Efficacy and safety of dovitinib in pretreated advanced squamous non-small cell lung cancer with FGFR1 amplification: A single-arm, phase II study

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Purpose: FGFR1 amplification is one of the most common potential driving oncogenes in squamous cell carcinoma (SCC), which accounts for 20% of non-small cell lung cancer (NSCLC). This phase II study evaluated the efficacy and toxicity profile of dovitinib, an orally active fibroblast growth factor receptor (FGFR) inhibitor, in advanced lung SCC patients.

Experimental Design: Patients with histological confirmed advanced squamous cell NSCLC and previously treated with at least one cytotoxic chemotherapy were enrolled. All patients had FGFR1 gene amplification more than 5 copies by fluorescent in situ hybridization (FISH). Each 7-day treatment cycle consisted of dovitinib 500mg orally administration on days 1 to 5 and 2 days off. Primary endpoint was overall response rate and secondary endpoints included PFS, OS and toxicity. Exploratory analysis for FGFR1-3 mRNA expression was performed. The mRNA in situ hybridization (ISH) assay was performed using the RNA scope 2.0 assay system and the FGFR1 probe provided by Advanced Cell Diagnostics.

Results: All 26 patients were male with the median age of 68 years (range, 52–80). Most patients were ever smokers (96%) and had good ECOG (0-1) performance status (85%). The median number of dovitinib treatment cycles administered was 2.5 (range, 1-12). The overall response rate (ORR) was 11.5% (95% CI, 0.8–23.8) and disease control rate (DCR) was 50% (95% CI, 30.8–69.2). There were 3 partial responses (PR) and 10 stable diseases (SD). Duration of response in 3 patients who achieved PR was 4.5+, 5.1+ and 6.1 months, respectively. After the median follow-up duration of 15.7 months (range, 1.2–25.6), the median overall survival (OS) was 5.0 months (95% Confidential Interval, 3.61–6.39) and progression-free survival (PFS) was 2.9 months (95% CI, 1.54–4.26). The most common grade 3 or higher AEs suspected to be related to dovitinib treatment were fatigue (19.2%), anorexia (11.5%), and hyponatremia (11.5%) and 12 patients (46%) required dose reduction of dovitinib. Further analysis for FGFR1 mRNA, only modest overlap (31.2%) of FGFR1 expression at the mRNA level with FGFR1 amplification was found. The expression of FGFR1 mRNA was not associated with degree of FGFR1 gene amplification nor FGFR2 or FGFR3 mRNA expression.

Conclusion: Dovitinib treatment showed modest efficacy in advanced squamous cell lung cancer patients with FGFR1 amplification. Further studies to evaluate other biomarkers correlated with the efficacy of dovitinib in SCC should be warranted.

A novel patient-derived cell line originated at the time of crizotinib resistance displays a mesenchymal phenotype

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Lung cancers that harbor genomic ALK alterations are clinically responsive to pharmacologic ALK inhibition. Crizotinib, an orally available small-molecule inhibitor of the ALK tyrosine kinase, was approved for the treatment of ALK+ lung cancer patients. Unfortunately, as seen with other tyrosine kinases inhibitors (TKIs) in clinical use, most patients whose disease initially responds to crizotinib eventually develop progressive disease. To elucidate mechanisms of acquired resistance to ALK TKIs, we established and characterized novel ALK+ cell lines from patients with acquired resistance to ALK TKI therapy. In particular, we developed a cell line (designated STM) from a patient with an EML4-ALK (E6;A20, variant 3) fusion that developed acquired resistance to crizotinib. Fluorescence in situ hybridization confirmed that the cell line retained the ALK rearrangement. STM cells had decreased sensitivity to crizotinib and second-generation ALK inhibitors, including ceritinib, alectinib, and X-396. Morphologic changes were observed in this patient-derived cell line, the tumor cells had a spindle form, characteristic of the epithelial-mesenchymal transition (EMT). Loss of expression of the epithelial marker, E-cadherin, was accompanied by strong expression of the...