

Background

Reovirus is a segmented double-stranded RNA virus with minimal pathogenicity in humans.

- Reovirus replicates in cells with an activated Ras signalling pathway, while sparing normal cells.
- Reovirus serotype 3 Dearing has demonstrated inherent selective oncolytic activity, both *in vitro*, *in vivo* and after systemic delivery in humans.
- Synergistic tumour kill has been observed combining reovirus with radiotherapy and chemotherapy, in particular with taxanes, in a range of cancer models, justifying clinical evaluation of the combination.

Study Design

A phase I study to evaluate the safety, feasibility and biological effects of IV administration of Reolysin in combination with docetaxel in patients with advanced cancers.

Patient Population

- Patients with advanced cancer refractory to standard therapy or for whom no standard therapy exists, age ≥ 18 years, ECOG score < 2.

Primary Objective

- To determine the safety, dose-limiting toxicity (DLT), and maximum tolerated dose (MTD) of Reolysin when administered with docetaxel

Secondary Objectives

- To evaluate the humoral and cellular immune response to reovirus when given with docetaxel
- To evaluate pharmacokinetics of docetaxel when combined with reolysin
- To describe any antitumour activity.

Design

- Open-label, dose-escalating, non-randomised, three-centre phase I study of Reolysin given IV with docetaxel every 3 weeks. Docetaxel given on day 1, and Reolysin days 1-5.
- 24 patients treated to date.

DLT Definition

Toxicities were graded using NCI/CTC version 3.0. DLT was defined as follows:

- **Hematological:** ANC < 500/μl lasting for ≥ 7 days, or ANC < 500/μl with sepsis; platelet count < 25,000/μl
- **Non-hematological:** Grade ≥ 2 cardiotoxicity or neurotoxicity and any drug related Grade 3/4 toxicity except flu like symptoms, nausea and vomiting without appropriate treatment or prophylaxis;
- **Other:** Inability to tolerate a full 5-day dosing course due to toxicity

Viral replication

- RT-PCR of blood, urine, stool and sputum pre and post Reolysin treatment.
- Intratumoral reovirus replication in patient's biopsies (RT-PCR/EM).

Neutralising anti-reovirus antibody

- At baseline and weekly post treatment for first 2 cycles.
- Used anti-reo polyclonal anti-serum as positive control.

Tumor evaluation

- Every 2 treatment courses (CT scan ± tumor marker)

Table 1: Patients Characteristics

Characteristics	No. of Patients
Gender	
Male	20
Female	4
Age, yr	
Median	60
Range	33-79
Previous chemo lines	
0	1
1	13
2	7
>2	3
Cancer Diagnosis	
Oesophagus	6
Melanoma	4
Prostate	4
Unknown 1*	2
Pancreas	4
Breast	1
Stomach	1
Mesothelioma	1
Hepatocellular	1

Table 2: Patients treated at each dose level and DLT observed

Cohort	No. of Patients	Reolysin dose (TCID ₅₀)	Total number of cycles (range)	DLT Event
1	4	3 x 10 ⁹	16 (1-6)	-
2	4	1 x 10 ¹⁰	20 (2-8)	-
3	16	3 x 10 ¹⁰	58 (1-8)	G4 Neutropaenia

Safety and Toxicity

- No MTD has been reached.
- Toxicities were ≤ grade 3, with one grade 4 neutropaenia.
- The main drug-related adverse events were neutropaenia, fever, sweating, nausea, and fatigue.

Table 3: Antitumour activity in Evaluable Patients (n=17)

Best Response	No. of Patients	Tumour Types	Reduction
Partial Response	2	Breast	CR in liver; SD in bone
		Stomach	↓32% in lymph nodes
Minor response	3	Mesothelioma	↓23% in lymph nodes
		Prostate	↓30% in PSA
		SCC H+N	↓26% in lymph node
Stable Disease	10	Prostate	
		Unknown 1*	
		Melanoma	
		Oesophagus	
		Pancreas	

Figure 1: Liver mets at baseline

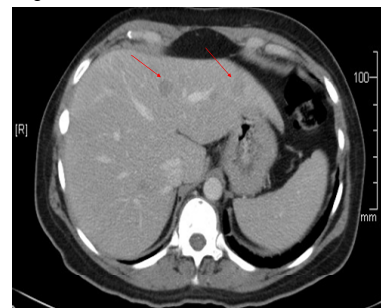
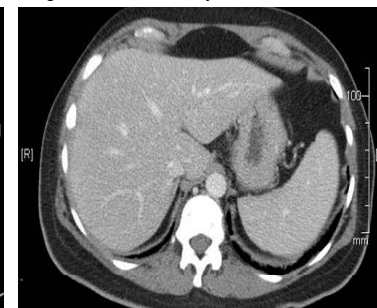


Figure 2: CR after 6 cycles



Conclusions

- Reolysin is well tolerated when administered intravenously in combination with docetaxel, with minimal toxicity observed.
- The recommended dose has been defined at TCID₅₀ 3x10¹⁰ with docetaxel 75mg/m².
- No viral shedding has been reported to date in blood, urine, saliva and stools.
- Objective radiological evidence of anticancer activity in a variety of cancer indications has been observed.
- Phase II studies with this combination are justified and are due to start