

# A phase-I study of the combination of intravenous reolysin (wild-type reovirus) and gemcitabine (REO-GEM) in patients with advanced cancer.

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**Background:** REOLYSIN contains a proprietary formulation of reovirus, (reovirus serotype 3, Dearing strain.) Reovirus is a naturally occurring, non-enveloped virus with limited pathogenicity in humans. REO replicates specifically in transformed Ras-activated cells due to inhibition of the dsRNA-activated protein kinase, resulting in cell-lysis. GEM has shown efficacy in a wide range of tumors commonly driven by activated Ras, and causes cell cycle arrest in S phase. Results from isobologram analysis suggest potential synergies of REO and GEM. **Endpoints:** Endpoints were the maximum tolerated dose (MTD), dose limiting toxicity (DLT), and safety profile of REOGEM and to establish a RP2D. Secondary endpoints were to evaluate the immune response, to evaluate pharmacokinetics of REOGEM and to describe any antitumor activity. **Results:** Since July 2007, 16 heavily pre-treated pts with disease progression prior to trial entry (9M/6F, median age 56 years, ECOG 0/1: 3/12) were entered into this trial. After 2 pts had Grade  $\geq 3$  toxicities during the first cycle (1 pt: GGT and Trop-I increase and PD; 1 pt: Trop-I increase and unspecific ST-changes) considered probably related to both agents the protocol was amended and the dose of REO was adjusted to  $1 \times 10^9$  TCID<sub>50</sub>, d1 of each cycle (C-1) and increased in subsequent cohorts to  $3 \times 10^9$ ,  $1 \times 10^{10}$ , and  $3 \times 10^{10}$  TCID<sub>50</sub>. In total 45 cycles were administered (median 3) resulting in mild and expected toxicities including fever, headaches, rhinorrhea, fatigue and myelosuppression. The MTD was not reached. Of the 10 pts evaluable for response, 2 pts (breast and nasopharyngeal) had PR and/or clinical response and 5 pts had SD for 3-8 cycles, amounting for a disease control rate (CR+PR+SD) of 70%.

**Study Design**

An open-label, dose-escalating, two-centre Phase-I trial studied the combination of iv REO, d1-5 and iv GEM, d1 and 8, qw3. The REO starting dose was  $3 \times 10^9$  TCID<sub>50</sub> over 1-hour, increasing in successive cohorts and GEM was given at a fixed dose of 1000mg/m<sup>2</sup> over 30-min

**Study population:**

- Patients with advanced cancer refractory to standard therapy or for whom no therapy exists  $\geq 18$  years ECOG  $\leq 2$

**Primary Objective**

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

**Secondary Objectives**

- To evaluate pharmacokinetics
- To evaluate the humoral and cellular immune response to reovirus when given with gemcitabine
- To describe any antitumoral activity.

Cohort	No of pts	REO TCID <sub>50</sub>	GEM D 1 + 8	DLT
-1	3	$1 \times 10^9$ , D1	1000mg	
1	4	$3 \times 10^9$ , D1	1000mg	
2	4	$1 \times 10^{10}$ , D1	1000mg	
3	3	$3 \times 10^{10}$ , D1	1000mg	1 patient Grade 3 LFT's increase

Patients & Treatment Characteristics	
Characteristics	Number of Patients*
<b>Gender</b>	
Male	10
Female	4
<b>Age, yr, median</b>	56
<b>Performance Status</b>	
ECOG 0	3
ECOG 1	11
<b>Previous Treatment</b>	
1	3
2	4
3	3
4	1
5	3
<b>Cancer Diagnosis</b>	
CRC	3
Nasopharyngeal	1
Head&Neck	1
Fibrosarcoma	1
CUP	1
Breast	1
Bladder	1
Oesophagus	2
NSCLC	1
Cervix	1
Cholangiocarcinoma	1

Best response*	No of Patients	Tumor type	Reduction (%) or improvement	Duration of Treatment (Cycles)
Partial response	1	Nasopharyngeal	- 51	8
Minor response	1	Breast	-4 and clinical response	6
Stable disease	5	Fibrosarcoma NSCLC Bladder Head & neck CRC	Clinical improvement of Facial Nerve Palsy	4 4 4 3 3

\* For the current analysis 10 patients were evaluable for response

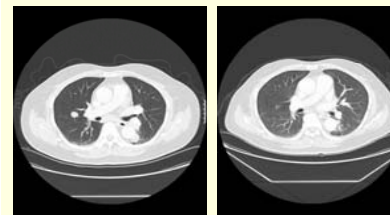


Figure 1: Partial response of a metastasis in the right middle lobe of the lung after 4 cycles of REO GEM in a nasopharyngeal cancer patients who was previously deemed to be gemcitabine resistant.

Treatment side effects CTC version 3.0	Grade 1 (pts)	Grade 2 (pts)	Grade 3 (pts)
<b>Constitutional</b> (fever, chills, fatigue, myalgia)	6		1
<b>Hematological</b> ANC PLT		1	3
<b>GI</b> Nausea/Vomiting Diarrhea AST/ALT/SGGT	2 1	1 2	1

## Conclusions

- After initial adjustment of REO the combination of REO-GEM was well tolerated and resulted in disease control for a majority of pts.
- A phase 2 dose of REO  $1 \times 10^{10}$ , d1 and GEM 1000mg/m<sup>2</sup>, d1 and 8, q3wks was recommended and phase-2 trials are underway.

\*A dose adjustment of REO to  $1 \times 10^9$  TCID<sub>50</sub>, d1 of each cycle (C-1) and increased in subsequent cohorts to  $3 \times 10^9$ ,  $1 \times 10^{10}$ , and  $3 \times 10^{10}$  TCID<sub>50</sub> was performed after 2 pts (not represented in these tables) developed Grade  $\geq 3$  toxicities.

**References:**

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