



PHASE I/II TRIAL OF ONCOLYTIC REOVIRUS (REOLYSIN®) IN COMBINATION WITH CARBOPLATIN/PACLITAXEL IN PATIENTS WITH ADVANCED SOLID CANCERS

¹Karapanagiotou E, ²Pandha HS, ³Hall G, ³Chester J, ³Melcher A, ¹De Bono J, ¹Gore ME, ¹Nutting CM, ¹Harrington KJ.

¹The Royal Marsden Hospital NHS Foundation Trust, London, UK. ²University of Surrey, Guildford, UK. ³Leeds Institute of Molecular Medicine, Leeds, UK

Background

- Reovirus is a segmented double-stranded RNA virus with minimal pathogenicity in humans.
- Reovirus replicates in cells with an activated Ras signaling pathway, while sparing normal cells
- Activated Ras inhibits the anti-viral effects of double stranded RNA-activated protein kinase (PKR), allowing reovirus infection, replication and subsequent oncolysis
- 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 a range of cancer models justifying clinical evaluation of the combination

Study design

Dose targeted phase I/II trial of feasibility, safety and biological effects of iv administration of Reolysin plus carboplatin and paclitaxel in patients with advanced cancer

Primary Objective

- Safety, dose-limiting toxicity (DLT), and maximum tolerated dose (MTD) of Reolysin with carboplatin and paclitaxel

Secondary Objectives

- humoral and cellular immune response to reovirus
- pharmacokinetics of paclitaxel and carboplatin when combined with Reolysin
- to measure tumour responses and duration of response
- to assess viral replication and shedding

Design

- open-label, dose escalating, non-randomised, two centre phase I/II trial of Reolysin (d1-5) given iv with paclitaxel (175mg/m², day 1) and carboplatin (AUC5, d1) every 3 weeks for 8 cycles.

DLT Definition

- ANC <0.5x 10⁹ for >7 days or with sepsis, Platelets <25 x 10⁹/L, any other drug related non-haematological grade 3/4 toxicity, with the exceptions of flu-like symptoms, nausea and vomiting, inability to tolerate at least one course of therapy due to toxicity

Conclusions

- Reolysin is well-tolerated when administered iv in combination with paclitaxel and carboplatin.
- The recommended dose has been defined at TCID₅₀ 3X10¹⁰ with paclitaxel (175mg/m²) and carboplatin AUC5.
- Objective radiological evidence of anticancer activity has been documented.
- Of note, 4/4 PRs and 4/5 SD were in H&N disease.

Table 1: Patients characteristics

Male: female	9: 5	
Age	55.4±10.9 (39-79)	
PS (%)	0	10 (71.4)
	1/2	4 (28.6)
Cancer type (%)	H&N SCC	5 (35.7)
	NPC	5 (35.7)
	Melanoma	2 (14.3)
	Endometrial ca	1 (7.1)
	Peritoneal adenoca	1 (7.1)
Treatment line (%)	2 nd	10 (71.4)
	2 nd plus	4 (28.6)

Table 2: Patients treated at each Reolysin dose level

Reolysin dose (TCID ₅₀)	Number of patients	Cohort
3 * 10 ⁹	3	1
1 * 10 ¹⁰	3	2
3 * 10 ¹⁰	8	3 & Ph.II

Safety and Toxicity

- ✓ No MDT has been reached
- ✓ toxicities were mainly grade 1 and 2
- ✓ lymphopenia grade 4 was observed
- ✓ Reolysin-related adverse events were: fever, rash, itching, myalgia, hypotension

Antitumour activity

Partial response (PR)	4	28.6%
Stable disease (SD)	5	35.7%
Progressive disease (PD)	4	28.6%
Unknown (pts on treatment)	1	7.1%

Figure 1: SCC with liver metastases at baseline



Figure 3: SCC at baseline

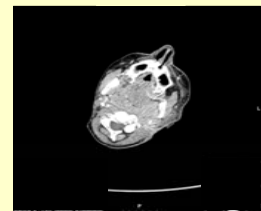


Figure 2: SCC after 6 cycles

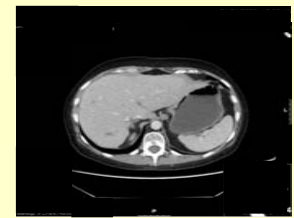
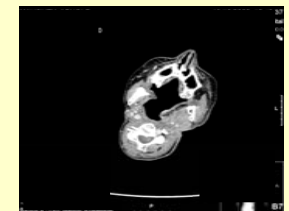


Figure 4: SCC after 3 cycles



The combination of Reolysin with chemotherapy was able to blunt the initial antiviral immune response. Responses were attenuated in contrast to data from the phase I iv study of Reolysin alone (White et al Gene Ther 2008; 15: 911-20)

