

RESULT INTERPRETATION AND SUBSEQUENT ACTION

EGFR mutation was not detected by NGS. However, the patient was positive for EML4-ALK fusion, which is prevalent in 1-2% of lung adenocarcinoma patients globally. Additionally, the patient was also positive for PD-L1 expression. Based on the findings of the NGS panel, Gefitinib was discontinued and the patient was put on 250mg Crizotinib, twice daily. As of 3rd June, 2018, Crizotinib has shown effective tumor shrinkage and the patient is now stable.

DISCUSSION

Dual *ALK* and *EGFR* positivity is a rare occurrence in lung adenocarcinoma. *EGFR* mutations are generally mutually exclusive of *ALK*, *ROS1* and *BRAF* mutations. In fact, until 2016, only 20 cases of dual *ALK* and *EGFR* positivity were reported. Since the patient showed disease progression on Gefitinib, further investigation was warranted.

Tissue from the initial biopsy was exhausted upon *ALK* and *EGFR* screening and re-biopsy was done in order to obtain sufficient tissue for further molecular analysis. H&E staining of the second biopsy, revealed a tumor content of <10%, which was insufficient to carry out further investigation.

Due to insufficient tumor content, liquid biopsy was done. Although, currently liquid biopsy is only approved for detecting the *EGFR* T790M mutations, several studies have shown good concordance rates between tissue and liquid biopsies. Validation studies conducted on the PulmoCORE Comprehensive panel, revealed a tissue-blood concordance rate of 89.7%.

The patient showed disease progression despite being treated with Gefitinib. A possible explanation for the lack of response could be attributed to low *EGFR* mutation burden. If the frequency of *EGFR* mutated cells/clones is very low, it would be unlikely that the patient would demonstrate a measurable response to any anti-*EGFR* TKI therapy. The low *EGFR* mutation burden may also explain the discrepancy between the RT-PCR and NGS results. The low limit of detection of RT-PCR compared to NGS, could explain why *EGFR* mutation might not have been captured by NGS.