A novel mechanism of crizotinib resistance in a ROS1+ NSCLC patient

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Molecular analysis of a tumor biopsy from a proto-oncogene 1 receptor tyrosine kinase positive (ROS1+) patient with acquired crizotinib resistance revealed a novel mutation in the v-kit Hardy Zuckerman 4 feline sarcoma viral oncogene homolog receptor tyrosine kinase (KIT) that can potentially be targeted by KIT inhibitors.

Chromosomal rearrangements of the gene encoding ROS1 in approximately 1-2% of non-small cell lung cancers (NSCLC). Treatment of ROS1+ patients with crizotinib, a small-molecule tyrosine kinase inhibitor, often results in durable tumor regression. However, despite initial treatment success patients typically develop resistance to crizotinib and disease progression inevitably ensues. Understanding the mechanism of resistance to crizotinib and identifying new targets for therapy will help guide patient treatment.

A group of investigators performed molecular analysis of tumor samples from a ROS1+ 38-year-old woman with a smoking history of 15 pack years diagnosed with stage IV lung adenocarcinoma. Tumor biopsies were collected before crizotinib treatment and after 15 months of crizotinib therapy when disease progression and crizotinib resistance was noted. Fluorescence in situ hybridization (FISH) analysis or DNA sequencing was performed on tumor samples to identify any gain or loss in the ROS1 fusion gene and SNaPshot, a multiplex assay targeting several oncogenic genes, was used to identify novel gene mutations. In vitro analysis of drugs targeting the newly identified gene mutation was accomplished by growing cells expressing the mutation in the laboratory

and exposing the cells to drugs targeting the novel mutation and measuring cell proliferation.

The results published in the *Journal of Thoracic Oncology*, the official journal of the International Association for the Study of Lung Cancer (IASLC), revealed that there was no change in the ROS1 fusion gene in the crizotinib resistant tumor samples compared to the pretreatment tumor samples by DNA sequencing or FISH analysis. SNaPshot analysis of the crizotinib resistant tumor identified a novel mutation in the KIT gene encoding the amino acid substitution, pD816G. The drug ponatinib, a KIT tyrosine kinase inhibitor, demonstrated inhibition of KITD816G kinase activity. Further, in ROS1+ cells expressing KITD816G the addition of ponatinib resensitized cells to crizotinib.

The authors comment that, "Although our results demonstrate that ponatinib can overcome KIT-mediated resistance in vitro, it remains unknown whether ponatinib can overcome this or other KIT activating mutations in patients. Detection of KIT mutations may allow enrollment of patients with ROS1+ cancer (or other oncogenes), onto clinical trials of KIT inhibitors, however it is likely that dual inhibition of both KIT and ROS1 would need to be maintained based on our results."

More information: Rafal Dziadziuszko et al. An activating KIT mutation induces crizotinib resistance in ROS1 positive lung cancer, *Journal of Thoracic Oncology* (2016). DOI: 10.1016/j.jtho.2016.04.001

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