Review of the use of ceritinib, a newly approved anaplastic lymphoma kinase (ALK) inhibitor, in crizotinib-resistant anaplastic lymphoma kinase-rearranged non-small cell lung cancer

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BACKGROUND
Lung cancer is the second most common cancer related death in America. Non-small cell lung cancer (NSCLC) is the more common variant of lung cancer, and represents roughly 85-90% of diagnosed lung cancers.

Several mutations have been studied in NSCLC, including EML4-ALK fusion protein abnormalities, EGFR, K-Ras, and BRAF mutations.

ALK abnormalities, which are the target of several new therapies, are found in approximately 5% of NSCLC patients.

Unlike the typical population at risk for developing lung cancer, ALK positive NSCLC is seen more frequently in young adults and those who have smoked fewer than 100 cigarettes or who have smoked less than 10 to 15 pack-years.

Crizotinib was the first drug available for NSCLC that was positive for ALK mutations. Accelerated approval for crizotinib was granted by the FDA in August 2011, with regular approval being granted in November 2013, for locally advanced or metastatic NSCLC that is ALK positive.

Ceritinib is a second generation targeted therapy for ALK positive NSCLC. In April 2014, the FDA granted accelerated approval for ceritinib in the treatment of ALK positive NSCLC in patients who experience progression while being treated with crizotinib, or those who were intolerant to crizotinib.

PURPOSE
The purpose of this poster is to provide a summary of data on ceritinib, that shows exceptional potency against ALK mutations, and its promising ability to overcome resistance developed during crizotinib therapy.

METHODS
PubMed searches and information from package inserts for Xalkori ® (crizotinib) and Zykadia ® (ceritinib) were used to find major clinical trials. These trials studied the use of ceritinib as a treatment option for ALK-Rearranged (ALK Positive) Non-Small Cell Lung Cancer (NSCLC) and the use of ceritinib in crizotinib-resistant NSCLC. Results from the studies were used to determine the potency of ceritinib over that of crizotinib.

RESULTS
Ceritinib (LDK378) binds to ALK a transmembrane receptor tyrosine kinase and neutralizes it to prevent it from transmitting extracellular growth factor signaling to intracellular signaling cascades. The lack of binding of D1177K ligand to ALK prevents its activation thereby leading to loss of signaling through RAS, RAF, MEK, ERK, PI3K, AKT, mTOR, STAT3/5 pathways. The resulting effect of Ceritinib is increased apoptosis and decreased proliferation of lung cells expressing the ALK mutations.

Molecular analysis was done on crizotinib resistant ALK rearranged NSCLC, which yielded seven different mutations that lead to acquired resistance. It is suggested that this acquired resistance emerges as mutations in secondary sites that ultimately affect the binding of crizotinib, and may arise through various mechanisms including chronic crizotinib exposure. In many of the crizotinib-resistant cell lines studied, ceritinib was able to overcome these resistances and showed efficacy in the cell lines; however, ceritinib was unable to overcome all resistances.

REFERENCES
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CONCLUSIONS
A conclusion can be drawn from a review of the Phase 1 studies; which earned ceritinib its FDA indication for use in ALK positive NSCLC patients, who experienced progression while being treated with crizotinib, or were intolerant to crizotinib that, ceritinib is 20 times more potent than crizotinib.

Further clinical trials are currently being conducted to evaluate the efficacy of ceritinib as compared to standard chemotherapy regimens in both treated and untreated NSCLC. Also, a new phase I trial is testing the combination of ceritinib and an experimental Hsp90 inhibitor.

The future of targeted therapy for NSCLC looks promising.