

# A Phase 1 study to evaluate the feasibility, safety and biological effects of intratumoural administration of wild type reovirus (Reolysin) in combination with radiation in patients with advanced malignancies.

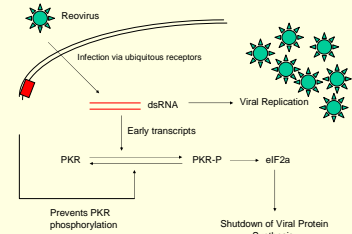
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**Background:** Wild-type reovirus (REOLYSIN®) is a dsRNA virus which results in asymptomatic infection in humans and has been demonstrated to replicate in and prove cytopathic to Ras activated cells, while sparing normal cells

## Mechanism of Tumour Selectivity of Reovirus



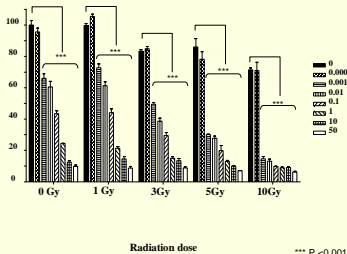
**Methods:** An open label, dose escalating, multicentre phase I study of intratumoural injections of REOLYSIN with concurrent fractionated radiotherapy in patients with advanced solid tumours. The primary objectives are to determine the feasibility and safety of this intervention as well as assessing the antitumour activity, viral replication and the development of immune response. Patients were treated in sequential 3-patient cohorts.

**Results:** 22 patients have been treated to date with 15 having completed the study. Treatment has been well tolerated, with mostly Grade 1 or 2 toxicities including fatigue, lymphopenia, fever and neutropenia. Grade 3 toxicities including cellulitis and diarrhoea were not related to treatment. Of 11 patients treated in the Ia trial, three patients (oesophageal, squamous skin carcinoma and squamous cell scalp) experienced significant partial responses. Of the six patients who have completed the Ib portion, three patients experienced tumour regression including one significant partial response in a patient with colorectal cancer.

## Objectives of Reovirus plus Radiotherapy Phase 1 trial

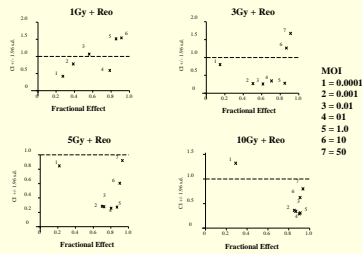
- Primary:**
  - Determine the safety and tolerability of escalating doses and frequencies of intratumoural reovirus when combined with increasing radiation doses
- Secondary:**
  - Evaluation of reovirus excretion
  - Detection of neutralizing anti-reovirus antibodies
  - Detection of reovirus replication in tumour
  - Description of anti-tumour activity

## In vitro Combination Effect is Greatest at Mid-Range MOIs



Twigger et al. Clinical Cancer Research in press

## In Vitro Combination Index Analysis Shows Synergism



Twigger et al. Clinical Cancer Research in press

## Study Design

Phase	Patients x Cohort	Reovirus Dose (TCID50)	RT (Gy)	Virus doses	Days of virus administration
Ia	3	1x10 <sup>9</sup>	20 Gy in 5F	2	2,4
Ia	3	1x10 <sup>8</sup>	20 Gy in 5F	2	2,4
Ia	3	1x10 <sup>7</sup>	20 Gy in 5F	2	2,4
Ib	3	1x10 <sup>10</sup>	36 Gy in 12F	2	2,4
Ib	3	1x10 <sup>9</sup>	36 Gy in 12F	4	2,4,9,11
Ib	3	1x10 <sup>8</sup>	36 Gy in 12F	6	2,4,9,11,16,18

