Real-World Characterization and Frequency of *TSC1* and/or *TSC2* Alterations Collected from Tumor Tissue and Liquid Biopsies from the Tempus Genomic Database in Patients With Advanced Cancer

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Objective

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

KEY FINDINGS

- **In a real-world database of patients with cancer assessed by next-generation sequencing on solid tumor biopsies, inactivating alterations in *TSC1* and/or *TSC2* occurred in 8.4% of patients with pancreatic neuroendocrine tumors and 8.4% of patients with urothelial carcinoma, and were present in 1.7% of patients overall**
- **Similar prevalence between primary and metastatic samples suggests *TSC1* and *TSC2* alterations are commonly not acquired, although the samples were not longitudinal**
- **The majority of inactivating alterations in *TSC1* and *TSC2* occurred in TMB low and microsatellite stable tumors, and with a low frequency of co-occurring oncogenic driver mutations suggesting that these *TSC1* and *TSC2* inactivating alterations are not passenger mutations and may be actionable therapeutic targets in these patients**
- **These real-world observations are consistent with prior findings from The Cancer Genome Atlas program. The PRECISION 1 trial (NCT05103358) is evaluating *nab*-sirolimus in cancers harboring inactivating alterations in *TSC1* or *TSC2***

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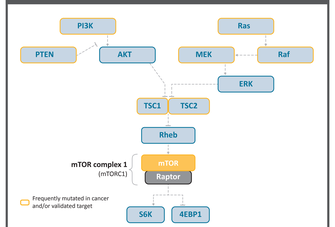
BACKGROUND

- 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**)
- Inactivating alterations in *TSC1* and/or *TSC2* have been observed in several types of cancer;[5] patients with these alterations may benefit from a therapeutic strategy that targets mTOR

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



- *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[6]
  - Nine of 14 (64.3%) patients with malignant PEComas bearing *TSC1* and/or *TSC2* inactivating alterations in the AMPECT trial (NCT02494570) demonstrated confirmed responses to *nab*-sirolimus[7]
  - Five of 7 (71.4%) patients in the pan-tumor Expanded Access Program (NCT03817515) harboring inactivating alterations in *TSC1* and/or *TSC2* had confirmed responses to *nab*-sirolimus[8]
- PRECISION 1 (NCT05103358), a currently enrolling, tumor-agnostic study, will assess the clinical benefit of *nab*-sirolimus in patients with malignant solid tumors bearing inactivating alterations in *TSC1* and/or *TSC2*
- We characterized and enumerated the prevalence of *TSC1* and/or *TSC2* alterations across tumor types using next-generation sequencing (NGS) data, derived from tissue and liquid biopsies, from a large real-world patient population with advanced malignancies

METHODS

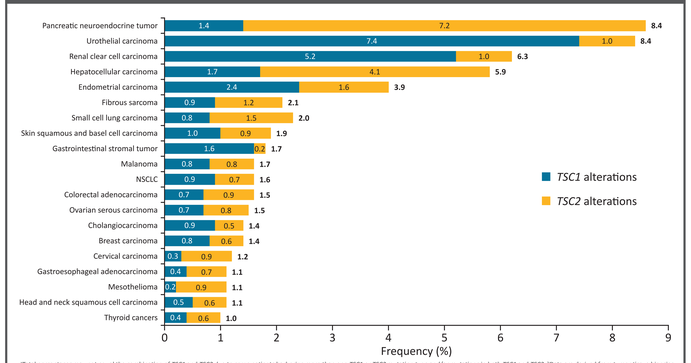
- NGS data from tissue and liquid biopsies obtained from the Tempus database (as of April 28, 2023) were used to analyze the prevalence of *TSC1* and/or *TSC2* alterations across tumor types
- In tumor tissue, somatic *TSC1* and *TSC2* alterations were categorized as known/likely inactivating alterations, deletions (copy number loss), or variants of uncertain significance (VUS). Analysis of liquid biopsies did not include copy number loss detection
  - Known/likely inactivating alterations were further classified as in-frame deletions, frameshift variants, missense variants, multi-hits (more than one type of alteration), splice region variants, and start lost and stop gained (leading to early termination of the gene product) mutations
  - Known/likely inactivating alterations in *TSC1* and *TSC2* from tumor tissue-derived biopsies were further characterized for co-mutations, tumor mutational burden (TMB), and microsatellite instability status
- *TSC1* and *TSC2* analyses were performed separately for the metastatic analysis, where the earliest samples with either a *TSC1* or *TSC2* mutation were selected at the patient level for each. Additionally, some patients had an unknown metastatic status, and were not included in this analysis

