ASTRO TARGETING CANCER CARE

ASCO American Society of Clinical Oncology

MULTIDISCIPLINARY HEAD and NECK CANCER SYMPOSIUM EXPANDING TREATMENT HORIZONS

News Release

Embargoed until February 18, 2016, 8:00 a.m., MT

Contact: Liz Gardner
703-286-1600
liz.gardner@astro.org

Erin L. Boyle
703-839-7336
erin.boyle@astro.org

Study maps distinct molecular signatures of HPV-positive throat cancer patients by smoking status

Novel molecular profiles may support more aggressive treatment decisions for some patients

SCOTTSDALE, Ariz., February 18, 2016—Throat cancer patients exposed to both human papillomavirus (HPV) and tobacco smoke demonstrate a pattern of mutations along several key cancer genes, according to research presented today at the 2016 Multidisciplinary Head and Neck Cancer Symposium. These distinct molecular profiles of heavy and light smokers who develop HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) may inform decisions related to treatment intensity by establishing additional prognostic criteria for this subset of patients.

Researchers examined the molecular characteristics of OPSCC caused by HPV in an effort to determine which DNA mutations predict lower disease free and survival rates among HPV-positive throat cancer patients who smoke. Whereas most patients with OPSCC caused by HPV have an excellent prognosis for disease free survival, those who also smoke generally face more dire prognoses.

The 66 cases of HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) in this study were split into heavy and light smoking behavior groups based on pack years. This metric of smoking frequency over long stretches of time is determined by multiplying the number of years a person has smoked by their average number of packs of cigarettes smoked per day. Forty of the 66 patients reported more than 10 pack years (e.g., more than one pack per day for 10 years or two packs per day for five years), and 26 patients reported fewer than 10 pack years.

"Throat cancer patients who smoked and had a history of fewer than 10 pack years had significantly better disease free and overall survival rates than the heavier smoking group," said Jose P. Zevallos, MD, MPH, FACS, assistant professor and director of oncologic research in the division of head and neck surgical oncology at the University of North Carolina, Chapel Hill and member of the Lineberger Comprehensive Cancer Center. "Our analyses identified several key differences in molecular mutational profiles of the two groups that may shape these outcomes."

Overall mutation rates were higher for HPV-positive OPSCC patients in the >10 pack year group than those in the <10 pack year group. *HLA-A* mutations occurred more often in the heavy smoking group, and mutations associated with tobacco exposure and poor survival occurred almost exclusively within the heavy smoker group, including those in *TP53* (6 percent vs. 0 percent, p = 0.428), *CDKN2A (*2 percent vs. 0 percent, p = 0.758), *FAT1* (14 percent vs. 6 percent, p = 0.688), *CASP8* (8 percent vs. 0 percent, p = 0.565), *NOTCH1* (18 percent vs. 0 percent, p = 0.092), *FGFR3* (10 percent vs. 0 percent, p = 0.325), and *KRAS* (4 percent vs. 0 percent, p = 0.232) genes. Researchers on the study note that these are preliminary data and that they are currently recruiting additional participants to add to the small sample size and fully power the between-group tests.

"I think what is most striking is that these genes are mutated almost exclusively in smokers," said Dr. Zevallos. "This molecular profile suggests that while HPV-positive OPSCC carcinogenesis initiates similarly, tumors in patients who smoke acquire novel mutations not traditionally associated with HPV-associated cancers." Analyses indicated that the molecular profile of HPV-positive smokers bears similarities to the profile for HPV-negative head and neck cancer, although the profile

does maintain several important molecular characteristics of HPV-positive cancer, including frequent *PIK3CA* and *MLL-3* mutations.

Differences in immune-related and tobacco-related gene mutations by smoking status identified in this study may explain why HPV-positive cancer in smokers may be more aggressive. Findings could impact which treatment options are recommended to HPV-positive OPSCC patients by informing clinical trials to establish new molecular parameters to guide determinations of treatment intensity.

