Impact of Prior Chemotherapy or Radiation Therapy on Tumor Mutation Burden in NSCLC

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Background

• Higher tumor mutation burden (TMB) in non-small cell lung cancer (NSCLC) correlates with increased expression of tumor-specific neo-antigens and with clinical efficacy of immune check point inhibitors.1

• Nivolumab plus ipilimumab improved progression-free survival in patients with NSCLC and high tumor mutation burden.2

• Tissue samples subject to TMB analysis may be obtained after exposure to cytotoxic chemotherapy or radiation therapy – both of which introduce somatic mutations in DNA and can influence the number of identified mutations.

• The role of TMB as a potential predictive marker for immunotherapy is evolving, and the impact of prior therapy on TMB could influence interpretation.

Methods

• Eligible cases were from patients with confirmed NSCLC, available clinical annotation and tumor molecular profiling including TMB analysis at a CLIA-certified genomics laboratory (Caris Life Sciences, Phoenix, AZ) using the Illumina NextSeq platform.

• NGS was performed on genomic DNA isolated from FFPE tumor samples using the NextSeq (952-genes).

• Tumor mutation burden (TMB) was estimated from 592 genes (1.4 megabases MB) sequenced per patient by counting all non-synonymous missense mutations found per tumor that had not been previously described as germline alterations.

• Treatment history was obtained for each patient under an IRB approved protocol to determine whether patients had received chemotherapy or radiation therapy in the year prior to collection of the tissue subject to TMB analysis.

• Data analysis was performed using either the Wilcoxon rank test or the chi-square test of deviance to evaluate whether TMB was statistically significantly different between groups, correcting for smoking status or oncogene status (R software).

• Oncogenes included in analysis are EGFR, ALK, ROS1, BRAF, RET, and NTRK. P-values were assessed using the Wilcoxon rank-sum test with (p-adjusted) and without (p-value) correcting for smoking status.

Results

Figure 1. Sample Selection Summary

Table 1. Patient and Tumor Characteristics

Table 2. Comparison of TMB Between Cohorts

Figure 2. Comparison of TMB Prior To or After Treatment

Table 3. Comparison of TMB Adjusted for Presence of Oncogene

Figure 3. TMB by Tissue Source (Primary vs. Metastasis)

Conclusions

• Though cytotoxic chemotherapy and radiation therapy can introduce somatic mutations, prior exposure to either was not associated with a significant difference in TMB.

• TMB was higher when the specimen source was from a metastatic site compared to the primary site.

• Prior exposure to therapy did not impact TMB after adjusting for presence of an oncogene.

References


