**Anaplastic Lymphoma Kinase (ALK)-rearranged (ALK+) lung cancer early-onset precision drug-escape through Polycomb Repressive Complex-2 (PRC-2) epigenetic reprogramming**

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**Background and Objective**. West Virginia has the highest disparity in lung cancer-mortality rate of 59.6 deaths/100,000 in 2012, compared with 45.0 deaths/100,000 in U.S. Precision therapy for ALK+ lung cancer has improved outcome but is still limited by acquired drug-resistance. Molecular mechanisms underlying drug-resistance emergence are not fully understood.

**Methods.** ALK+ H3122 and patient-derived biopsied-lung tumor cells were evaluated *in vitro* and *in vivo* using RNA-seq, cell viability assay, QPCR, ChIP-QPCR, and murine xenograft analyses.

**Results.** ALK+ lung cancer displayed tumor plasticity and escaped ALK inhibitor early after treatment initiation. Early-onset drug-resistant cells were marked by autocrine TGFβ2-mediated cellular reprogramming with enhanced epithelial-mesenchymal-transition and cancer stem cell markers. Upregulated HOXB3 expression correlated with the adaptive drug-resistant cell state, emerged through dynamic PRC-2 epigenetic remodeling. Deregulated EZH2/UTX histone-methyltransferase/demethylase balance impacted the poised chromatin state of HOXB3 promoter $H3K27me^3$/$H3K4me^3$ histone marks. EZH2-inhibitor (GSK126) promoted ALK precision drug-resistance, while UTX-inhibitor (GSK-J4) eradicated drug-resistance emergence.

**Discussion and Conclusions**. Our findings provide novel insights into initial emergence of molecular adaptive drug-resistance in ALK+ lung cancer. Therapeutic modulation of the EZH2/UTX epigenetic balance profoundly impacts ALK inhibitor treatment outcome, with translational implications for preemptive combination therapy to prevent drug-resistance.