Analysis of inactivating alterations in *TSC1* and *TSC2* in advanced genitourinary (GU) cancers from a real-world patient population in the Foundation Medicine genomic database

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Objective

- **To characterize and enumerate the frequency of *TSC1* and *TSC2* alterations in genitourinary (GU) cancers across a large real-world genomic database of patients with advanced cancer using data from tumor tissue biopsies**

KEY FINDINGS

- **In a large real-world database of patients with advanced cancer, 1,828 (4.0%) of the 46,068 patients with GU cancers had at least one inactivating alteration in *TSC1* or *TSC2***
- ***TSC1* and/or *TSC2* inactivating alterations were present in 9.2% of patients with bladder cancer, 6.4% of patients with kidney cancer, and 0.6% of patients with prostate cancer**
- **GU cancers with *TSC1* and/or *TSC2* inactivating alterations were frequently microsatellite stable and of low tumor mutational burden (TMB)**
- **The PRECISION 1 study (NCT05103358) is currently enrolling patients with solid tumors harboring *TSC1* and/or *TSC2* inactivating alterations**
- **Limitations of this exploratory, real-world study include the timing of sampling (at initial diagnosis vs disease progression) and the absence of clinically matched outcomes data. More research is needed to understand the clinical and prognostic implications of these data**

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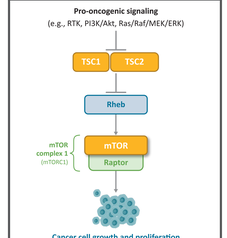
BACKGROUND

- Overactivation of the PI3K-Akt-mTOR pathway is implicated in a number of cancers, including GU cancers[1], and can result from inactivation of the tumor suppressor genes *TSC1* and *TSC2* (**Figure 1**)[2]

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



- *nab*-Sirolimus, a nanoparticle albumin-bound, IV-administered mTOR inhibitor, is approved for treatment of patients with advanced malignant perivascular epithelioid cell tumors (PEComa)[3], a group of rare aggressive tumors that can originate in GU tissues[4,5]
- Of patients with malignant PEComa and known inactivating alterations in *TSC1* or *TSC2*, 9 of 14 (64.3%) patients in AMPECT (NCT02494570)[3,6], and 5 of 7 (71.4%) patients in the pan-tumor Expanded Access Program (NCT03817515)[6] had confirmed responses to *nab*-sirolimus
- PRECISION 1 (NCT05103358), a tumor-agnostic study assessing the clinical benefit of *nab*-sirolimus in patients with malignant solid tumors harboring inactivating alterations in *TSC1* and/or *TSC2*, is currently enrolling
- In the current study, *TSC1* and *TSC2* mutational data from a real-world genomic database were analyzed to enumerate the frequency and characteristics of the alterations in GU cancers

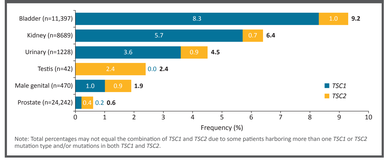
METHODS

- Next-generation sequencing (NGS) data collected (August 2014 to July 2023) from patients with GU cancers (excluding hematological, neuroendocrine, and sarcoma malignancies), were analyzed using Foundation Medicine's FoundationCORE database. Prevalence of *TSC1* and/or *TSC2* inactivating alterations among patients with GU cancers were enumerated; *TSC1* and *TSC2* variant types, tumor mutational burden (TMB), microsatellite instability (MSI), and co-occurring gene alterations were characterized among commonly occurring GU cancers
- *TSC1* and *TSC2* variants were categorized according to likelihood of inactivation—"**known**", "**likely**", "**ambiguous**", or "**unknown**"—based on Foundation Medicine's assessments for identification
  - **Known** variants comprised recurrent somatic short variants, copy number alterations, and rearrangements involving known fusion partners, or other functional events
  - **Likely** variants included short variants or rearrangements that disrupt tumor suppressor genes or are located in known hotspot regions, or other functional events
  - **Ambiguous** variants included non-focal amplifications
  - **Unknown** variants were those with unknown somatic or functional status and insufficient data in the literature
- Specimens with a **known** or **likely** pathogenic alteration in *TSC1* and/or *TSC2* were designated as *TSC1* and/or *TSC2* inactivating alterations. Specimens were classified as wild-type if they were without **known/likely** pathogenic *TSC1* or *TSC2* alterations, or if they had **ambiguous** or **unknown** variants