"Because HPV-positive throat cancers respond well to treatment, patients often are given the option of choosing less aggressive treatment with fewer side effects," explained Dr. Zevallos. "Our study begins to set criteria-based changes in tumor DNA that can be used to predict more aggressive cases that should be given more intense treatment. We hope that this information will one day help to guide more personalized treatments for HPV-positive throat cancers."

Cases were drawn from a North Carolina population-based epidemiologic study conducted from 2001 to 2006 and were examined for mutations across more than 800 genes. Mutations were measured against the Catalogue of Somatic Mutations in Cancer (COSMIC), an online database of information on mutations in an expert-curated selection of key cancer genes that is maintained by the Sanger Institute as part of its Cancer Genome Project. Somatic mutations, which do not occur in reproductive cells and therefore are not passed on to children, were compared for both frequency and copy number variations, as well as their association with survival outcomes.

The abstract, "Molecular Profile of HPV-positive Oropharyngeal Squamous Cell Carcinoma Stratified by Smoking Status," will be presented in detail during the K. Kian Ang Commemorative Plenary Session on Thursday, February 18, 2016, at 10:30 a.m. Mountain time at the 2016 Multidisciplinary Head and Neck Cancer Symposium in Scottsdale, Arizona. To speak with Dr. Zevallos, contact the ASTRO media relations team at 480-905-7935 (February 18-19 only), 703-286-1600 or press@astro.org.

The 2016 Multidisciplinary Head and Neck Cancer Symposium is sponsored by the American Society for Radiation Oncology (ASTRO), the American Society of Clinical Oncology (ASCO) and the

American Head & Neck Society (AHNS). The two-and-a-half day meeting includes interactive educational sessions focused on topics such as novel multidisciplinary therapies, directed therapy, treatment guidelines, prevention, surveillance and supportive care, as well as 13 oral abstract presentations of the current science of relevance to the head and neck cancer community. A total of 262 abstracts will be presented, including 249 posters. Keynote speakers include Tanguy Seiwert, MD, of the University of Chicago, to present "Immunotherapy for Head and Neck Cancer;" Robert I. Haddad, MD, of Brigham and Women's Hospital, to present "Personalized Treatment for Head and Neck Cancer -- The Time is Now;" Quynh-Thu Le, MD, FASTRO, of the Stanford School of Medicine, to present "Precision Therapy in Head and Neck Cancer -- From Technology to Biomarker-based Risk Stratification;" and Neil Hayes, MD, MPH, of the UNC School of Medicine, to present "Genome Atlas and Sequencing Data: How We Use This Going Forward."

ABOUT ASTRO

ASTRO is the premier radiation oncology society in the world, with more than 10,000 members who are physicians, nurses, biologists, physicists, radiation therapists, dosimetrists and other health care professionals who specialize in treating patients with radiation therapies. As the leading organization in radiation oncology, the Society is dedicated to improving patient care through professional education and training, support for clinical practice and health policy standards, advancement of science and research, and advocacy. ASTRO publishes three medical journals, International Journal of Radiation Oncology • Biology • Physics (www.redjournal.org), Practical Radiation Oncology (www.practicalradonc.org) and Advances in Radiation Oncology (www.advancesradonc.org); developed and maintains an extensive patient website, RT Answers (http://www.rtanswers.org); and created the Radiation Oncology Institute (www.roinstitute.org), a nonprofit foundation to support research and education efforts around the world that enhance and confirm the critical role of radiation therapy in improving cancer treatment. To learn more about ASTRO, visit www.astro.org.

ABOUT ASCO

Founded in 1964, the American Society of Clinical Oncology (ASCO) is the world's leading professional organization representing physicians who care for people with cancer. With nearly 40,000 members, ASCO is committed to improving cancer care through scientific meetings, educational programs and peer-reviewed journals. ASCO is supported by its affiliate organization, the Conquer Cancer Foundation, which funds ground-breaking research and programs that make a tangible difference in the lives of people with cancer. For ASCO information and resources, visit www.asco.org. Patient-oriented cancer information is available at www.cancer.net.

