Novel Approaches to Genetic Testing and Overcoming Treatment Resistance Highlighted at AACR Meeting

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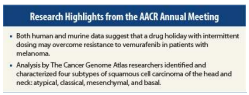
Figures:

Darrin Stuart, PhD

David N. Hayes, MD, MPH



Below are brief summaries of highlights from the very full, comprehensive collection of studies presented at the American Association of Cancer Research (AACR) Annual Meeting in Washington, DC. The abstracts describe a potential strategy to overcome resistance and genetic characterization of squamous cell carcinoma of the head and neck.

Intermittent Vemurafenib May Overcome Resistance

Vemurafenib (Zelboraf) is considered an advance in the treatment of melanoma, but most patients who respond to the drug develop resistance. Two separate experimental studies suggest that an intermittent dosing strategy has the potential to overcome resistance seen with standard continuous dosing.[1] At an AACR press conference, the studies were discussed by **Darrin Stuart, PhD**, Senior Research Investigator at the Novartis Institutes for Biomedical Research in Emeryville, California. Postdoctoral fellow and first author on the abstract, **Meghna Das Thakur, PhD** presented the entire body of work as part of the Clinical Trials of Targeted Agents in Solid Tumors Symposium held during the AACR meeting.

Previous studies showed that xenografts of *BRAF*-expressing tumors in mice not only developed resistance to vemurafenib, but were actually dependent on vemurafenib for proliferation. Withdrawal of vemurafenib caused the tumors to stop growing and even regress in some cases.

In a human study, Dr. Stuart and colleagues at the Royal Marsden Hospital in London evaluated 42 melanoma patients with vemurafenib-resistant tumors. In 14 of 19 cases in which post-relapse computed tomography scans were available, tumors demonstrated evidence of decreased tumor growth rate.

Next, mice were implanted with *BRAF(V600E)*-expressing tumor xenografts and treated with vemurafenib 4 weeks on and 2 weeks off (intermittent strategy) or continuously. None of the tumors in the intermittent-dosage group developed resistance.

Dr. Stuart said that these results suggest a drug holiday with intermittent dosing is a worthy strategy to pursue to overcome resistance to vemurafenib.

Genetics of Squamous Cell Carcinoma of the Head and Neck

Comprehensive genetic analysis by The Cancer Genome Atlas (TCGA) identified four different subtypes of squamous cell carcinoma of the head and neck.[2] Significant mutations were found in the

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following genes: *CDKN2A, TP53, PIK3CA, NOTCH1, HRAS*, and *NFE2L2*.

Some of the genetic patterns observed in this analysis overlapped with those seen in squamous cell non–small cell lung cancer and other squamous cell cancers, noted **David N. Hayes, MD, MPH**, Associate Professor at the University of North Carolina, Chapel Hill. Dr. Hayes said squamous cell carcinoma of the head and neck is the eighth tumor type to be analyzed by the TCGA project.

Among the 279 patients with untreated squamous cell carcinoma of the head and neck included in the study, 80% were tobacco-related and 13% were human papillomavirus (HPV)-positive.

Dr. Hayes and colleagues described four genetic subtypes of squamous cell carcinoma of the head and neck:

1. atypical subtype with no amplification of *EGFR*, *HPV* positive, and a high rate of PI3 kinase (*PIK3CA*) mutations

2. classical subtype, also seen in squamous cell lung cancer, associated with two key mutations: *KEAP1* and *NFE2L2*

3. mesenchymal subtype, mostly mutations of *FGR1* and *FGR*

4. basal subtype, highly associated with *TP63* amplifications and overexpression

The study also showed that HPV-positive and other patients have infrequent *EGFR* gene amplification, and that HPV-positive tumors have a high rate of *PIK3CA* gene mutations. HPV-positive patients almost never have *p53* alterations. In addition, some potentially actionable or druggable mutational targets for HPV-negative patients were identified, including *EGFR, FGR*, *PIK3CA*, *HRAS*, and *CCND1*.

"This dataset confirms that there is a clear genetic difference between HPV-positive patients who usually have a better prognosis and are easier to treat than HPV-negative patients," said **Giuseppe Giaccone, MD, PhD**, Associate Director for Clinical Research at Georgetown University Medical Center's Lombardi Comprehensive Cancer Center, Washington, DC, and the Director of Clinical Research for the MedStar Health Cancer Network's Washington Region. ■

Disclosure: Drs. Stuart, Hayes, and Giaccone reported no potential conflicts of interest.

References

1. Thakur MD, Fisher R, Salangsong F, et al: Modeling vemurafenib resistance in melanoma reveals a strategy to forestall drug resistance. AACR Annual Meeting. Abstract LB-144. Presented April 8, 2013.

2. Hayes DN, Grandis J, El-Naggar AK, et al: Comprehensive genomic characterization of squamous cell carcinoma of the head and neck in the Cancer Genome Atlas. AACR Annual Meeting. Abstract 1117. Presented April 7, 2013.

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