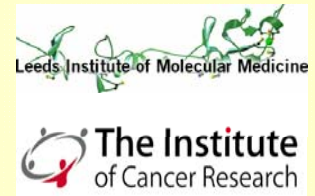




# PHASE I/II TRIAL OF ONCOLYTIC REOVIRUS (REOLYSIN®) IN COMBINATION WITH CARBOPLATIN/PACLITAXEL IN PATIENTS WITH ADVANCED SOLID CANCERS WITH EMPHASIS ON SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (SCCHN)

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## 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

### 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/m<sup>2</sup>, day 1) and carboplatin (AUC5, d1) every 3 weeks for ≤8 cycles. Because of responses seen in SCCHN in Phase 1, a Phase 2 study was completed in this target population.

### DLT Definition

- ANC <0.5x 10<sup>9</sup> for >7 days or with sepsis, platelets <25 x 10<sup>9</sup>/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 TCID<sub>50</sub> 3x10<sup>10</sup> with paclitax (175mg/m<sup>2</sup>)/carboplat (AUC 5).
- Neutralising anti-reovirus antibody (NARA) response ablated/delayed by the chemotherapy.
- Of note, there were 8 PR (42%) and 6 SD (32%) among 19 evaluable pts (>1 cycle) with head and neck cancer, mostly SCCHN refractory to prior platinum-based chemotherapy for recurrent/metastatic disease. One additional PR and one SD were observed in 4 patients with malignant melanoma.
- A US/EU double-blind, randomized Phase 3 multi-center study in this target population is underway.

Table 1: Patients characteristics

Male:Female	24:7	
Age, median (range)	59 (27-79)	
PS (%)	0	(71)
	1/2	(29)
Cancer type (%)	H&N SCC	19 (61)
	Nasopharyngeal	5 (16)
	Melanoma	4 (13)
	Endometrial ca	1 (3)
	Peritoneal adenoca	1 (3)
	Sarcoma	1 (3)
Treatment line (%)	2 <sup>nd</sup>	15 (48)
	3 <sup>rd</sup> plus	11 (35)

Table 2: Patients treated at each REOLYSIN dose level

REOLYSIN dose (TCID <sub>50</sub> )	Number of patients	Cohort
3*10 <sup>9</sup>	3	1
1*10 <sup>10</sup>	3	2
3*10 <sup>10</sup>	25	3 & Ph.II

## Safety and Toxicity

- No MTD was reached.
- Grade 3/4 toxicity seen with the chemotherapy combination included anemia, neutropenia, lymphopenia, thrombocytopenia and hypotension.
- Most common (Grade 1-2) REOLYSIN-related adverse events included fever, rash, itching, myalgia.

Table 3: Best response in H&N ca refract. to prior chemo for recurrent/metastatic disease\*

Partial Response (PR)	8	42%
Stable Disease (SD)	6	32%
Progressive Disease (PD)	5	26%

\*18 of 19 patients were platinum refractory

Figure 1: Poorly differentiated SCC H&N at baseline. Prior treatment history of palliative RT, cisplatin/ 5FU and carboplatin/5FU.



Figure 2: Same patient after 3 cycles. Response continuing in cycle 6.

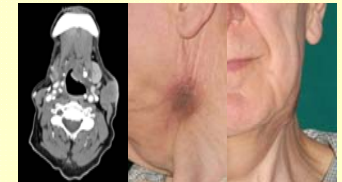


Figure 3: SCC pre-treatment. Rapid progression < 3 wks before study. Prior treatment history of cisplatin/ 5-FU, and cisplatin.



Figure 4: Same patient after 3 cycles. Response continuing in cycle 6.



Figure 5: REOLYSIN combined with chemotherapy was able to blunt the initial antiviral immune response in contrast to REOLYSIN alone.

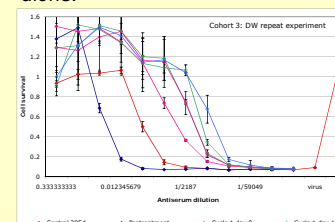


Figure 6: Overall Survival of 19 evaluable Head and Neck patients grouped by best response on study.

