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THE POWER OF SHARED PURPOSE: Transforming Gynecologic Cancer Care

Analysis of inactivating *TSC1* and *TSC2* alterations in a real-world patient population with advanced gynecological cancers in the Foundation Medicine genomic database

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Objective

- To characterize and enumerate the frequency of *TSC1* and *TSC2* mutations in gynecological cancers across a large real-world patient population with advanced cancer using data from tumor tissue biopsies

KEY TAKEAWAYS

- In a large real-world database of patients with advanced cancer, 1342 (2.4%) of the 54,911 patients with gynecological cancers harbored at least one inactivating alteration in *TSC1* or *TSC2*
- *TSC1* and/or *TSC2* inactivating alterations were present in 3.6% of endometrial cancers, 2.0% of ovarian cancers, and 1.5% of cervical cancers
- Across endometrial, ovarian, and cervical cancers, genes frequently mutated in tumors with wild-type *TSC1* and *TSC2* were similar to genetic mutations co-occurring in tumors with alterations in *TSC1* and/or *TSC2*
- Most ovarian cancers were characterized as TMB-low and MSS, regardless of *TSC1* and/or *TSC2* mutation status; increased TMB and MSI signatures were enriched in endometrial cancers with *TSC1* and/or *TSC2* alterations; similar TMB and MSI patterns were observed among cervical cancers with and without *TSC1* or *TSC2* mutations
- 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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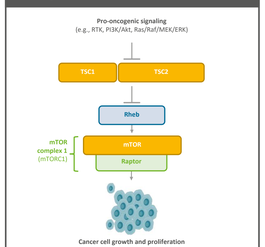
BACKGROUND

- Overactivation of the PI3K-Akt-mTOR pathway has been implicated in a number of cancers, including gynecological cancers,[1] and can result from inactivation of the tumor suppressor genes *TSC1* and/or *TSC2* (**Figure 1**)[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 (mTORi), is approved in the United States for treatment of patients with advanced malignant perivascular epithelioid cell tumors (PEComa),[3] a group of rare aggressive tumors that can originate in gynecological tissues[4–6]
- Confirmed responses to *nab*-sirolimus have been observed among patients with inactivating alterations in *TSC1* or *TSC2*:
  - 9 of 14 patients with malignant PEComa in the phase 2 AMPECT study (NCT02494570)[7]
  - 5 of 7 patients in a pan-tumor Expanded Access Program (NCT03817515)[8]
- 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 gynecological cancers

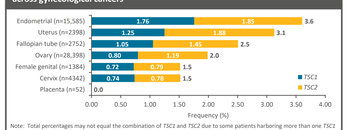
METHODS

- Next-generation sequencing (NGS) data collected from unique patient specimens (August 2014 to July 2023) from patients with advanced gynecological cancers (excluding hematological, neuroendocrine, and sarcoma malignancies), were analyzed using the FoundationCORE database
- Prevalence of *TSC1* and/or *TSC2* inactivating alterations among patients with gynecological cancers were enumerated; *TSC1* and *TSC2* variant types, tumor mutational burden (TMB), microsatellite instability (MSI or microsatellite stable [MSS]), and co-occurring gene alterations were further characterized among commonly occurring gynecological cancers
- *TSC1* and *TSC2* variants were categorized according to likelihood of inactivation—"**known**", "**likely**", "**ambiguous**", or "**unknown**"—based on Foundation Medicine's assessments for pathogenicity
  - **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 without *TSC1* or *TSC2* alterations present, and those with *TSC1* or *TSC2* alterations of ambiguous or unknown significance, were classified as wild-type *TSC1* and *TSC2*

RESULTS

- As of July 26, 2023, NGS data were available for 54,911 patients with advanced gynecological solid tumor malignancies in the Foundation Medicine database, 1342 (2.4%) of which had inactivating alterations in *TSC1* and/or *TSC2*
  - Among gynecological cancers with *TSC1* or *TSC2* alterations, 44.8% were in *TSC1* and 56.3% were in *TSC2*; and the median age of patients with such cancers at time of testing was 64 years (IQR: 55–71)

Figure 2. Frequency of known/likely inactivating alterations in *TSC1* and/or *TSC2* across gynecological 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*.

- Advanced endometrial (n=15,585), ovarian (n=28,398), and cervical (n=4342) cancers were the most common gynecological cancers observed in our FMI database search (**Figure 2**) and are characterized further
- Analysis of tumor histologies showed 99.8% of endometrial cancers were adenocarcinomas, 65.8% of ovarian cancers were serous carcinomas, and 61.8% of cervical cancers were squamous cell carcinomas
- Among endometrial, ovarian, and cervical cancers:
  - Most *TSC1* and *TSC2* inactivating alterations were short variants (60.2%–100%); rearrangement alterations ranged from 0.0%–24.0%; copy number deletions were less frequent in endometrial and cervical cancers (0.0%–5.9%), but more frequent in ovarian cancers (up to 22.1%)
  - *TP53* was one of the most commonly observed mutations across these cohorts
  - Regardless of *TSC1* and/or *TSC2* mutation status, *PIK3CA* and *PTEN* were commonly mutated in endometrial and cervical cancers, but less so in ovarian cancers
  - Patterns of TMB and MSI status varied across tumor type cohorts and by *TSC1* and/or *TSC2* mutation status

