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Methods: Patient-derived pancreatic ductal adenocarcinoma (PDA) xenografts were obtained under an approved IRB protocol and continually propagated in SCD mice for use in efficacy experiments. Immunohistochemistry: TMA's containing 56 distinct PDA samples were stained for SSRP1 and scored based on % positive cells and intensity. Pilot PCL0137 efficacy studies: SOD mice (n=5/treatment group, 2 tumors/mouse) were implanted with 2.5-2.6 mm of the designated patient PDA ~10 days following implantation (tumor volumes ~200 mm3) treatment commenced. For oral administration, mice received vehicle (30 mg/kg CBL0137) or gavage following a 5 days/2 days off schedule for 4 weeks. For iv studies, mice were injected either vehicle (0.5 mg/kg CBL0137) 3x/week or 2x/week or 1x/week (40 mg/kg) GEM 3x/week or 1x/week. Tumors were measured 3-2 times per week using digital calipers. Tumor volume was calculated using standard equation: \( V = \frac{L \times W^2}{2} \) where \( L \) is longest dimension and \( W \) is measured perpendicular to \( L \). Mice were followed until total tumor burden of mouse reached ~2000 mm3, all controls completed the study of 28 days, whichever came first. Data is presented as a mean fold tumor growth by normalizing the tumor volume on Day X by that of Day 1. Comparisons between treatment groups were performed by ANOVA.

Combination efficacy studies: These studies were performed as described above with the following modifications. Treatment commenced when the mean tumor volume per group was ~25-50 mm3. Mice were treated with 80-90 mg/kg CBL0137 (as in the previous paragraph) or 40 mg/kg gemcitabine administered iv every 4th day (Q4d) for 4 weeks. Mice were followed until at least one tumor per mouse reached 1000 mm3 or up to 90 days from start of treatment.

Conclusions: FACT represents a potential target for cancer therapy due to its level of expression compared to normal tissue, association with an aggressive malignant phenotype, metastatic disease and poor overall survival (Garcia et al, 2013 Cell Reports (in press) http://dx.doi.org/10.1016/j.celrep.2013.06.013). It is found in a large proportion of PDA.

CBL0137, which targets FACT, caused a 49.76% reduction in FACT positive PDA xenografts derived from patient tumors when administered orally daily or intravenously once per week.

CBL0137 produced a similar antitumor effect to gemcitabine and Abraxane against a gemcitabine/Abraxane-sensitive PDA during the treatment period and appeared to enhance the antitumor effect of Abraxane and delay the recurrence of tumors in combination with gemcitabine at a dose, in which it was ineffective itself.

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