## Patient Characteristics

Tumour type	Age	Sex	Reovirus dose (TCID50)	Radiation dose
Oesophageal	56	M	1x10 <sup>8</sup>	20 Gy
Melanoma	58	M	1x10 <sup>8</sup>	20 Gy
Pancreas	67	M	1x10 <sup>8</sup>	20 Gy
Ovarian*	58	F	1x10 <sup>8</sup>	20 Gy
Unknown primary squamous cell	41	F	1x10 <sup>8</sup>	20 Gy
Squamous cell of the scalp	71	M	1x10 <sup>8</sup>	20 Gy
Small cell lung cancer	70	M	1x10 <sup>8</sup>	20 Gy
Metastatic undifferentiated carcinoma of unknown origin	60	F	1x10 <sup>8</sup>	20 Gy
Squamous cell of ear	46	M	1x10 <sup>10</sup>	20 Gy
Squamous cell carcinoma	83	F	1x10 <sup>10</sup>	20 Gy
Metastatic colorectal	60	M	1x10 <sup>10</sup>	20 Gy
Laryngeal cancer	77	M	1x10 <sup>10</sup>	20 Gy
Melanoma	66	F	1x10 <sup>10</sup>	36 Gy
Non-small cell lung cancer	67	M	1x10 <sup>10</sup>	36 Gy
Ovarian	59	F	1x10 <sup>10</sup>	36 Gy
Metastatic colorectal	69	M	1x10 <sup>10</sup>	36 Gy
Squamous cell carcinoma of head & neck	59	F	1x10 <sup>10</sup>	36 Gy
Squamous cell carcinoma of head & neck	56	M	1x10 <sup>10</sup>	36 Gy
Melanoma	64	F	1x10 <sup>10</sup>	36 Gy
Ovarian	69	F	1x10 <sup>10</sup>	36 Gy
Melanoma	73	M	1x10 <sup>10</sup>	36 Gy
Melanoma	38	M	1x10 <sup>10</sup>	36 Gy
Melanoma	57	F	1x10 <sup>10</sup>	36 Gy
Melanoma	53	F	1x10 <sup>10</sup>	36 Gy

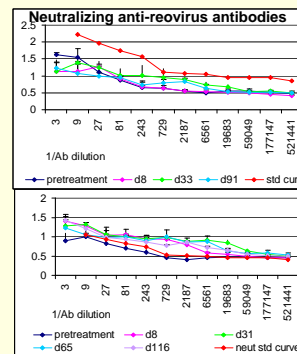
## Toxicity

- No dose limiting-toxicity has been observed.
- Mild toxicity (Grade 1-2)
  - Fever
  - Chills
  - Flu like symptoms
  - Fatigue
  - Asymptomatic lymphopenia
  - Skin erythema and mucositis

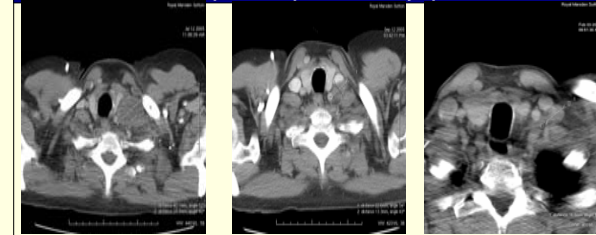
Grade 3 toxicities on treatment per patient.

Toxicity	Number
Diarrhoea	2
Vomiting	1
Dyspnoea	1
Fatigue	1
Dysphagia	1
Pain	1
Facial	1
Cellulitis	1
Anaemia	1

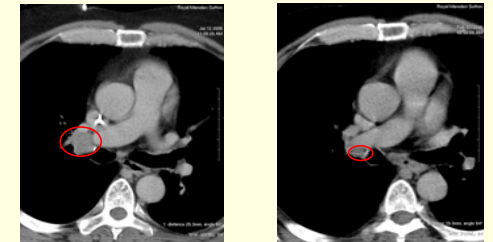
No grade 3 toxicity related to drug



## Local response; supraclavicular lymph node



## Response outside of the radiation field.



## Conclusions:

- The use of intratumoural injections of wild type reovirus combined with radiation is tolerated without significant toxicity
- The Maximum tolerated dose (MTD) or Dose Limited Toxicity (DLT) have not been defined
- Multiple injections combined with longer course radiation appears feasible
- Interim results demonstrated partial responses and stable disease in some patients
- Response data and final immunological data to be collated at study completion
- Phase 2 study to assess Response to combination of Reolysin and radiation currently underway