Characterization of *TSC1* and *TSC2* inactivating alterations in endometrial cancers

- Inactivating alterations in *TSC1* and/or *TSC2* were found in 3.6% of endometrial cancers (**Figure 2**)
- Endometrial cancers with inactivating alterations in *TSC1* and/or *TSC2* were:
  - Enriched for co-occurring mutations in *PTEN* and *ARID1A* relative to the wild-type cohort (**Figure 3A** and **3B**)
  - TMB-high in 61.2% and 54.5% were MSI-high (MSI-H) vs wild-type tumors that were mostly TMB-low and MSS (**Figure 4A** and **4B**)

Characterization of *TSC1* and *TSC2* inactivating alterations in ovarian cancers

- Inactivating alterations in *TSC1* and/or *TSC2* were present in 2.0% of ovarian cancers (**Figure 2**)
- Regardless of *TSC1* and/or *TSC2* mutation status, mutations in *TP53* were the most frequently observed mutation in ovarian cancers (**Figure 5A** and **5B**)
- Most ovarian cancers were TMB-low and MSS (**Figure 6A** and **6B**) independent of *TSC1* and/or *TSC2* mutation status

Characterization of *TSC1* and *TSC2* inactivating alterations in cervical cancers

- Inactivating alterations in *TSC1* and/or *TSC2* were present in 1.5% of cervical cancers (**Figure 2**)
- *PIK3CA* and *TP53* were the top two mutations observed in cervical cancers regardless of *TSC1* and/or *TSC2* mutation status (**Figure 7A** and **7B**)
- Cervical cancers with inactivating alterations in *TSC1* and/or *TSC2* were TMB-high in 39.7% of tumors and 12.9% were MSI-H, similar to the TMB and MSI status of wild-type tumors (**Figure 8A** and **8B**)

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

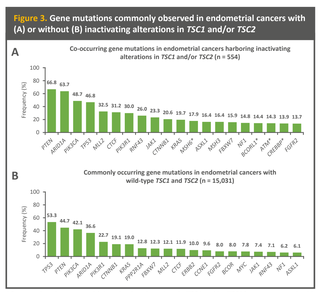


Figure 5. Gene mutations commonly observed in ovarian cancers with (A) or without (B) inactivating alterations in *TSC1* and/or *TSC2*

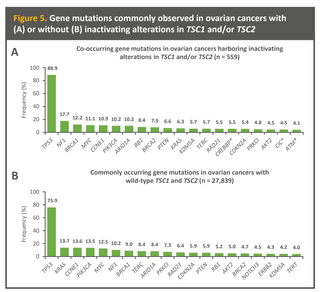
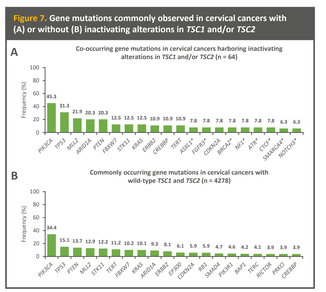


Figure 7. Gene mutations commonly observed in cervical cancers with (A) or without (B) inactivating alterations in *TSC1* and/or *TSC2*



*Co-mutations in tumors with inactivating alterations in *TSC1* and/or *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 endometrial cancer with inactivating alterations in *TSC1* and/or *TSC2* (top) or tumors with wild-type *TSC1* and *TSC2* (bottom)

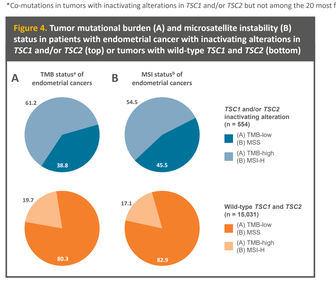


Figure 6. Tumor mutational burden (A) and microsatellite instability (B) status in patients with ovarian cancer with inactivating alterations in *TSC1* and/or *TSC2* (top) or tumors with wild-type *TSC1* and *TSC2* (bottom)

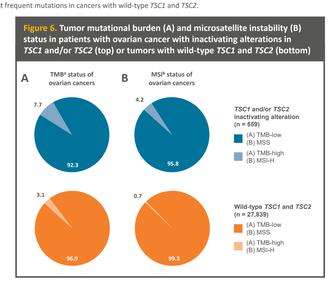
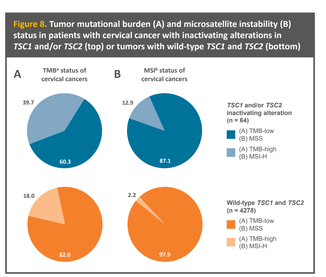


Figure 8. Tumor mutational burden (A) and microsatellite instability (B) status in patients with cervical cancer with inactivating alterations in *TSC1* and/or *TSC2* (top) or tumors with wild-type *TSC1* and *TSC2* (bottom)



[a]Tumor mutational burden (TMB) status of the specimen was 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. [b]Microsatellite instability (MSI) status of the specimen was 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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For disclosures of co-authors please see abstract.

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