Long-term treatment with dexamethasone induces senescence and progressive loss of proliferation potential in lung adenocarcinoma cells expressing high levels of the glucocorticoid receptor

Mugdha Patki, Yanfang Huang, Mike Wilson, Abby Fielder, Larry Matherly, Lisa Polin, Manohar Ratnam Wayne State University/Karmanos Cancer Institute, Detroit, MI

We have previously demonstrated that in non-squamous non-small cell lung cancer (nsNSCLC) cells expressing relatively high levels of the glucocorticoid receptor (GR), dexamethasone (Dex) induces reversible G1 arrest that is virtually complete by 72h of Dex treatment. We have also shown that this effect of Dex protects the cells from the cytotoxicity of pemetrexed, a mainstay chemotherapy in advanced nsNSCLC that entails co-administration of Dex. Further, induction of G1 arrest by Dex was confirmed by FLT-PET imaging of tumor lesions in patients treated with Dex for 24h. Here we report the effects of long-term treatment of nsNSCLC cells with Dex. The nsNSCLC cell line models included A549 (GRhi), H292 (GRhi), H1650 (GRlo) and H1299 (GRlo) cells as well as clonal recombinant H1299 cells overexpressing GR. In only the GRhi cells, Dex caused an increase in p21 peaking on Day 7 and declining by Day 14. The cells retained proliferation potential on Day 3 as measured by colony formation. By Day 7 of Dex treatment, the GRhi cells but not the GRlo cells exhibited a senescence phenotype, marked by cytosolic beta-galactosidase activity and increases in p16 and p15 at the mRNA and protein levels as well as significant increases in cell size. The GRhi cells displayed a progressively decreasing ability to form colonies until 6 weeks of Dex treatment. The extent of this loss of proliferation potential was related to relative GR expression levels among the Dex-sensitive cells. When mice bearing xenografts of H1299 (GRlo) or isogenic recombinant H1299-GR (GRhi) cells were implanted with slow release Dex pellets, tumor growth was inhibited only in the H1299-GR cells. Evaluation of a tissue microarray as well as a cDNA array from clinical nsNSCLC tumors showed that about 20 percent of the tumors showed uniform expression of GR that were comparable to the levels required for Dex to induce senescence in vitro or to inhibit tumor growth in vivo. The results suggest that long-term administration of Dex could serve as an additional treatment option for a small cohort of lung adenocarcinoma patients that harbor uniform high levels of GR in their tumor lesions.

Phase I/II trial of X-396, a novel anaplastic lymphoma kinase (ALK) inhibitor, in patients with ALK+ non-small cell lung cancer (NSCLC)

Karen L. Reckamp, Jeffrey R. Infante, George R. Blumenschein, Heather Wakelee, Corey A. Carter, Jon P. Gockerman, Christine Lovly, Gary Dukart, Kimberly Harrow, Chris Liang, James J. Gibbons, Leora Horn City of Hope Comprehensive Cancer Center, Duarte, CA, Tennessee Oncology, PLLC/SCRI, Nashville, TN, The University of Texas MD Anderson Cancer Center, Houston, TX, Stanford University School of Medicine, Stanford, CA, Walter Reed Medical Center, Bethesda, MD, Novella Clinical, Morrisville, NC, Vanderbilt Ingram Cancer Center, Nashville, TN, Xcovery Holding Company, Palm Beach Gardens, FL

Background: X-396 is a novel, potent anaplastic lymphoma kinase (ALK) small molecule tyrosine kinase inhibitor (TKI) with additional activity against MET, ABL, Axl, EPHA2, LTK, ROS1 and SLK. It has demonstrated significant anti-tumor activity in both ALK TKI-naïve and crizotinib-resistant models of ALK fusion-positive NSCLC.

Methods: In this multicenter phase I/II study, patients (pts) with advanced solid tumors were enrolled in the phase I dose escalation portion of the study and given X-396 on a continuous 28-day schedule (NCT01625234). Doses from 25 up to 250 mg once daily were evaluated and 225 mg was selected for further evaluation in the phase II expansion. Patients in this phase were required to have ALK+ NSCLC and measurable disease. Cohorts included pts who were 1) ALK TKI-naïve, 2) pts who progressed on prior crizotinib and had not received a 2nd generation ALK TKI, 3) pts who progressed on a 2nd generation ALK TKI (may also have received crizotinib), 4) pts with central nervous system (CNS) metastases, and 5) pts with leptomeningeal disease. All pts were assessed for adverse events (AEs) using CTCAE version 4.03, response to therapy was assessed using RECIST 1.1.

Results: As of the October 15, 2015 data cutoff, 53 pts (29 men, 24 women) have been enrolled. Median age is 56 (20-79) years, the majority of patients had ECOG performance status 1 (68%). The most common drug-related AEs included rash (47%), nausea (28%),