THE ASSOCIATION BETWEEN NEUROTROPHIC TROPOMYCIN RECEPTOR KINASE (NTRK) VARIANTS OF UNKNOWN SIGNIFICANCE (VUS’S) AND RESPONSE TO IMMUNE CHECKPOINT INHIBITORS IN SOLID TUMORS

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Background Since the available predictive biomarkers of response to immune checkpoint inhibitors (ICIs) have limited predictive power, additional biomarkers are needed. Neurotrophic tropomycin receptor kinase (NTRK) fusions are rare. Therefore, their association with response to ICIs is not well understood. NTRK variants of unknown significance (VUS’s) are common, but their clinical relevance is unknown. Here, we explored the association between NTRK VUS’s and the response to ICIs in solid tumors.

Methods The cBioCancer Genomics Portal was used to obtain genomics data. The association between NTRK VUS’s and median overall survival (mOS) was explored in ICI-treated cohort comprising a total of 166 patients. The cohort includes patients with cancers of the skin (melanoma), colon, rectum, lung, unknown primary, bladder, head and neck, stomach, esophagus, brain, breast and kidney who had received at least one dose of ICIs. The log rank test was used to compare Kaplan-Meier survival curves.

Results Among the 1661 patients included in this cohort, 144 patients (8.7%) NTRK VUS’s. NTRK1, NTRK2 and NTRK3 VUS’s were reported in 39 (2.3%), 24 (1.4%) and 52 (3.1%) patients, respectively. Co-occurrence of more than 1 NTRK VUS’s was reported in 29 (1.7%) patients. Only 2 patients had NTRK fusions (LMNA-NTRK1 and ZNF710-NTRK3). All other patients had NTRK VUS’s including missense, nonsense, nonstop, splice site and frameshift deletion alterations. The mOS in patients with NTRK VUS’s was better than patients without NTRK VUS’s (34 m vs. 17 m, p<0.0001). Compared to patients without NTRK VUS’s, mOS was better in patients with NTRK3 VUS’s (not reached (NR) vs. 17 m, p<0.0001) and a trend for better mOS was seen in patients with NTRK1 and NTRK2 VUS’s (23 m vs. 17 m, p=0.754) and (23 m vs. 17 m, p=0.904), respectively. Controlling for age, a multivariable Cox regression model showed that besides NTRK3 VUS’s (HR: 0.65, p=0.0078), tumor type (melanoma vs. non-melanoma) (HR: 0.3, p<0.0001) and absence of liver metastasis (HR: 0.57, p<0.0001) were other factors associated with better mOS.

Conclusions NTRK VUS’s were associated with better mOS in patients with solid tumors treated with ICIs. The statistical significance was limited to NTRK3 alterations but a trend for better mOS was evident in NTRK1 and NTRK2. Prospective validation and efforts to understand the underlying mechanisms are warranted.

Ethics Approval This study was performed utilizing retrospective, de-identified clinical data. Therefore, this study is considered institutional review board (IRB) exempt.

Consent This study was performed utilizing retrospective, de-identified clinical data. Therefore, no patient consent was necessary from the subject.

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