ABOUT AHNS

The American Head & Neck Society (AHNS) is the single largest organization in North America for the advancement of research and education in head and neck oncology. The mission of the American Head and Neck Society is: to promote and

advance the knowledge of prevention, diagnosis, treatment, and rehabilitation of neoplasms and other diseases of the head and neck; to promote and advance research in diseases of the head and neck, and; to promote and advance the highest professional and ethical standards. For more information, visit www.ahns.info.

###

Embargoed until Thursday, February 18, 2016, 8:00 a.m., MT

2016 Multidisciplinary Head and Neck Cancer Symposium
News Briefing, Thursday, February 18, 2016, 7:00 a.m., MT

Plenary Session: Thursday, February 18, 2016, 10:30 a.m. – 12:00 p.m. MT, Arizona Ballroom A-G, JW Marriott Camelback Inn Resort and Spa

2 Molecular Profile of HPV-positive Oropharyngeal Squamous Cell Carcinoma Stratified by Smoking Status

J. P. Zevallos[1], E. Yim[2], P. Brennan[3], A. Y. Liu[4], J. M. Taylor[2], M. Weissler[1], D. Anantharaman[3], B. Abedi-Ardekani[3], A. F. Olshan[4], and N. N. Hayes[5]; [1]University of North Carolina Hospitals, Chapel Hill, NC, [2]Department of Otolaryngology/Head and Neck Surgery, University of North Carolina at Chapel Hill, Chapel Hill, NC, [3]International Agency for Research on Cancer, Lyon, France, [4]Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, [5]University of North Carolina School of Medicine, Chapel Hill, NC

Purpose/Objective(s): HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) among smokers represents a distinct clinical entity with intermediate prognosis compared to HPV-positive never smokers and HPV-negative cases. Despite recent advances in head and neck cancer genomics, the number of HPV-positive cases evaluated to date has been modest and the interplay between smoking and HPV has not been fully evaluated. The purpose of this study is to characterize the mutational profile of HPV-positive OPSCC by smoking status. We hypothesize a higher frequency of *TP53* and *CDKN2A* mutations in HPV-positive OPSCC among heavy smokers.

Materials/Methods: Targeted next-generation sequencing of >800 genes including all commonly mutated genes in cancer was performed in 66 HPV-positive OPSCC cases stratified by smoking status (<10 pack year vs. >10 pack years). Cases were identified from a NC population-based epidemiologic study conducted from 2001-2006 with follow-up for vital status. Copy number variation was also examined. Mutation frequency was compared to previously reported frequencies in the COSMIC database.

Results: Sixty-six HPV-positive OPSCC cases were examined, including 40 HPV+ OPSCC >10 pack year and 26 HPV+ <10 year pack smokers. Disease free and overall survival were significantly better in the <10 pack year history group. The most commonly mutated genes in both groups were *HLA-A*, *PIK3CA*, and *MLL-3*. Several differences in mutation frequency and copy number variation were noted between <10 and >10 pack year smokers: *TP53*, *CDKN2A*, *KRAS*, and *NOTCH1* mutations were found almost exclusively among >10 pack year smokers and were associated with worse survival, while *HLA-A* mutations were more common in the <10 pack year cohort (73.1% vs. 47.5%, p=0.047).

Conclusion: This study provides a molecular basis for the intermediate prognosis in patients with dual HPV/tobacco exposure. In addition to expected tobacco-associated mutations in the >10 pack year group, we demonstrate a novel immune signature in the <10 pack year group. If validated, these findings could further stratify risk in HPV-positive OPSCC and provide novel mutational parameters for treatment de-intensification.

Author Disclosures: J.P. Zevallos: None. E. Yim: None. P. Brennan: None. A.Y. Liu: None. J.M. Taylor: None. M. Weissler: None. D. Anantharaman: None. B. Abedi-Ardekani: None. A.F. Olshan: None. N.N. Hayes: None.