

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 (reovirus serotype 3) is a Dearing strain, naturally occurring, ubiquitous, non-enveloped human reovirus. The community-acquired infection is mild and limited to the upper respiratory and GI tract. The virus inhibits the double-stranded RNA-activated protein kinase (PKR) and replicates specifically in transformed cells possessing an activated Ras pathway producing lysis. 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 will be enrolled in the first stage and up to a total of 52 pts in the second stage if at least 1 pt in the first stage experiences partial response or stable disease for at least 6 months.

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 is 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:		21
Gender:	Female	13
	Male	8
Age:	Median	51 (Range 22-70)
ECOG PS:	0	10
	1	11
Tumor types:	Malignant fibrous histiocytoma	5
	Osteosarcoma	5
	Synovial sarcoma	4
	Leiomyosarcoma	4
	Liposarcoma	1
	Ewing Sarcoma	1
	Undiff. Round cell sarcoma	1
Previous Txt:	Chemotherapy alone	9
	Chemo + XRT	9
	Other biological agents	5
	More than 3 previous regimens	8
	1-3 previous regimens	10
	No previous regimens	3
Efficacy:	Stable Disease	1 after cycle 10, (currently - cycle 11) 1 after cycle 4 6 after cycle 2
	Too early to evaluate	5

Results (cont)

Toxicities:

Constitutional (fever, chills, fatigue, myalgias):		
Grade 1:		18 patients
Respiratory (cough, congestion):		
Grade 1:		10 patients
Hematological:		
ANC:	Grade 2	1 patient
	Grade 3	4 patients
	Grade 4	1 patient (1 day in Cycle 2 and 3)
PLT:	Grade 2	2 patients
Anemia:	Grade 1	1 patient
GI:		
Vomiting:	Grade 1	1 patient
Diarrhea:	Grade 1	7 patients
Other:		
AST/ALT:	Grade 2	1 patient (C1D8, C2D8)
Palpitations: 2 patients (both had osteosarcoma with large lung mets). 1 patient had objective findings (arrythmia) received β -blockers (etiology: possible hypoxia).		

Conclusions

- Reolysin is well tolerated and shows promise for the treatment of metastatic sarcoma.
- Promising early results:
 - 1 patient SD after cycle 10.
 - 1 patient SD after cycle 4.
 - 6 patients SD after cycle 2.
- Second stage of accrual currently open.
- Mild toxicity with constitutional "flu-like" symptoms the most commonly reported toxicity
- Cycle 2 seems to be better tolerated than cycle 1
- Accrual is ongoing.
- Other trials are examining Reolysin in combination with chemotherapy.

Example of stable disease

