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

Abstract #6552

Barbara Burtness[1], Alexander Y Deneka[2], Yasmine Baca[3], Ilya G. Serebriiskii[2], Mitchell I Parker[2,4], Emmanuelle Nicolas[2], Jong-Woo Lee[1], Trisha Wise-Draper[5], Ammar Sukari[6], Erica A Golemis[2]

[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

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 *TP53* 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 subsites 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://p53.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.

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Contact: Barbara Burtness at barbara.burtness@yale.edu
Erica Golemis at Erica.Golemis@fccc.edu,

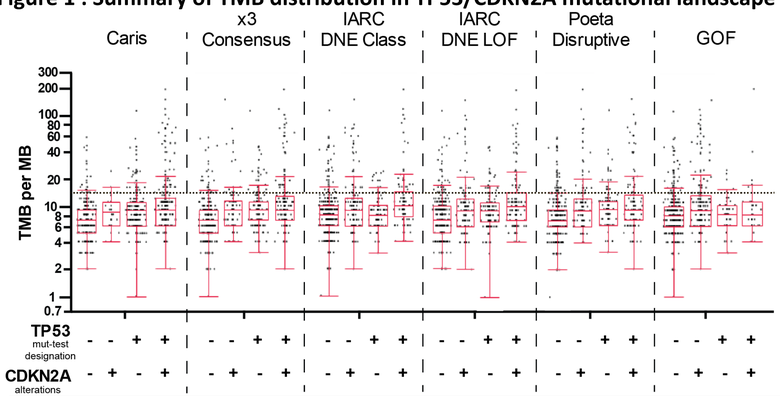
Table 1: Patient demographic information and subtype distribution

Head and Neck Cancer Type	Female	Average age Female	Male	Average age Male	Total
Cancer of the oral cavity	91	62.9	194	61.2	285
Cancer of the oropharynx	39	62.7	186	61.3	225
Advanced	26	59.6	77	65.1	103
Cancer of the nasopharynx	25	54.9	68	54.4	93
Cancer of the glottic larynx	12	63.5	73	66.3	85
Cancer of the supraglottic larynx	18	58.7	50	66.4	68
Occult Primary	8	68.6	31	64.2	39
Others	5	67.0	32	64.3	37
Maxillary sinus tumors	12	59.3	21	60.0	33
Cancer of the hypopharynx	4	57.8	23	66.5	27
Ethmoid sinus tumors	4	59.8	6	71.7	10
Cancer of the lip	2	59.5	3	59.3	5
Grand Total	246		764		1010

Table 2: Distribution of TP53/CDKN2A mutations

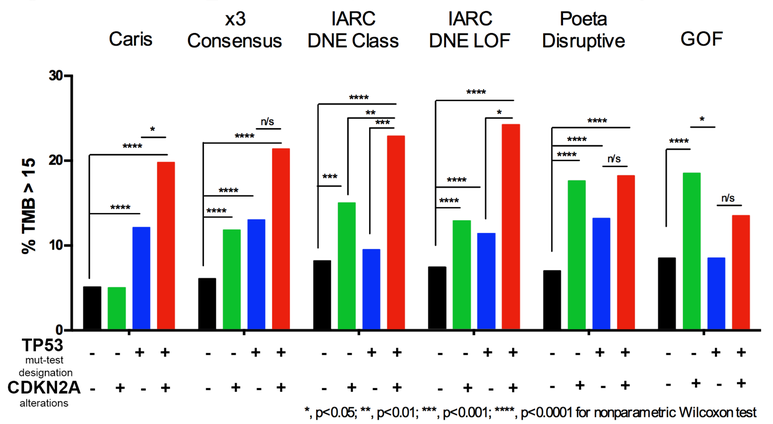
Mutation class	Caris	x3 Consensus	IARC DNE Class	IARC DNE LOF	Poeta Disruptive	GOF
TP53 nonmutated/CDKN2A WT	363	464	563	524	535	639
TP53 nonmutated/CDKN2A MT	41	115	201	174	171	276
TP53 MT/CDKN2A WT	332	231	132	171	160	56
TP53/CDKN2A co-mutated	274	200	114	141	144	39

Figure 1 : Summary of TMB distribution in TP53/CDKN2A mutational landscape



	Caris				x3 Consensus				IARC DNE Class				IARC DNELOF				Poeta				GOF			
N	351	40	314	262	442	110	223	192	539	193	126	109	499	170	166	132	514	165	151	137	610	265	55	37

Figure 2 : % of TMB ≥ 15 with TP53/CDKN2A mutational landscape indicated



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 number of cases with GOF *TP53*.