RESULTS

Tumor tissue biopsies

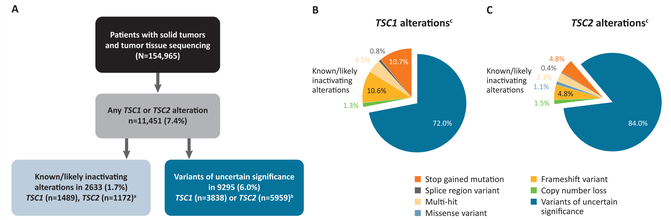
- Tumor tissue NGS results from 154,965 patients were analyzed from the Tempus database
- *TSC1* and *TSC2* inactivating alterations were most frequently identified in pancreatic neuroendocrine tumors (8.4%), urothelial (8.4%), renal clear cell (6.3%), and hepatocellular (5.9%) carcinomas (**Figure 2**)
- Inactivating alterations in *TSC1* and *TSC2* were identified in 2633 (1.7%) patients (**Figure 3A**)
- Inactivating alterations in *TSC1* (n=1489 [56.6%]) were more common than *TSC2* inactivating alterations (n=1172 [44.5%]), and were generally mutually exclusive, with only 1% having inactivating alterations in both
- Inactivating alterations in *TSC1* and *TSC2* were most commonly stop gained mutations or frameshift variants (**Figure 3B**, **3C**)

Figure 2. Inactivating alterations in *TSC1* and *TSC2* genes occurred in multiple solid tumor types[a,b]



[a]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*. [b]Data are derived from tumor tissue biopsies. **NSCLC**, non-small cell lung cancer.

Figure 3. Patients with tumor tissue bearing *TSC1* or *TSC2* alterations in the Tempus database (A); and distribution of the types of *TSC1* (B) and *TSC2* (C) alterations



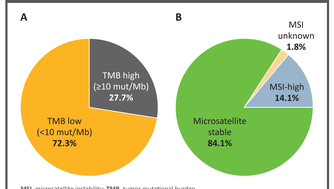
[a]28 patients had both *TSC1* and *TSC2* known/likely inactivating alterations. [b]502 patients had both *TSC1* and *TSC2* variants of uncertain significance. [c]A patient may have more than one of the mutation types shown, therefore the total percentage may exceed 100; alterations accounting for <0.1% are not shown.

- *TSC1* and *TSC2* VUS (primarily missense) were identified in 9295 (6.0%) patients, and accounted for 72.0% of *TSC1* variants and 84.0% of *TSC2* variants (**Figure 3**)
- Detection of both *TSC1* and *TSC2* alterations was similar among non-paired primary versus metastatic tumors (*TSC1*, 1.1% vs 0.91%; *TSC2*, 0.82% vs 0.60%)
- In tumors with known/likely inactivating alterations in *TSC1* or *TSC2*, other commonly mutated genes were of limited clinical actionability, and included *ARID1A* (44%), *KMT2C* (44%), and *RB1* (40%) (**Figure 4**)
- Among tumors with known/likely inactivating alterations in *TSC1* or *TSC2*, TMB was low (<10 mut per Mb) in most (72.3%) tumors (**Figure 5A**) and most (84.1%) were microsatellite stable (**Figure 5B**)

Liquid biopsies

- Liquid biopsy sequencing results from 53,502 patients were analyzed from the Tempus database
- The most common tumor types harboring inactivating alterations in *TSC1* or *TSC2* in this cohort were hepatocellular carcinoma (5.2%), urothelial carcinoma (3.6%), gastrointestinal stromal tumor (2.1%), small cell lung carcinoma (1.6%), and endometrial carcinoma (1.5%)
- The frequency of *TSC1* and *TSC2* inactivating alterations was generally lower in liquid biopsies than in tumor tissue biopsies, likely reflecting the variable shedding of tumor DNA into the plasma and differences in assay capabilities

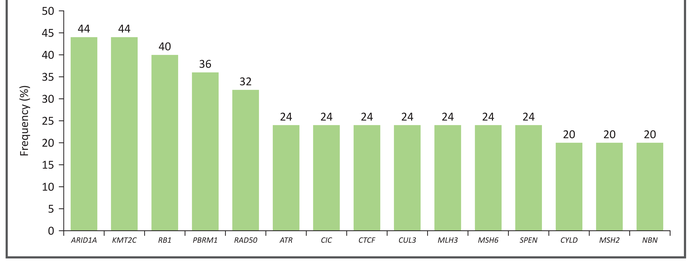
Figure 5. TMB (A) and (B) microsatellite instability status in tumors bearing *TSC1* or *TSC2* inactivating alterations



MSI, microsatellite instability; **TMB**, tumor mutational burden

- Inactivating alterations in *TSC1* and *TSC2* were identified in 489 (0.9%) patients, whereas VUS were identified in 2717 (5.1%) patients
  - Of all *TSC1* alterations (inactivating and VUS) the inactivating alterations in *TSC1* consisted of stop gained mutations (9.3%), frameshift variants (4.9%), splice region variants (2.2%), and multi-hits (0.8%)
  - Of all *TSC2* alterations (inactivating and VUS) the inactivating alterations in *TSC2* comprised stop gained mutations (7.1%), splice region variants (3.4%), frameshift variants (2.2%), multi-hits (0.3%), missense variants (0.1%), and disruptive in-frame deletions (0.05%)

Figure 4. Frequency of co-occurring mutations in tumor tissue bearing *TSC1* or *TSC2* inactivating alterations



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