

# A Phase II Study of Intravenous REOLYSIN (Wild-type reovirus) in the Treatment of Patients with Bone and Soft Tissue Sarcomas Metastatic to the Lung



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## Introduction

REOLYSIN contains a proprietary form of reovirus, (reovirus serotype 3, Dearing strain.) Community-acquired infection is mild and limited to the upper respiratory and GI tract. Ras activation inhibits or reverses autophosphorylation of PKR, thus inhibiting its antiviral effects. This allows replication and oncolysis to occur specifically in Ras-transformed cells. In *in vitro* and *in vivo* studies in Ewing's sarcoma, rhabdomyosarcoma, synovial sarcoma, and osteosarcoma cell lines revealed significant antitumor activity.

## Patients and Methods

### Study Design:

This Phase II open-label, single agent study was designed to characterize the efficacy and safety of Reolysin given IV every 28 days (4 weeks) in patients (pts) with bone or soft tissue sarcoma with lung metastasis using a Simon two-stage design. 38 pts were enrolled in the first stage and the trial was permitted to proceed to full enrolment of 52 pts after 1 pt in the first stage experienced complete response, partial response or stable disease for at least 6 months. The study has completed enrolment.

### Inclusion Criteria:

1. Bone/soft tissue sarcoma metastatic to the lung unresponsive to, or untreatable by standard therapy. Acceptable histology: osteosarcoma, Ewing sarcoma, malignant fibrous histiocytoma, synovial sarcoma, fibrosarcoma and leiomyosarcoma
2. Have  $\geq 2$  measurable lesions in the lung
3. All adverse effects of previous treatment be at grade 1 or less
4. At least 16 yrs of age
5. No chemotherapy, radiotherapy, immunotherapy, hormonal therapy or surgery in the past 28 days
6. ECOG performance status of  $\leq 2$
7. Life expectancy of at least 3 months
8. Baseline labs: ANC  $\geq 1,500$ ; Platelets  $\geq 100K$ ; Hgb  $\geq 9.0g/dL$ ; SCr  $\leq 1.5 \times ULN$ ; Bilirubin  $\leq 1.5 \times ULN$ ; AST/ALT  $\leq 2.5 \times ULN$ ; neg. pregnancy test
9. Informed consent and willing to comply with visits, treatment plan, lab tests

### Exclusion Criteria:

1. Concurrent therapy with any other investigational anticancer agent
2. Inadequate pulmonary function
3. Immunosuppressive therapy; have known HIV infection, active hepatitis B/C
4. Pregnant or breast feeding woman
5. Clinically significant pulmonary or cardiac disease including pre-existing arrhythmia, uncontrolled angina pectoris, myocardial infarction 1 year prior to study entry, or grade 2 or higher compromised LVEF
6. Dementia or altered mental status
7. Any severe, acute or chronic medical or psychiatric condition

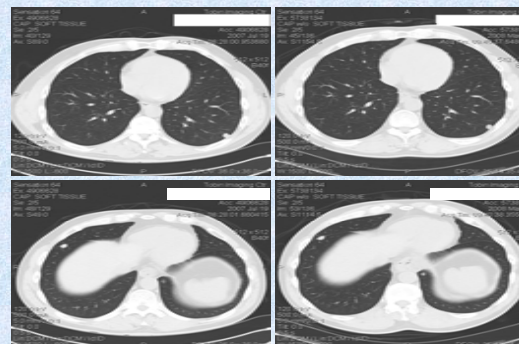
### Treatment Plan:

REOLYSIN was given at a dose of  $3 \times 10^{10}$  (TCID<sub>50</sub>) mixed in 250 mL of NS over 60 min, daily for 5 days every 28 days (1 cycle).

## Results

<b>Total enrollment:</b>		<b>N=52</b>
<b>Gender:</b>	Female	23 (44%)
	Male	29 (56%)
<b>Age:</b>	Median yrs	49 (Range 19-78)
<b>ECOG PS:</b>	0	12 (34%)
<b>(N=35)</b>	1	23 (66%)
<b>Tumor types:</b>	Synovial sarcoma	14 (27%)
	Leiomyosarcoma	12 (23%)
	Osteosarcoma	8 (15%)
	MFH	8 (15%)
	Other	10 (19%)
<b>Previous Tx:</b>	Chemotherapy Alone	22 (42%)
	Chemo and XRT	22 (42%)
	Biological Agents	15 (29%)
	XRT Alone	2 (4%)
	None	6 (12%)
<b>Efficacy:</b>	(Interim F/U Results)	<b>N=36 with F/ U Scans</b>
	CR/PR	0
	SD $\geq 8$ wks	18 (50%)
	$\geq 16$ wks	15 (42%)
	$\geq 24$ wks	5 (14%)
	PD	18 (50%)

### Stable Disease $\geq 80$ wks in Pt. with Synovial Sarcoma



## Results (cont)

<b>Toxicities:</b>		<b>N= 25 at IDD (%)</b>
<b>Constitutional:</b> (Fever, fatigue, myalgia):	Gr. 1	(88)
<b>Respiratory (cough, congestion):</b>	Gr. 1	(56)
<b>Hematological:</b>		
ANC:	Gr. 2	(4)
	$\geq$ Gr. 3	(16)
PLT:	Gr. 2	(8)
Anemia:	Gr. 1	(4)
<b>GI:</b>		
Diarrhea:	Gr. 1	(40)
AST/ALT:	Gr. 1-2	(12)

Transient palpitations in 2 patients (both had osteosarcoma with large lung mets). 1 patient had objective findings (arrhythmia) received  $\beta$ -blockers (etiology: possible hypoxia).

## Conclusions

- REOLYSIN is well tolerated and shows promise for the treatment of metastatic sarcoma
- Promising interim results in 36 pts with post C 2 F/U Scans:
  - SD  $> 8$  wks in 50%
  - SD  $> 16$  wks in 42%
  - SD  $> 24$  wks in 14%
- Mild toxicity with constitutional "flu-like" symptoms the most commonly reported toxicity
- Cycle 2 seems to be better tolerated than cycle 1
- Enrolment completed
- Other Phase 2-3 trials are examining REOLYSIN in combination with chemotherapy