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Tumor-targeted SN38 inhibits growth of early stage non-small cell lung cancer (NSCLC) in a KRas/p53 transgenic mouse model

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Abstract

 Non-small cell lung cancer (NSCLC) is the leading cause of cancer death worldwide, with a 5-year survival of only 16%. Potential strategies to address NSCLC mortality include improvements in early detection and prevention, and development of new therapies suitable for use in patients with early and late stage diagnoses. Controlling the growth of early stage tumors could yield significant clinical benefits for patients with comorbidities that make them poor candidates for surgery: however, many drugs that limit cancer growth are not useful in the setting of long-term use or in comorbid patients, because of associated toxicities. In this study, we explored the use of a recently described small molecule agent, STA-8666, as a potential agent for controlling early stage tumor growth. STA-8666 uses a cleavable linker to merge a tumor-targeting moiety that binds heat shock protein 90 (HSP90) with the cytotoxic chemical SN38, and has been shown to have high efficacy and low toxicity, associated with efficient tumor targeting, in preclinical studies using patient-derived and other xenograft models for pancreatic, bladder, and small cell lung cancer. Using a genetically engineered model of NSCLC arising from induced mutation of KRas and knockout of Trp53, we continuously dosed mice with STA-8666 from immediately after tumor induction for 15 weeks. STA-8666 significantly slowed the rate of tumor growth, and was well tolerated over this extended dosing period. STA-8666 induced DNA damage and apoptosis, and reduced proliferation and phosphorylation of the proliferation-associated protein ERK1/2, selectively in tumor tissue. In contrast, STA-8666 did not affect tumor features, such as degree of vimentin staining, associated with epithelial-mesenchymal transition (EMT), or downregulate tumor expression of HSP90. These data suggest STA-8666 and other similar targeted compounds may be useful additions to control the growth of early stage NSCLC in patient populations.

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