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Abstract

Introduction

Tumor mutational burden (TMB) is a promising biomarker of clinical response to immune checkpoint inhibitors in metastatic cancers[1,2,3] and melanoma-specific survival[4]. There are also significant gender-specific differences in TMB with men having consistently higher TMB than women[4]. This relationship is provocative given the well-documented female melanoma survival advantage[5,6], and has not been investigated in early-stage primary tumors naïve to treatment.

Approach

Here we present preliminary findings on sex, survival, and tumor mutational burden from Stages II and III primary melanoma tumors, none of which have received immunotherapy using the MSK IMPACT™ next generation sequencing assay. Our team evaluated survival in 581 primary melanoma tumors procured by the parent P01 grant; 251 from patients who died with melanoma within five years (median survival, 2.4 years), and 330 from individuals who have lived at least five years (median follow up 8.5 years).

Preliminary Results

In the full dataset, we found the expected female survival advantage (log rank test P=0.049). After controlling for multiple comparisons using maximally selected ranked statistics[7] the protective effect of high TMB on survival disappeared (HR=0.43, 95%

CI=0.19 to 0.97, P=0.037). When stratified by sex, high TMB was associated with significantly improved melanoma specific survival among men (p=0.024), but not women (P=0.9).

Broader Impacts

Our study is the first to investigate the relationship between sex, tumor mutational burden, and mortality in an early stage primary cohort that has not received immunotherapy. In our small sample, we observed the expected protective effect of TMB on survival, but no evidence of gender differences in TMB or survival, despite the robust, consistent, and well-documented female survival advantage [5,6]. Our results are an important first step to increasing our understanding of the relationship between mutational burden, survival, and biological sex.

Limitations

These results are exploratory and have not been adjusted for potential confounding factors such as stage, Breslow score, gender, or age.

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