

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 (by Ras mutation or upstream activation by EGFR mutation or overexpression) 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 ≥ 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 ≤ 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

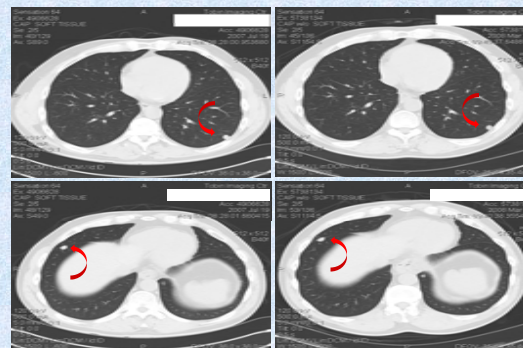
Treatment Plan:

REOLYSIN was given at a dose of 3×10^{10} TCID₅₀ mixed in 250 mL of NS over 60 min, daily for 5 days every 28 days (1 cycle).

Results

Total enrollment:		N=53
Gender:	Female	23 (43%)
	Male	30 (57%)
Age:	Median yrs	49 (Range 19-78)
ECOG PS:	0	28 (53%)
	1	24 (45%)
	2	1 (2%)
Tumor types:	Synovial sarcoma	14 (26%)
	Leiomyosarcoma	12 (23%)
	Osteosarcoma	8 (15%)
	MFH	9 (17%)
	Other	10 (19%)
Previous Tx:	Chemotherapy Alone	22 (42%)
	Chemo and XRT	23 (43%)
	Biological Agents	15 (28%)
	XRT Alone	2 (4%)
	None	6 (11%)
Efficacy:	(Final F/U Results)	N=44 with F/ U Scans
	CR/PR	0
	SD ≥ 8 wks	19 (43%)
	≥ 16 wks	17 (39%)
	≥ 24 wks	6 (14%)
	>52 wks	2 (5%)
	PD	25 (57%)

SD >80 wks in Pt. with Synovial Sarcoma with Lung Mets



Results (cont)

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

One patient had transient optic neuritis. Transient palpitations in 2 patients (both had osteosarcoma with large lung mets). 1 patient had objective findings (arrhythmia) received β -blockers (etiology: possible hypoxia).

Conclusions

- REOLYSIN is well tolerated and shows promise for the treatment of metastatic sarcoma
- Promising interim results in 44 pts with post C 2 F/U Scans:
 - SD > 8 wks in 43%
 - SD > 16 wks in 39%
 - SD > 24 wks in 14% (Synovial, Leiomyosarcoma, Ewing, Chordoma, Unspec. spindle cell, Alveolar sarcoma)
- Mild toxicity with constitutional "flu-like" symptoms the most commonly reported toxicity.
- Cycle 2 seems to be better tolerated than cycle 1.
- Enrolment completed. Phase 3 Study under discussion.
- Other Phase 2-3 trials are examining REOLYSIN in combination with chemotherapy.