Oncolytic Virus Therapy in Pancreatic Cancer: Clinical Efficacy and Pharmacodynamic Analysis of REOLYSIN® in Combination with Gemcitabine in Patients with Advanced Pancreatic Adenocarcinoma

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Background

- **Pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis, with a 1-yr survival rate of ~18% for all stages of the disease.**
- **The standard treatment options for metastatic disease include FOLFIRINOX or gemcitabine/nab-paclitaxel, however both these treatment regimens are more toxic than gemcitabine alone.**
- **REOLYSIN® (Reovirus serotype 3) has shown extensive antitumor activity in preclinical models, as well as synergistic activity with cytotoxics, including gemcitabine, in various cancer types.**
- **REOLYSIN® antitumor activity is due to the ability of reovirus to preferentially replicate in cells with activated RAS pathway. In addition to direct cytotoxic effects, REOLYSIN ® can trigger an antitumor immune response.**

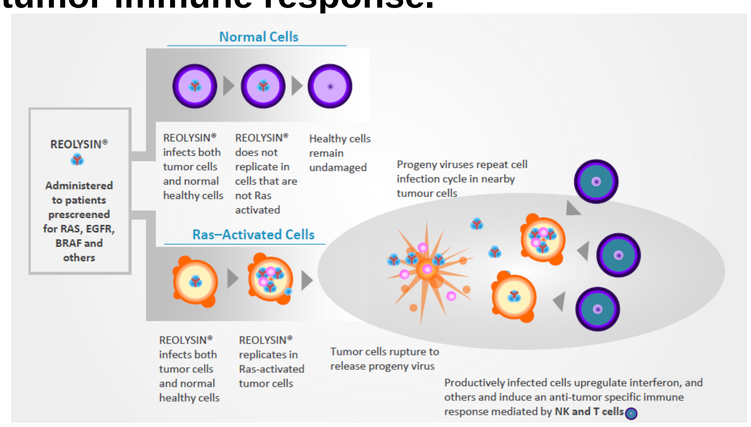

Figure 1: Reovirus mechanism of action

- **Due to the high frequency of KRAS pathway activation in PDAC, we hypothesized that REOLYSIN® may improve the efficacy of chemotherapy.**
- **Therefore, this study was initiated to test the safety and efficacy of the combination of REOLYSIN® with gemcitabine in previously untreated patients with advanced PDAC.**

Methods

- **Patients with a diagnosis of chemotherapy-naïve, surgically unresectable or metastatic PDAC were eligible for the study.**
- **The primary objective was Clinical Benefit Rate (CBR=CR+PR+SD ≥12 weeks).**
- **Secondary objectives were: progression-free survival (PFS); overall survival (OS); toxicity, tolerability; pharmacodynamics.**
- **Eligible patients were treated with gemcitabine at 800 mg/m^2 on days 1 and 8, and REOLYSIN® at 1 x 10^{10} $TCID_{50}$ administered IV on days 1, 2, 8 and 9 every 3 weeks. Tumor assessment was performed every 2 cycles.**
- **A Simon-two stage design was used for this study. In stage 1, at least 3/17 patients must have achieved CBR in order to proceed to stage 2.**

Patient demographics

Parameter	REO 017 (n=34)
Age (median)	66
≥65 years	53%
Sex (M/F)%	53/47
ECOG PS • 0-1 • 2	 94% 6%
Ethnicity • Caucasian • Asian	71% 3%
Metastatic disease at baseline (%)	91
Median no. of cycles (schedule)	4 (Q3wk)
Previous chemo/radiotherapy	5%
Post-PD therapy	53%

Safety

Table 1. Most Commonly Identified Toxicities for REOLYSIN® in Combination with Gemcitabine (> 10% of patients)

TOXICITY	Total (%)	Grade 3 (%)	Grade 4 (%)
HEMATOLOGIC			
• Anemia	35	24	3
• Neutropenia	32	15	12
• Thrombocytopenia	15	6	0
NON-HEMATOLOGIC			
• Diarrhoea	24	0	0
• Nausea	29	0	0
• Vomiting	24	0	0
• Fatigue	71	9	0
• Chills/Flu-like symptoms	51	0	0
• Oedema	33	0	0
• Fever	56	0	0
• AST increased	12	6	0
• Anorexia/Weight loss	33	0	0
• Dyspnoea	50	6	0

Clinical efficacy

- **34 patients recruited, 29 evaluable for response.**
- **CBR of 83%; one PR, 23 SD and five PD as best response.**

