for IA vs IB, p=0.29). Patients with a high-risk PS (>27) had a three-fold increased risk of distant recurrence compared to patients with a low-risk PS score. In stage I patients, the estimated risk of distant recurrence for tumors with high-risk prognostic scores was significantly higher (36%, 95%CI 28%-46%) than in low-risk PS tumors (15%, 95%CI 8%-29%, p=0.0005).

Conclusions: The prediction of risk of distant recurrence in resected lung adenocarcinoma patients can be improved over that obtained by the current standard of pathological stage by incorporating tumor expression of proliferation markers (CCP score). Improved risk stratification can help identify patients in need of additional treatment and prioritize patients for trials of emerging new therapies.

Strong pharmacological activity of locally administered next-generation antisense oligonucleotides (ASOs) in orthotopic lung cancer mouse models

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Lung cancer is the second most common cancer type and the leading cause of cancer-related death in both men and women in the United States. Although recent advances in genomic expression profiling of lung cancer has provided more individualized treatment based on target specific genetic alteration(s) in patients, there is a still high unmet medical need as many important driver mutations remain undruggable by conventional therapeutic approaches. Antisense oligonucleotide (ASO) technology offers a novel therapeutic modality to selectively target currently undruggable pathways. We have recently demonstrated that systemic delivery of unformulated next generation (Gen 2.5) ASO targeting human STAT3 mRNA (STAT3-Rx/AZD9150) leads to robust pharmacological activity in various preclinical animal models of lung cancer. Importantly, STAT3-Rx/AZD9150 displayed strong anti-tumor activity in patients with advanced treatment-refractory lymphoma as well as non-small cell lung cancer (NSCLC) in clinical trials*.

Although local delivery of ASOs has been proposed as a means to treat various pulmonary diseases, ASO pharmacology in lung tumors has not been previously evaluated. In this study, we evaluated the activity of an antisense inhibitor (targeting MALAT1 gene) given by different administration routes (by either a local (intratracheally=IT) or a systemic (subcutaneously=SC) delivery) in orthotopic lung cancer xenograft models. For this, human NSCLC A549 or H460 cells were injected to nude mice via tail vein and 2 weeks later, the tumor-bearing animals were treated with Gen 2.5 MALAT1 ASO either IT (at 10 to 20 mg/kg, 3 times per week) or SC (at 25 to 50 mg/kg, 5 times per week) for 3 weeks. Reductions in MALAT1 RNA levels in human tumor cells and mouse lung were greater with local delivery at lower doses compared to systemic delivery as assessed by qRT-PCR or in-situ hybridization using species-specific primers/probes (73% reduction at 20 mg/kg by IT dosing vs 50.5% reduction at 50 mg/kg by SC dosing in tumors; 72.5% vs 70% reduction in mouse lung at the same dosing regimen). Moreover, local administration of ASOs led to no notable increase in liver transaminase levels compared to systemic administration. Pharmacokinetic property-wise, the local administration showed greater and more even accumulation of drug in both tumor and lung tissues compared to the systemic route. Taken together, these findings suggest that local administration of Gen2.5 ASOs to lung malignancies may be a promising alternative approach to systemic delivery with greater potency and improved safety profile, especially in inhibiting lung cancer targets which cannot be tolerated when depleted systemically.


Impact of interleukin-22 on K-ras mutant lung cancer promotion and stemness properties

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Activating mutations of K-ras, which are found in approximately 30% of non-small cell lung cancer (NSCLC), are the most common genetic alterations associated with tobacco exposure in lung cancer. Unfortunately, pharmacologic attempts directly targeting K-ras have thus far failed; clearly stating the need for new strategies to bring clinical benefits to patients displaying such a molecular profile. Tumor-promoting inflammation is a cancer hallmark, and it is now apparent that the cytokines and growth factors released during inflammation influence