Real-world analysis of patients with advanced gastrointestinal cancers harboring inactivating alterations in *TSC1* and *TSC2* using the Foundation Medicine genomic database

Dustin Deming, MD[1]; Willis H. Navarro, MD[2]; Gopa Iyer, MD[3]; David J. Kwiatkowski, MD, PhD[4]

[1]University of Wisconsin Carbone Cancer Center, Madison, WI, USA; [2]Aadi Bioscience, Inc., Pacific Palisades, CA; [3]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]Brigham and Women's Hospital, Boston, MA, USA

Objective

- **To characterize and enumerate the frequency of *TSC1* and *TSC2* mutations in gastrointestinal (GI) cancers 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, 1,898 (1.4%) of the 138,671 patients with GI cancers harbored at least one known or likely inactivating alteration in *TSC1* or *TSC2***
- ***TSC1* and/or *TSC2* inactivating alterations were present in 6.8% of liver cancers, 1.6% of colorectal cancers, and 0.5% of pancreatic cancers**
- **Across GI malignancies, 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 *TSC1* and/or *TSC2* inactivating alterations in liver and pancreatic cancers occurred in the context of low TMB and MSS tumors; whereas increased TMB and MSI signatures were enriched in colorectal cancer with *TSC1* and/or *TSC2* 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**
- **The PRECISION 1 study (NCT05103358) is currently enrolling patients with solid tumors harboring *TSC1* and/or *TSC2* inactivating alterations**

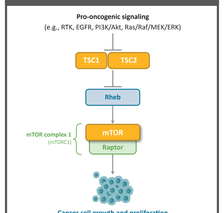
Presented at the ASCO Gastrointestinal Cancers Symposium; San Francisco, CA; January 18–20, 2024

Correspondence: MedInfo@AadiBio.com

BACKGROUND

- Gastrointestinal (GI) cancers have a poor prognosis as indicated by low 5-year survival rates in patients with advanced colorectal (15.6%), liver (3.5%), and pancreatic (3.2%) cancers[1]
- Overactivation of the PI3K-Akt-mTOR pathway, has been implicated in a number of cancers, including GI cancers[2], and can result from inactivation of the tumor suppressor genes *TSC1* and *TSC2* (**Figure 1**)[3,4]

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 for treatment of patients with advanced malignant perivascular epithelioid cell tumors (PEComa)[4], a group of rare aggressive tumors that can originate in GI tissues[5,6]
- Of patients with malignant PEComa and known inactivating alterations in *TSC1* or *TSC2*, 9 of 14 (64.3%) in the phase 2 AMPECT study (NCT02494570)[7,8], and 5 of 7 (71.4%) in the pan-tumor Expanded Access Program (NCT03817515)[9], 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/or *TSC2* mutational data from a real-world genomic database were analyzed to enumerate the frequency and characteristics of the alterations in GI cancers

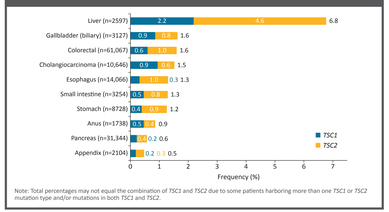
METHODS

- Next-generation sequencing (NGS) data collected from unique patient specimens (August 2014 to July 2023) from patients with gastrointestinal (GI) cancers (excluding hematological, neuroendocrine, and sarcoma malignancies), were analyzed using the FoundationCORE database. Prevalence of *TSC1* and/or *TSC2* inactivating alterations among patients with GI cancers were enumerated; *TSC1* and *TSC2* variant types, tumor mutational burden (TMB), microsatellite instability (MSI), and co-occurring gene alterations were further characterized among commonly occurring GI 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 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 138,671 patients with GI solid tumor malignancies in the Foundation Medicine database, 1898 (1.4%) of which had inactivating alterations in *TSC1* and/or *TSC2*
  - Among GI cancers with *TSC1* or *TSC2* alterations, 38.3% were in *TSC1* and 62.3% were in *TSC2*
  - Among patients with GI cancers, 56.8% were male, 43.2% were female, and the median age at time of testing was 63 years (IQR: 55–71)

