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

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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)

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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-naive 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-naive, 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%),
Liquid biopsies could be superior to tumor biopsy to provide a molecular profile in non-small cell lung cancer (NSCLC) patients

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Introduction: Approximately 30% of patients with an adenocarcinoma have a druggable driver mutation. However, the access to tumor tissue to perform the molecular profile is often limited. Circulating tumor DNA (ctDNA) can be used for detection and quantification of molecular abnormalities as a non-invasive tool. We performed a retrospective study to assess the concordance in molecular alterations between tissue biopsies and ctDNA in 20 NSCLC patients as well as the impact of treatment on ctDNA profile.

Methods: Plasma samples were collected from 17 consecutive treatment-naïve and 3 pre-treated advanced NSCLC patients from Gustave Roussy. For 10 patients a second blood sample was collected 21 days after starting chemotherapy to monitor the mutational profile. DNA was extracted from < 3 ml plasma and analyzed using the enhanced Tam-SeqTM assay covering regions from 35 genes. TAM-Seq data (generated using Illumina sequencing) were compared to a different NGS platform (Ion-torrent) as well as Sanger sequencing data from tissue biopsy samples analyzed in routine daily clinical practice.

Results: From May 2015 to June 2015, 20 patients were included (70% were male, 15% never-smoker, 75% had an adenocarcinoma subtype, and 70% a stage IV). Only 40% of tumor biopsies provided sufficient sample tissue for molecular analysis. ctDNA profiling was possible for all patients, which detected cancer mutations in 19 out of 20 patients. Median number of mutations in plasma was 2, predominantly located in KRAS, TP53 and EGFR mutation. Half of the mutations detected in ctDNA were observed at a frequency lower than 1%. In 10 NSCLC patients dynamic ctDNA changes after 21 days of treatment were evaluated. No new mutations were detected at day 21. Seven out of 10 patients experienced a partial response in CT scan by RECIST criteria. All of them had either a lower frequency of mutations or undetectable levels of mutations at day 21.

Conclusions: ctDNA can be used as a ‘liquid biopsy’ for molecular profiling of mutations in NSCLC patients in the absence of an invasive biopsy with a high concordance with tissue genomic profile. Also, ctDNA can potentially be used as a surrogate marker of response. Update in 35 patients will be presented during the conference.

The triptolide derivative MRx102 inhibits Wnt pathway activation and has potent anti-tumor effects in lung cancer

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Lung cancer is the leading cause of cancer-related deaths globally. Despite advances in treatment with targeted therapies and earlier detection, the 5-year survival rate remains a dismal 15%. Due to the low survival rate, there is a critical need for new therapies targeting lung cancer. Most lung cancers have increased activation of Wnt signaling and/or Wnt protein expression, which makes Wnt a strong potential target for the development of new lung cancer therapeutics. Triptolide is a natural compound isolated from the Thunder God Vine, Tripterygium wilfordii, which has been used in traditional Chinese medicine to treat autoimmune disorders and inflammation. We previously showed that triptolide increases WIF1 expression by decreasing WIF1 promoter methylation, thereby inhibiting the Wnt pathway. Though triptolide