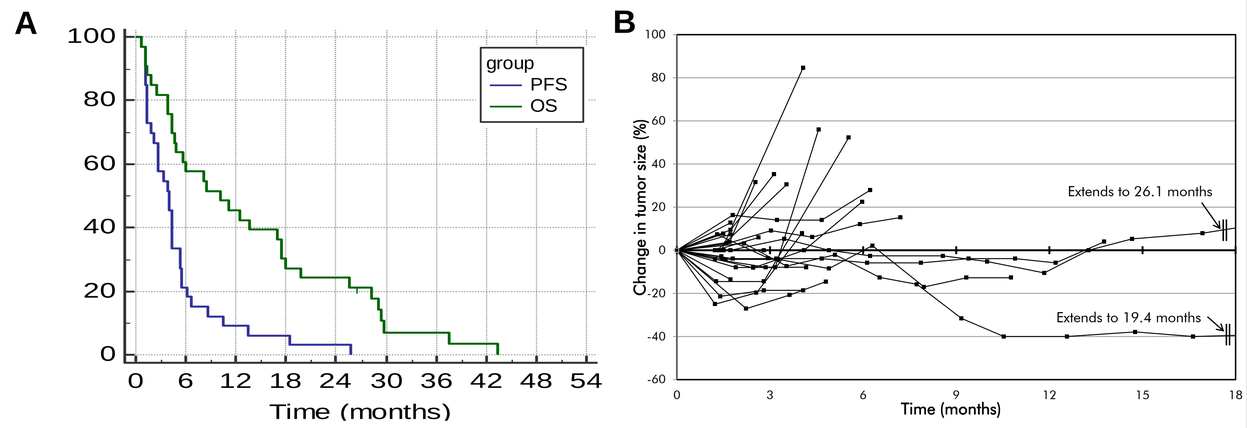

Figure 2: (A) Survival analysis for 33 patients results in a median PFS of 4 months and a median OS of 10.2 months, with 1- and 2-year survival of 45% and 24%, respectively. (B) Spider plot showing the change in tumor size at each 6 week time point for 29 patients.

Pharmacodynamic analysis

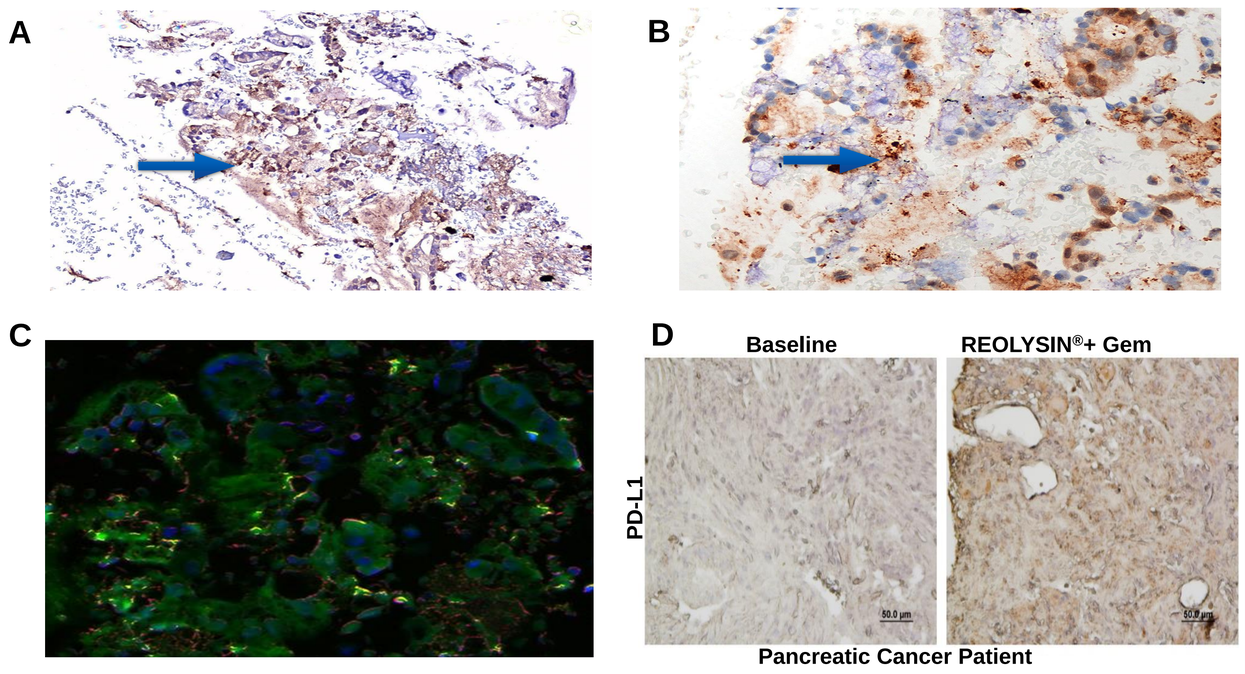

Figure 3: We obtained on-treatment biopsy from the primary pancreatic tumor of one patient with KRAS G12D mutation which displayed positive staining for reoviral protein (A) and caspase-3 (B) by immunohistochemistry (IHC). Fluorescent *in situ* hybridization (FISH) demonstrated co-expression of reovirus and caspase-3 proteins as indicated by the fluorescent yellow consistent with productive lytic infection and ongoing apoptosis (C). Following REOLYSIN® therapy, IHC data shows the upregulation of immune marker PD-L1(D).

Conclusions

- **REOLYSIN® in combination with gemcitabine has demonstrated clinical benefit in patients with advanced PDAC, with promising survival advantage and a favorable toxicity profile.**
- **Pharmacodynamics analysis show reovirus replication within pancreatic tumor and associated apoptosis in one patient with long term SD.**
- **Upregulation of immune checkpoint marker PD-L1 suggests combining oncolytic viral therapy with anti-PD-L1 inhibitors in future trials.**