RESULTS

- As of July 26, 2023, NGS data were available for 46,068 patients with GU solid tumor malignancies in the Foundation Medicine database, 1828 (4.0%) of which had inactivating alterations in *TSC1* or *TSC2* (**Figure 2**)
  - Known or likely inactivating alterations in *TSC1* (84.6%)
  - Among patients with GU cancers, 86.3% were male, 13.7% were female, and the median age at time of testing was 68 years (IQR: 60–75)
- The most common GU tumor types with inactivating alterations in *TSC1* or *TSC2* were bladder cancer (9.2%), kidney cancer (6.4%), and urinary cancer (4.5%) (**Figure 2**)

Figure 2. Inactivating alterations in *TSC1* and/or *TSC2* genes occurred in multiple GU cancers



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*.

- Across GU malignancies, bladder, kidney, and prostate cancers were the most common types of GU cancers observed in the database and are characterized further in this analysis
  - Analysis of histologies across tumor types showed 88.6% of bladder cancers were urothelial carcinoma, 34.2% and 32.1% of kidney cancers were renal cell and clear cell carcinoma, respectively, and 97.8% of prostate cancers were acinar adenocarcinoma
  - Across GU tumor types, the majority of *TSC1* and *TSC2* inactivating alterations were short variants (73.3% – 92.1%). The frequency of copy number deletions were low (5.2% – 9.5%) across all tumor types. Rearrangement alterations were more frequent in prostate cancers (20.0% – 20.6%) than in bladder or kidney cancers (1.4% – 7.6%)
  - Mutations in *TP53* were commonly observed across all 3 tumor types among those with and without *TSC1* and *TSC2* alterations
  - Regardless of *TSC1* and *TSC2* mutation status, *CDK2NA* and *CDK2NB* were commonly mutated in bladder and kidney cancers, but not in prostate cancers
  - TMB and MSI status patterns were similar across GU tumor types, with or without *TSC1* or *TSC2* alterations; most patients had tumors with a low TMB (<10mutations/megabase) and were microsatellite stable (MSS)

Characterization of *TSC1* and *TSC2* alterations in bladder cancers

- Inactivating alterations in *TSC1* and/or *TSC2* were found in 9.2% of bladder cancers (**Figure 2**)
- Bladder cancers with inactivating alterations in *TSC1* and/or *TSC2* were enriched for co-occurring mutations in *TERT*, *CDKN2A*, *CDKN2B*, and *FGFR3* (**Figure 3A** and **3B**)
- TMB was low (<10 mutations/megabase) in 62.4% of bladder cancers with *TSC1* and/or *TSC2* mutations, which was similar in bladder cancers with wild-type *TSC1* and *TSC2* (**Figure 4A**)
- Almost all of the bladder cancer specimens evaluated had MSS tumors (>98%), regardless of *TSC1* and *TSC2* mutational status (**Figure 4B**)

Characterization of *TSC1* and *TSC2* alterations in kidney cancers

- Inactivating alterations in *TSC1* and/or *TSC2* were found in 6.4% of kidney cancers (**Figure 2**)
- Among kidney cancers with alterations in *TSC1* and/or *TSC2*, the 3 most frequently co-occurring mutations were in *VHL*, *TERT*, and *TP53* (**Figure 5A**)
  - In contrast, the top 3 mutations observed in kidney cancers with wild-type *TSC1* and *TSC2* were *VHL*, *CDKN2A*, and *PBRM1* (**Figure 5B**)
- Regardless of *TSC1* and/or *TSC2* mutational status, most kidney cancers were TMB-low (**Figure 6A**) and MSS (**Figure 6B**)

Characterization of *TSC1* and *TSC2* alterations in prostate cancers

- Inactivating alterations in *TSC1* and/or *TSC2* were found in 0.6% of prostate cancers (**Figure 2**)
- Prostate cancers with inactivating alterations in *TSC1* and/or *TSC2* were enriched for co-occurring mutations in *TP53* relative to the wild-type cohort (**Figure 7A** and **7B**)
- TMB was high (≥10 mutations/megabase) in 40% of prostate cancers with *TSC1* and/or *TSC2* alterations, but in only 4.2% of prostate cancers with wild-type *TSC1* and *TSC2* mutations (**Figure 8A**)
  - The greater frequency of high TMB may be attributed to the enrichment of *TP53* in prostate cancers with *TSC1* or *TSC2* alterations
- Prostate cancers with wild-type *TSC1* and *TSC2* were enriched for MSS tumors in relation to tumors with inactivating alterations in *TSC1* and/or *TSC2* (**Figure 8B**)

