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Presentation Title:	Systemic gene therapy with tumor suppressor TUSC2/FUS1 nanoparticles (**Oncoprex™**) for recurrent/metastatic lung cancer
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Location:	Exhibit Hall A4-C, Poster Section 27
Poster Section:	27
Poster Board Number:	6
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Abstract Body:

Background: The tumor suppressor gene TUSC2/FUS1 (TUSC2) is frequently inactivated early in lung cancer development. TUSC2 mediates apoptosis in cancer cells but not normal cells by upregulation of the Apaf-1-dependent apoptotic pathway. DOTAP:cholesterol nanoparticles encapsulating a TUSC2 expression plasmid (DOTAP:chol-TUSC2) showed preferential uptake by cancer cells and prolonged survival in mouse xenograft metastatic lung cancer models.

Methods: Patients with recurrent and/or metastatic lung cancer previously treated with platinum-based chemotherapy were treated with escalating doses of intravenous DOTAP:chol-TUSC2 every 3 weeks. The primary end point was assessment of DOTAP:chol-TUSC2 toxicity and determination of the MTD. TUSC2 plasmid expression in pretreatment and 24 hour posttreatment tumor specimens from subjects consenting to tumor biopsies was analyzed with quantitative RT-PCR analysis using a TUSC2 plasmid sequence-specific probe, in situ proximity ligation assay for TUSC2 protein, and apoptosis signaling nanoscale PCR array.

Results: Thirty-one patients were treated at 6 dose levels ranging from 0.01 to 0.09 mg/kg and 7 had paired pre- and posttreatment biopsies. RT-PCR analysis detected high TUSC2 plasmid expression in 6 of 7 posttreatment tumor specimens but not in pretreatment specimens and negative controls. Immunohistochemical staining has been performed on 1 paired specimen, demonstrating low background TUSC2 protein staining in the pretreatment tissue compared with high intense TUSC2 protein staining in the posttreatment tissue. RT-PCR gene expression profiling analysis of apoptotic pathway genes in one paired specimen demonstrated significant upregulation and downregulation of genes involved in both the intrinsic and extrinsic apoptotic pathways. Among 4 patients treated without premedications, all 4 developed grade 2 or 3 fever. Among the 27 patients premedicated with dexamethasone and diphenhydramine, the highest fever was grade 2, which occurred in 2 subjects. The only dose-limiting toxicities were 2 episodes of transient grade 3 hypophosphatemia, resulting in an MTD of 0.06 mg/kg. Twenty-three patients who received 2 or more doses were evaluable for response, with 5 achieving stable disease (2.6-10.8 months) and 18 progressing. One patient with stable disease had evidence of a durable metabolic response on positron emission tomography imaging. The pretreatment apoptotic index was predictive of disease stability. Median survival time was 9.1 months.

Conclusions: DOTAP:chol-TUSC2 can be safely administered intravenously in lung cancer patients and results in demonstrable gene and protein expression in tumors. It appears to regulate apoptotic pathway genes with evidence of antitumor activity. The MTD for phase II testing is 0.06 mg/kg every 3 weeks. Based on promising preclinical data, a trial in combination with erlotinib is planned.