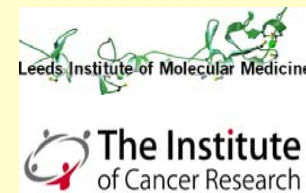




PHASE I/II STUDY OF ONCOLYTIC REOVIRUS PLUS CARBOPLATIN/PACLITAXEL IN PATIENTS WITH ADVANCED SOLID CANCERS WITH EMPHASIS ON SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (SCCHN)

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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

- ❑ To measure tumour responses and duration of response.
- ❑ Humoral and cellular immune response to reovirus.
- ❑ Pharmacokinetics of paclitaxel and carboplatin when combined with REOLYSIN.
- ❑ 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, 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 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.
- Recommended dose has been defined at TCID₅₀ 3x10¹⁰ with paclitaxel (175mg/m²)/carboplatin (AUC 5).
- 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. Response (SD or better) in the evaluable H&N patients is predictive of a statistically significant increase in life span. Survival curves will be presented once all of the evaluable H&N patients are deceased.
- A US/EU double-blind, randomized Phase 3 multi-center study in this target population is underway.

Table 1: Patient 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 carcinoma	1 (3)
	Peritoneal adenocarcinoma	1 (3)
Treatment line (%)	2 nd	15 (48)
	3 rd plus	11 (35)

Table 2: Patients treated at each REOLYSIN dose level

REOLYSIN dose (TCID ₅₀)	Number of patients	Cohort
3x10 ⁹	3	1
1x10 ¹⁰	3	2
3x10 ¹⁰	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.

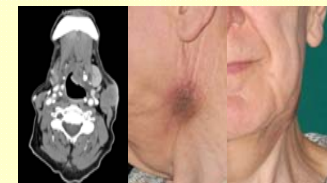


Figure 3: SCC pre-treatment. Rapid progression < 3 wks before study. Prior treatment history of cisplatin/ 5-FU, and cisplatin.



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

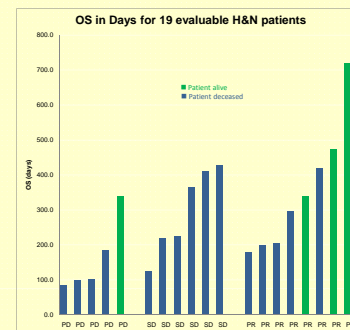


Figure 5: Overall Survival (OS) of 19 evaluable Head and Neck patients grouped by best response on study.

The survival curve is asymmetrical and therefore the use of median survival is not warranted. The mean OS in all 24 H&N cancer pts (4 pts still alive) was 8+ mos.

The mean OS of the PR and the PR + SD is statistically significantly greater than mean survival of the PD (hazard ratio 0.2, p = 0.0249 and hazard ratio 0.27, p = 0.04 respectively, 95% CI.)