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



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 GI malignancies, colorectal and pancreatic cancers were the most common types of GI cancers observed in the database and liver cancers had the highest frequency of known/likely inactivating alterations in *TSC1* and/or *TSC2* and are characterized further in this analysis
  - *TP53* was the most commonly observed mutation across all 3 GI tumor types
  - Regardless of *TSC1* and *TSC2* mutation status, *KRAS* was commonly mutated in colorectal and pancreatic cancers, but not in liver cancer
  - TMB and MSI status patterns were similar across GI tumor types, with or without *TSC1* or *TSC2* alterations, most patients had tumors with a low TMB (<10 mutations/megabase) and were microsatellite stable (MSS)

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

- Inactivating alterations in *TSC1* and/or *TSC2* were found in 6.8% of liver cancers[a] (**Figure 2**)
  - Hepatocellular carcinoma represented 97% of this cohort
- *TSC1* and *TSC2* inactivating alterations included short variants (75.4% and 77.3%), copy number deletions (19.3% and 17.6%), and rearrangements (5.3% and 5.0%), respectively
- Liver cancers with inactivating alterations in *TSC1* and/or *TSC2* were enriched for co-occurring mutations in *TP53* and *RB1* relative to the wild-type cohort (**Figure 3A** and **3B**)
- Regardless of *TSC1* and/or *TSC2* mutation status, most liver cancers had low TMB and were MSS (**Figure 4A** and **4B**)

[a]Liver cancer histologies included hepatocellular carcinoma and hepatoblastoma

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

- 1.6% of colorectal cancers[a] had inactivating alterations in *TSC1* and/or *TSC2* (**Figure 2**)
  - Colon adenocarcinoma represented 81% of this cohort
- *TSC1* and *TSC2* inactivating alterations included short variants (88.3% and 88.2%), copy number deletions (5.5% and 10.4%), and rearrangements (6.3% and 7.3%), respectively
- Mutations in *APC*, *TP53*, and *KRAS* were frequently expressed across all colorectal cancers; colorectal cancers with inactivating alterations in *TSC1* and/or *TSC2* were enriched for co-occurring mutations in *RNF43*, *BRAF*, *FBXW7*, *PTEN*, and *BRCA2* (**Figure 5A** and **5B**)
- Colorectal cancers with inactivating alterations in *TSC1* and/or *TSC2* had a high TMB (≥10 mutations/megabase) in 39% of tumors and 32% were MSI-high (MSI-H) (**Figure 6A** and **6B**)

[a]Colorectal cancer histologies included colon adenocarcinoma, rectum adenocarcinoma, rectum myoepithelial carcinoma

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

- 0.5% of pancreatic cancers[a] had inactivating alterations in *TSC1* and/or *TSC2* (**Figure 2**)
  - Pancreas ductal adenocarcinoma represented 79% of this cohort
- *TSC1* and *TSC2* inactivating alterations included short variants (81.4% and 78.4%), copy number deletions (10.0% and 6.3%), and rearrangements (8.6% and 15.3%), respectively
- Regardless of *TSC1* and *TSC2* mutation status, pancreatic cancers frequently expressed mutations in *KRAS*, *TP53*, and *CDKN2A*; however, they were expressed in higher frequencies among tumors with wild-type *TSC1* and *TSC2* (**Figure 7A** and **7B**)
- Almost all pancreatic cancers, with or without inactivating alterations in *TSC1* and/or *TSC2* had low TMB and were MSS (**Figure 8A** and **8B**)

[a]Pancreatic cancer histologies included pancreas acinar cell carcinoma, pancreas ductal adenocarcinoma, pancreas ductal carcinoma, pancreas hepatoid carcinoma, pancreas mucinous cystadenocarcinoma, pancreatoblastic carcinoma, pancreas pancreatoblastoma, pancreas intraductal papillary mucinous tumor, pancreas solid and papillary tumor, and pancreas solid pseudopapicolon tumor

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

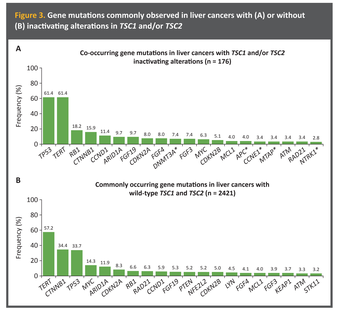


Figure 5. Gene mutations commonly observed in colorectal cancers with (A) or without (B) inactivating alterations in *TSC1* and/or *TSC2*

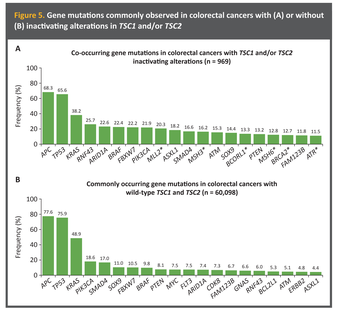


Figure 7. Gene mutations commonly observed in pancreatic cancers with (A) or without (B) inactivating alterations in *TSC1* and/or *TSC2*

