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

Myung-Ju Ahn, Sung Hee Lim, Jong-Mu Sun, Yoon-La Choi, Hye Ryun Kim, Soo-min Ahn, Se-Hoon Lee, Keunchil Park, Joo Hang Kim, Byoung Chul Cho

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

Karinna Almodovar-Garcia, Yingjun Yan, Yuanyuan Wang, Zhongming Zhao, Xingyi Guo, Yaomin Xu, Christine M. Lovly

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
mesenchymal markers, vimentin and N-cadherin in STM cells. Enhanced invasion and migration capabilities were observed in STM cells consistent with a mesenchymal phenotype. Src has been shown to play a role in E-cadherin regulation and EMT. Thus, treatment of cells with dasatinib, a Src inhibitor, suppressed cell growth in STM cells, but not in ALK+/TKI sensitive cell lines. The addition of a low dose of dasatinib sensitized STM cells to the anti-proliferative effects of crizotinib. STM cells were subjected to genetic analysis to identify new genetic anomalies that could be driving resistance. Top hits are being evaluated. To our knowledge, this is the first report that demonstrates EMT occurring in an ALK+ crizotinib resistant clinical sample. Collectively these data support EMT as a mechanism of resistance to crizotinib and identifies dasatinib as a potential therapeutic for treatment of crizotinib resistance associated with EMT.

Immune profiling of malignant pleural mesothelioma by flow cytometry identifies distinct T-cell activation and exhaustion phenotypes in PD-L1 positive versus PD-L1 negative tumors

Mark M. Awad,1 Mark A. Bittinger,1 Robert E. Jones,1 Xiaoyun Liao,2 Meghana Kulkarni,1 Lauren Keogh,1 Shohei Koyama,1 Christina G. Almonte,1 Abigail A. Santos,1 Jessie E. English,1 Nicholas A. Cacalano,1 Dana-Farber Cancer Institute, Boston, MA, 2Brigham and Women’s Hospital, Boston, MA

Although PD-L1 immunohistochemical staining appears to be a partially predictive biomarker of response to PD-1 inhibitors in some cancers, many PD-L1 positive tumors do not respond to these agents. Possible explanations for this observation are that some PD-L1 positive cancers may have a paucity of infiltrating lymphocytes and/or T cells within tumors may express multiple exhaustion markers. We have developed a method for comprehensive immune cell phenotyping using flow cytometry on solid tumors that have been dissociated into single cell suspensions. Applying this technique to 33 resected malignant pleural mesothelioma samples, here we show that compared to PD-L1 negative tumors, PD-L1 positive tumors have significantly more infiltrating CD45+ immune cells, a significantly higher proportion of infiltrating CD3+ T cells, a significant increase in proliferating CD4+ and CD8+ T cells, and a significantly higher percentage of CD3+ cells displaying the activation antigens HLA-DR+/CD38+. PD-L1 positive tumors also have a significantly higher proportion of FOXP3+/CD4+ regulatory T cells. We found that CD4+ and CD8+ T cells in PD-L1 positive samples are significantly more likely to express the T-cell exhaustion markers PD-1 and TIM-3 compared to PD-L1 negative samples. Flow cytometric analysis also identified two immunologically distinct PD-L1 positive mesothelioma samples: PD-1 positive, TIM-3 negative “single positive” tumors, and PD-1 positive, TIM-3 positive “double positive” tumors. Successful incorporation of comprehensive immune profiling by flow cytometry into prospective clinical trials should hopefully refine our ability to predict which patients will respond to immune checkpoint blockade and lead to rationally designed combination immunotherapy trials.

Novel epidermal growth factor receptor inhibitor accumulates in the brain and inhibits the growth of brain metastatic non-small cell lung cancer

Christina A. Jamieson,1 Michelle Muldong,1 Yun Oliver Long,2 Ida Deichaite,1 Alan Lewis,2 David W. Anderson,3 Nicholas A. Cacalano1 1University of California, San Diego, CA, 2Capella Therapeutics, San Diego, CA, 3University of Missouri, St. Louis, MO, 4University of California, Los Angeles, CA

Deaths from solid tumors are often not due to the primary lesion but to metastatic disease at distal sites such as the lung, liver, and brain. Patients with non-small cell lung cancer (NSCLC) experience brain metastases, a poor prognostic marker, at an incidence rate of 30-50%. A significant proportion of the metastatic tumors express activating mutations of the EGFR, including exon 19 deletions, which confer increased sensitivity to EGFR inhibitors such as erlotinib and gefitinib. Despite successful use of small molecule kinase inhibitors for the treatment of EGFR+ primary lung tumors, current therapeutics poorly inhibit the growth of NSCLC brain metastases due to difficulty crossing the blood-brain barrier. For this reason, NSCLC patients with brain metastases are often excluded from clinical trials with novel therapies and thus have access to very few emerging treatment options.

We have synthesized a novel class of compounds that inhibit the epidermal growth factor receptor (EGFR) in the nanomolar range in vitro, and demonstrate a high degree of selectivity for EGFR family members. The parent compound, LL001, from Capella Therapeutics, Inc., inhibited EGFR-mediated autophosphorylation and