Correlation of tumor mutational burden (TMB) with CDKN2A and TP53 mutations in HPV-negative head and neck squamous cell carcinoma (HNSCC)

Barbara Burtness1, Alexander Y Deneka2, Yasmine Baca3, Ilya G. Serebriiskii2, Mitchell I Parker2,4, Emmanuelle Nicolas2, Jong-Woo Lee1, Trisha Wise-Draper5, Ammar Sukari5, Erica A Golemis2

1 Department of Internal Medicine and Yale Cancer Center, Yale School of Medicine; 2 Molecular Therapeutics Program, Fox Chase Cancer Center; 3 Caris Biosciences; 4 Molecular & Cell Biology & Genetics (MCBG) Program, Drexel University College of Medicine; 5 University of Cincinnati Cancer Center; 6 Karmanos Cancer Center

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Background

- High tumor mutation burden (TMB) is a predictive biomarker for response to immune checkpoint inhibition
- Mutations in the tumor suppressors TP53 and CDKN2A are common in HNSCC; whether these mutations collaborate to increase TMB is not known
- Complicating assessment, there are multiple subclasses of TP53 mutation, including loss of function (LOF), dominant negative (DN), gain of function (GOF), and benign; each associated with distinct prognosis
- In this study, we assessed the relationship between TMB, and TP53 and CDKN2A mutation status, based on different TMB mutation classes.

Methods

- The patient cohort analyzed included 1010 HPV- HNSCC tumor samples (246 female) profiled with a 592-gene panel by Caris Life Sciences from 2015 to 2019
- P16 was tested by IHC (clone E6H4) and confirmatory HPV High Risk ISH was carried out using mRNA probes (HPV 16, 18 and 33).
- Predominant subtypes were oral cavity (285), oropharynx (225) and larynx (153). Data for TP53 were separately analyzed using 6 classifications:
  - (1) American College of Medical Genetics (ACMG) pathogenic variants. This captures essentially all TP53 mutations observed in the study cohort
  - (2) Consensus calls by ACMG, InterVar (PMID: 28132688), and ClinVar
  - (3, 4) Variants classified as DNE, or as DNE and LOF by the International Agency for Research on Cancer (IARC) (http://pdb.iarc.fr)
  - (5) Variants defined as damaging by Poeta et al (PMID: 18094376); TP53 mutations called by this classification was previously shown to predict poor prognosis in HNSCC (PMID: 25108461).
  - (6) Variants defined as GOF based on multiple publications
- CDKN2A mutations were almost invariably truncations or deletions, and all were considered.
- TMB was measured from 592 genes (1.4 megabases [MB] sequenced per tumor) by counting all nonsynonymous missense mutations found per tumor that had not been previously described as germline alterations (Figure 1).
- The threshold to define TMB-high was ≥15 mutations/MB. Data are plotted for each TP53 mutation classification (1-6) versus a comparison group that included wild type TP53 plus all mutations not called by the classification system.

Results

Whether loss of CDKN2A increases the frequency of tumors with high (>15) TMB depends on the type of TP53 mutation present.

Conclusions and Future Directions

- Mutation of TP53 and/or CDKN2A is associated with increased mean TMB relative to WT.
- Mean TMB was highest for tumors bearing damaging mutations in both genes.
- GOF TP53 mutation was not associated with increased TMB; however, this analysis had less power due to smaller numbers of cases with GOF TP53.