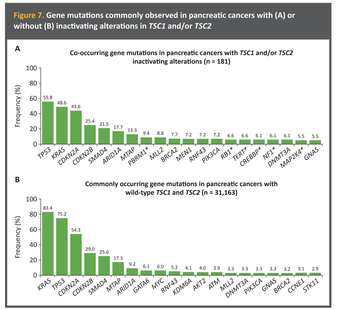


Figure 4. Tumor mutational burden[a] (A) and microsatellite instability[b] (B) status in patients with liver cancer with inactivating alterations in *TSC1* and/or *TSC2* (top) or tumors with wild-type *TSC1* and *TSC2* (bottom)

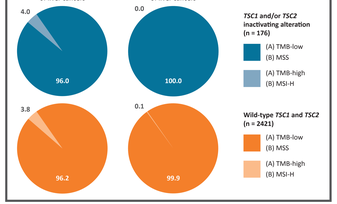


Figure 6. Tumor mutational burden[a] (A) and microsatellite instability[b] (B) status in patients with colorectal cancer with inactivating alterations in *TSC1* and/or *TSC2* (top) or tumors with wild-type *TSC1* and *TSC2* (bottom)

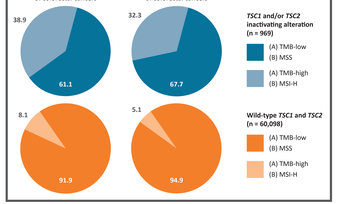
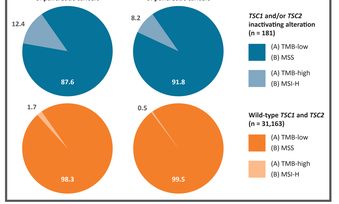


Figure 8. Tumor mutational burden[a] (A) and microsatellite instability[b] (B) status in patients with pancreatic cancer with inactivating alterations in *TSC1* and/or *TSC2* (top) or tumors with wild-type *TSC1* and *TSC2* (bottom)



[a]Tumor mutational burden (TMB) status of the specimen was 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.
[b]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.

Acknowledgments & Disclosures

We thank Ashwini Pai and Rebekah Hartwell of Aadi Bioscience, Inc. for their support of this project and for contributions made to the poster. We thank Norma Palma, PhD, formerly of Aadi Bioscience, Inc. for her contributions to this analysis. Medical writing and editorial assistance were provided by Heather Caballes, PhD and Andrea Humphries, PhD, CMPP, of Twist Medical, and were funded by Aadi Bioscience, Inc.

This study was funded by Aadi Bioscience, Inc. Dr. Dustin Deming reports research funding from Merck, Genentech, Bristol Myers Squibb, Aadi Bioscience, Inc., Pfizer, Curegenix, Promega, Natera, STRATA Oncology, Cornerstone Pharmaceuticals, Arcus, Guardant Health, Ipsen, Takeda, Eli Lilly, and Revolution Medicine; consulting or advisory board membership for Bayer, Pfizer, Seagen, Eli Lilly, Foundation Medicine, Illumina, Regeneron, and Aadi Bioscience, Inc.; and participation in the data safety monitoring board for Seagen. For the disclosures of his co-authors please refer to the abstract.

References

1. NCI. SEER statistics. https://seer.cancer.gov/statistics-network/explorer. Accessed November 3, 2023.
2. Millis SZ, et al. *Cancer.* 2019;125:1185-1199.
3. Huang J, Manning BD. *Biochem J.* 2008:412(2):179-190.
4. FYARRO® (sirolimus protein-bound particles for injectable suspension [albumin-bound]). Package insert. Aadi Bioscience, Inc.: Pacific Palisades, CA; December 2021.
5. Armah HB, Parwani AV. *Arch Pathol Lab Med.* 2009;133:648-654.
6. Bleeker JS, et al. *Sarcoma.* 2012;2012:541626.
7. Wagner AJ, et al. CTOS, November 16–19, 2022, Vancouver, BC. Poster 167.
8. Cranmer LD, et al. AACR, April 14–19, 2023, Orlando, FL. Poster LB288.
9. Dickson MA, et al. *J Clin Oncol.* 2021;39(15_suppl):3111.