**Abstract**

Small-bowel adenocarcinomas (SBA) is a rare malignancy with limited knowledge of the molecular mechanisms or clinical evidence-based guidelines for therapy. We conducted a comprehensive analysis of biomarkers with therapeutic relevance for SBA.

**Background**

Malignancies of the small bowel are among the rarest types of cancer, accounting for only 0.8% of all malignant tumors. Adenocarcinomas are the most common subtype of small-bowel adenocarcinoma, and an estimated 5,000 people will be diagnosed with the disease in 2023 (American Cancer Society). Delay in diagnosis of SBA is common with a majority of patients (46%) presenting at Stage III or IV disease.

Small-bowel adenocarcinomas share a striking resemblance to large-bowel (colorectal) adenocarcinomas, including similar metastatic sites of the liver and lung, Barrett’s esophagus, and a similar histopathology and clinical history. Specific therapy was performed per physician request and included a combination of sequencing (joint-generation sequencing (JGS), protein expression (immunochemistry), and gene amplification (CGH or FISH)).

**Results**

Two hundred sixty-four SBA cases were studied and grouped according to primary tumor site location.

**Conclusions**

- 50% of SBA patients do not carry biomarkers of cetuximab resistance such as KRAS, NRAS, PIK3CA (5/31 exhibited mutations) and BRAF V600E.
- We identified novel biomarkers associated with drug sensitivity: MET overexpression (MET inhibitors), low MMAT (inhibiting agents −tremetinib), low RRM1 (gemcitabine), and low PTEN (gemcitabine) and TGF (metastatic) and tissue.
- Tumor DNA sequencing identified somatic mutations: BRAF, NRG1, NRAS−MEK inhibitors; ATM−panitinib; RAF−BRAF, PD318907, RAF/RAS/RAF.
- BRAF V600E mutations were not observed in SBA, however non−V600E mutations were observed in both BRAF WT and MT SBA. The oncogenic role of non−V600E mutations which are prevalent in other cancer types (NGC1s) is being studied, including their therapeutic relevance.
- 50% do not carry ISH or sequence alterations, but had potentially favorable protein biomarkers by the IHC.

**References**