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10-2018

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**68P Pan-squamous genomic profiling stratified by anatomic tumor site and viral association**

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**Background:** Squamous cell carcinomas (SCC) have diverse anatomic etiologies but may share common genomic biomarkers. We profiled 7,871 unique SCCs across nine anatomic sites to investigate commonality in genomic alterations (GA), tumor mutational burden (TMB), human papillomavirus (HPV) association, and mutational signatures.

**Methods:** Tissue from over 8,100 unique SCC samples originating from nine anatomic sites (anogenital (anus, cervix, penis, vagina, vulva), esophagus, head and neck, lung, and skin) were sequenced by hybrid capture-based comprehensive genomic profiling to evaluate GA and TMB. About 3% of non-cutaneous SCC samples had UV signatures, indicative of potential primary site misdiagnoses, and were filtered from the analysis. Detection of HPV, including high-risk strains 16, 18, 31, 33, and 45, was implemented through de novo assembly of non-human sequencing reads and BLASTn comparison against all viral nucleotide sequences in the NCBI database.

**Results:** The proportion of HPV+ patients by anatomic site varied, with the highest being anal (91%) and cervical (83%). The mutational landscape of each cohort was similar, regardless of anatomic origin, but clustered based on HPV status. The largest differences in GA frequency as stratified by HPV- vs. HPV+ were TP53 (87% vs. 12%), CDKN2A (45% vs. 6%), and PIK3CA (22% vs. 33%). The median TMB in cases originating from HPV-associated sites was similar, regardless of HPV status. Higher median TMB was observed in lung and skin cases, which exhibited significant enrichment of mutational signatures indicative of tobacco- and UV-induced DNA damage, respectively.

**Conclusions:** HPV+ and HPV- SCC populations have distinct genomic profiles and, for the latter, anatomic site is correlated with TMB distribution, secondary to associated carcinogen exposure. As such, biomarkers such as TMB and UV signature can provide unexpected insight into site of origin misdiagnoses and may correlate with benefit from immune checkpoint inhibitors.

**Table: 68P**

Tumor Site	% HPV+	Median TMB (Interquartile Range)	% TMB >= 10	% TMB >= 20
Anogenital (n = 1213)	76	5 (6)	17	5
Head and Neck (n = 1843)	36	4 (5)	15	5
Esophageal (n = 416)	6	5 (4)	13	2
Lung (n = 3977)	5	9 (8)	43	9
Skin (n = 422)	8	40 (69)	68	62

**Legal entity responsible for the study:** Foundation Medicine, Inc.

**Funding:** Foundation Medicine, Inc.

**Disclosure:** M. Montesion, E.S. Sokol: Employee: Foundation Medicine, Inc. L.A. Albacker, G.M. Frampton, V.A. Miller, J.S. Ross, S.M. Ali: Employee and stock ownership: Foundation Medicine, Inc. All other authors have declared no conflicts of interest.