

Accepted Manuscript

Comprehensive pharmacogenomic profiling of human papillomavirus-positive and -negative squamous cell carcinoma identifies sensitivity to aurora kinase inhibition in *KMT2D* mutants

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PII: S0304-3835(18)30362-8

DOI: [10.1016/j.canlet.2018.05.029](https://doi.org/10.1016/j.canlet.2018.05.029)

Reference: CAN 13913

To appear in: *Cancer Letters*

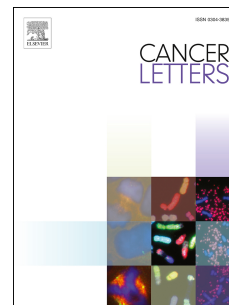
Received Date: 9 March 2018

Revised Date: 8 May 2018

Accepted Date: 20 May 2018

Please cite this article as: N.N. Kalu, T. Mazumdar, S. Peng, P. Tong, L. Shen, J. Wang, U. Banerjee, J.N. Myers, C.R. Pickering, D. Brunell, C.C. Stephan, F.M. Johnson, Comprehensive Pharmacogenomic Profiling of Human Papillomavirus-Positive and -Negative Squamous Cell Carcinoma Identifies Sensitivity to Aurora Kinase inhibition in *KMT2D* Mutants, *Cancer Letters* (2018), doi: 10.1016/j.canlet.2018.05.029.

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ABSTRACT

To address the unmet need for effective biomarker-driven targeted therapy for human papillomavirus (HPV)-associated head and neck squamous cell carcinoma (HNSCC) and cervical cancer, we conducted a high-throughput drug screen using 1122 compounds in 13 HPV-positive and 11 matched HPV-negative cell lines. The most effective drug classes were inhibitors of polo-like kinase, proteasomes, histone deacetylase, and Aurora kinases. Treatment with a pan-Aurora inhibitor, danusertib, led to G2M arrest and apoptosis *in vitro*. Furthermore, danusertib decreased tumor size compared with controls in patient derived xenograft models of HNSCC. To identify biomarkers predicting response, we determined associations between mutations and drug sensitivity. Our data and the Genomics of Drug Sensitivity in Cancer database showed that cancer cells with *KMT2D* mutations were more sensitive to Aurora kinase inhibitors than were cells without mutations. Knockdown of *KMT2D* in wild-type cells led to increased Aurora kinase inhibitor-induced apoptosis. We identified Aurora kinase inhibitors as effective and understudied drugs in HNSCC and CESC. This is the first published study to demonstrate that mutations in *KMT2D*, which are common in many cancers, correlate with drug sensitivity in two independent datasets.

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