CURAXIN CBL0137 DEMONSTRATES SIGNIFICANT ANTITUMOR ACTIVITY AGAINST FACT-POSITIVE PATIENT-DERIVED PANCREATIC DUCTAL ADENOCARCINOMA

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Background: Curaxin CBL0137 represents a novel class of small molecules that simultaneously activate p53 and inhibit cancer-associated stress response pathways, such as NF-kB and HSF-1. CBL0137 antitumor activity has been established in a broad range of tumor models both by oral and intravenous administration. The effects of CBL0137, culminating in tumor cell death, are mediated by the sequestering of the FACT (FAcilitates Chromatin Transcription) complex on chromatin thereby inhibiting its activity. FACT is a transcription and replication factor (composed of two subunits, Structure Specific Recognition Protein (SSRP1) and suppressor of Ty 16 (SPT16)), which is involved in transcription of genes with highly ordered chromatin structure as well as in replication and mitosis. FACT is expressed during early embryogenesis and in undifferentiated progenitors and stem cells of adult tissues while protein levels of both FACT subunits are almost undetectable in differentiated cells and tissues. FACT is expressed in several tumor types compared to equivalent normal tissues. In addition, FACT positive tumors have an aggressive malignant phenotype as illustrated by a correlation of FACT expression with high grade, the development of metastatic disease and worse overall survival. Thus, FACT represents a potentially important target for cancer therapy. In particular, a high proportion of pancreatic cancers express FACT as demonstrated by 70% of tested pancreatic tumors staining positive for the SSRP1 subunit (n = 58). Furthermore, 30% of these cases expressed a very high level of SSRP1.

Methods: To investigate whether CBL0137 could suppress the growth of pancreatic ductal adenocarcinoma, SCID mice were implanted subcutaneously with five independent pancreatic ductal adenocarcinoma tumors that were derived from patients (~10 mm3, n = 5 mice per treatment group; 2 tumors per mouse). Ten days following implantation of tumors, treatment commenced. Mice received either Captisol vehicle control or 90 mg/kg CBL0137 iv once per week for 4 weeks. Tumors were measured 2-3 times per week with a digital caliper. The study ended 7 days following the last injection.

Results: A marked decrease in tumor growth was observed for all five tested patient tumors treated once per week with CBL0137 compared to vehicle control. Specifically, tumor growth decreased 49-76% across the tested tumors. All five tested pancreatic adenocarcinomas were positive for FACT as determined by staining for SSRP1.

Conclusion: FACT represents a potential target for treatment therapy, particularly in pancreatic cancer. CBL0137 is an effective agent against FACT-positive pancreatic ductal adenocarcinomas. Studies to evaluate CBL0137 combinations with standards of care agents gemcitabine and Abraxane against patient-derived pancreatic ductal carcinoma xenografts are required to gain a greater understanding of the potential benefit that CBL0137 may have in the treatment of pancreatic cancer.