Title: A Recurrent ERBB2 Rearrangement in Invasive Mucinous Adenocarcinoma of the Lung

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Category: Clinical-Translational

Introduction: Amplification and activating variants of the ERBB2 (HER2) gene are recognized as oncogenic drivers and potential therapeutic targets in non-small cell lung cancer (NSCLC). However, ERBB2 rearrangements have rarely been reported in NSCLC and their significance is uncertain. A recurrent ERBB2 rearrangement in NSCLC was identified at our institution during routine clinical practice. This study aimed to evaluate the demographic, clinical, histopathologic, and molecular characteristics of NSCLC cases with ERBB2 rearrangements.

Methods: NSCLC specimens are routinely tested at the Hospital of the University of Pennsylvania using an RNA-based, anchored multiplex sequencing assay that detects oncogenic fusions and novel isoforms in 55 genes (Fusion Transcript Panel; FTP). A retrospective review of all FTP data was performed. NSCLC cases with ERBB2 fusions were selected and respective clinical notes, surgical pathology reports, tissue sections, and molecular results were reviewed.

Results: Three patients harboring an ERBB2 rearrangement were identified. Histologically, all tumors were classified as invasive mucinous adenocarcinoma of the lung. Comprehensive genomic profiling of each tumor found no other recurrent oncogenic drivers in EGFR, ALK, ROS1, BRAF, KRAS, MET, RET, NRG1, or FGFR. The rearrangement consisted of an in-frame ERBB2::SHC1 fusion joining exon 25 of ERBB2 to exon 2 of SHC1. The transcribed protein is predicted to fuse downstream of the ERBB2 tyrosine kinase domain (TKD) and upstream of the SHC1 phosphotyrosine-binding (PTB) and SH2 domains, leaving all functional domains of both proteins intact. All patients were female, never-smokers, in the age range of 50 to 60 yrs. Two patients were diagnosed at stage IVA and were treated with multiple chemotherapy regimens with subsequent disease progression (one patient alive with disease, one patient dead from disease). The third patient was diagnosed at stage IB and had no evidence of disease at 8 months post-surgery. None of the patients received ERBB2-targeted therapy.

Conclusions: We present three cases of invasive mucinous adenocarcinoma of the lung with a recurrent ERBB2::SHC1 fusion. Although ERBB2 alterations have been described in lung adenocarcinoma, this is the first report of an ERBB2::SHC1 fusion associated with mucinous histology. This rearrangement, which was shown to have oncogenic activity in NSCLC in one study, likely contributes to increased cell proliferation and survival based on the known functions of the proteins involved. The demographic, histologic, and mutual exclusivity of other known oncogenic drivers in our cases suggests that the ERBB2::SHC1 fusion may be a novel driver of a rare molecular subtype of NSCLC.