Figure 3. Gene mutations commonly observed in bladder cancers with (A) or without (B) inactivating alterations in *TSC1* and/or *TSC2*

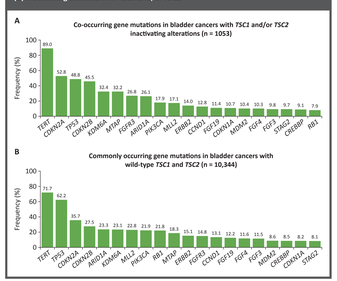


Figure 5. Gene mutations commonly observed in kidney cancers with (A) or without (B) inactivating alterations in *TSC1* and/or *TSC2*

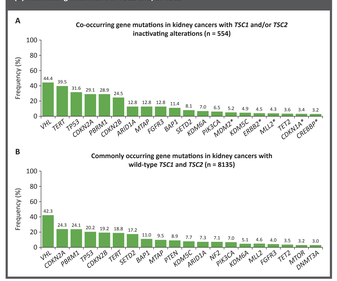
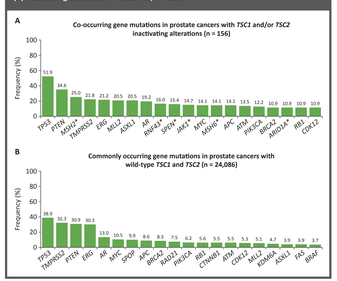


Figure 7. Gene mutations commonly observed in prostate cancers with (A) or without (B) inactivating alterations in *TSC1* and/or *TSC2*



*Co-mutations in tumors with inactivating alterations in *TSC1* and *TSC2* but not among the 20 most frequent mutations in cancers with wild-type *TSC1* and *TSC2*.

Figure 4. Tumor mutational burden (A) and microsatellite instability (B) status in patients with bladder cancer with inactivating alterations in *TSC1* and/or *TSC2* (top) or tumors with wild-type *TSC1* and *TSC2* (bottom)

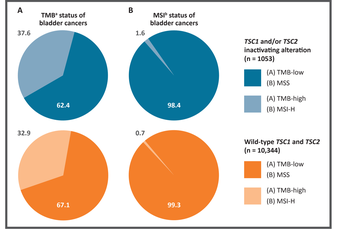


Figure 6. Tumor mutational burden (A) and microsatellite instability (B) status in patients with kidney cancers with inactivating alterations in *TSC1* and/or *TSC2* (top) or tumors with wild-type *TSC1* and *TSC2* (bottom)

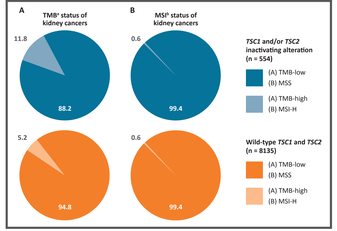
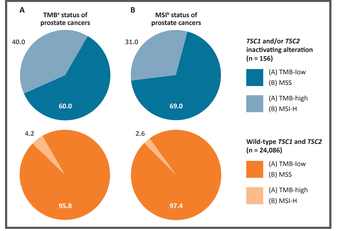


Figure 8. Tumor mutational burden (A) and microsatellite instability (B) status in patients with prostate cancer with inactivating alterations in *TSC1* and/or *TSC2* (top) or tumors with wild-type *TSC1* and *TSC2* (bottom)



*Tumor mutational burden (TMB) status of the specimen was annotated as either TMB-high (≥10 non-driver somatic coding mutations detected per megabase of genome sequenced) or TMB-low (<10 non-driver somatic coding mutations detected per megabase of genome sequenced). Specimens for which a TMB status could not be determined were not included.
†Microsatellite instability (MSI) status of the specimen was annotated as either MSI-H (microsatellite instability high) or MSS (microsatellite stable). Specimens for which an MSI status could not be determined were not included.

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