal evidence to determine the reported functional status
  - Known inactivating variants comprised:
    - Recurrent somatic short variants
    - Copy number alterations involving genes that are recurrently amplified/deleted
    - Rearrangements involving known fusion partners, or other functional events
  - Likely variant calls included short variants or rearrangements that disrupt tumor suppressor genes or are located in known hotspot regions, or other functional events
  - Ambiguous variant calls included non-focal amplifications
  - Unknown variants were classified as those with unknown somatic or functional status, and insufficient data in the literature
- Genomic *TSC1* and *TSC2* variants were then categorized as short variants (substitutions, insertions, and deletions), copy number alterations, or genomic rearrangements
- Patient samples with known/likely inactivating alterations in *TSC1* and *TSC2* were further characterized for co-mutations, microsatellite instability status, and tumor mutational burden (TMB)

RESULTS

- As of March 29, 2022, a total of 438,974 patients with advanced cancer had NGS data for tumor tissue available in the Foundation Medicine database and accessible via the FoundationInsights™ web-based platform (**Figure 2**)
- Of these patients, 18,719 (4.3%) had *TSC1* or *TSC2* variants of unknown significance (VUS), primarily missense (~89%), that were not known to be inactivating
- In all, 8464 (1.9%) patients had known/likely inactivating alterations in *TSC1* or *TSC2*, and 65 of these 8464 (0.8%) patients had co-occurring *TSC1* and *TSC2* inactivating alterations
- Of the known/likely inactivating alterations, 52.1% were *TSC1* and 48.6% were *TSC2*; alterations included short variants (85.0%), rearrangements (10.8%), and copy number deletions (17.9%)

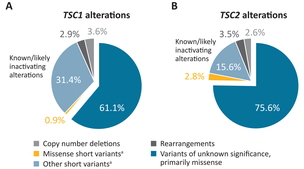
Figure 2. Patients with *TSC1* or *TSC2* alterations in the Foundation Medicine genomic database



[a]Percentages add up to more than 100% due to 65 (0.8%) patients harboring more than one *TSC1* or *TSC2* mutation type and/or mutations in both *TSC1* and *TSC2*.

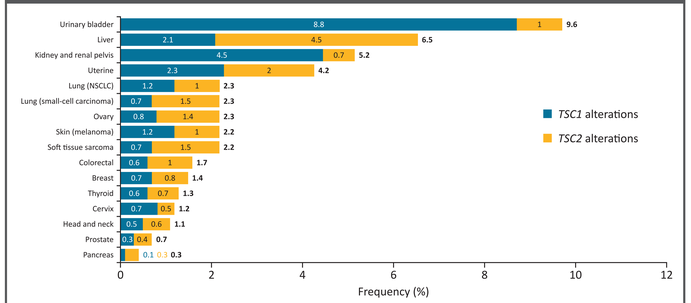
- Of the *TSC1* alterations identified (n=11,757), 4569 (38.9%) were known/likely inactivating alterations, and 7188 (61.1%) were VUS (**Figure 3A**)
  - Of the known/likely inactivating alterations in *TSC1*, 105 (2.3%) were missense short variants, 3690 (80.8%) were other types of short variants (e.g., insertion, deletion, nonsense and splice variants), 346 (7.6%) were rearrangements, and 428 (9.4%) were copy number deletions
- Of the *TSC2* alterations identified (n=17,757), 4340 (24.4%) were known/likely inactivating alterations, and 13,417 (75.6%) were VUS (**Figure 3B**)
  - Of the known/likely inactivating alterations in *TSC2*, 499 (11.5%) were missense short variants, 2775 (63.9%) were other types of short variants, 613 (14.1%) were rearrangements, and 453 (10.4%) were copy number deletions

Figure 3. Distribution of the types of *TSC1* (A) and *TSC2* (B) alterations



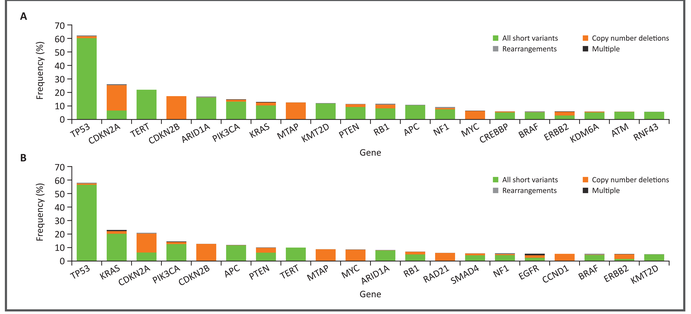
Note: Percentages do not add up to 100 due to rounding.
[a]Insertion, deletion, nonsense, and splice variants.

Figure 4. Inactivating alterations in *TSC1* and *TSC2* genes occurred in multiple solid tumor types



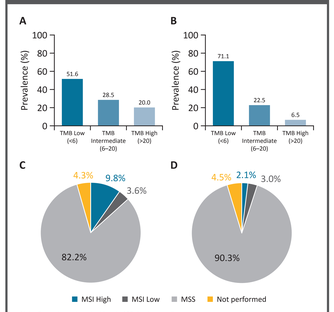
Note: Total percentages may not equal the combination of *TSC1* and *TSC2* due to some patients harboring more than one *TSC1* or *TSC2* mutation type and/or mutations in both *TSC1* and *TSC2*.
NSCLC, non-small cell lung cancer.

Figure 5. Other commonly occurring mutations in (A) patients with a *TSC1* or *TSC2* inactivating alteration and (B) the total patient population in the Foundation Medicine genomic database



- *TSC1* or *TSC2* inactivating alterations were most frequently identified in urinary bladder (9.6%), liver (6.5%), kidney and renal pelvis (5.2%), and uterine (4.2%) tumors (**Figure 4**)
- In tumors with known/likely inactivating alterations in *TSC1* or *TSC2*, the frequency of mutations in *TP53* (62.2%) and *CDKN2A* (26.2%) (**Figure 5A**) were similar to those in the total population of patients with tumor data in the Foundation Medicine database (58.0% and 21.0%, respectively) where the predominant tumor types are lung, colorectal, and breast tumors overall (**Figure 5B**)
- The patients with *TSC1* or *TSC2* inactivating alterations had a lower frequency of mutations in *KRAS* (10.5%) compared with the total population in the Foundation Medicine database (20.2%)
- While TMB was high (>20) in 20% of patients with known/likely inactivating alterations in *TSC1* or *TSC2*, TMB was low (<6 mutations per megabase) in approximately half (51.6%) of patients with known/likely inactivating alterations in *TSC1* or *TSC2* (**Figure 6A**). TMB was low in the majority (71.1%) of the total population of patients in the Foundation Medicine database (**Figure 6B**)
- Tumor samples with known/likely inactivating alterations in *TSC1* or *TSC2* were mostly microsatellite stable (82.2%) across tumor types (**Figure 6C**), and this was similar to the total patient population of the Foundation Medicine database (90.3%) (**Figure 6D**)

Figure 6. Tumor mutational burden and microsatellite instability status in patients with known/likely inactivating alterations in *TSC1* or *TSC2* (A, C) and in the total patient population of the Foundation Medicine database (B, D)



Note: Percentages do not add up to 100 due to rounding.
MSI, microsatellite instability; **MSS**, microsatellite stable; **TMB**, tumor mutational burden.

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