Phase I study of intra-pleural administration of GL-ONC1, an oncolytic vaccinia virus, in patients with malignant pleural effusion

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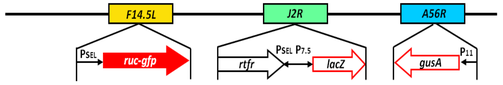
ABSTRACT

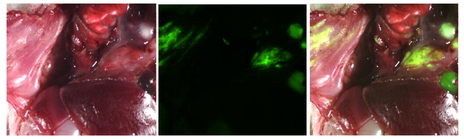
Background: GL-ONC1 is an attenuated vaccinia virus genetically engineered with the insertion of RUC (*Renilla* luciferase)-GFP, LacZ (beta-galactosidase), and gusA (beta-glucuronidase) genes. We investigated the feasibility, safety, and recommended dose of GL-ONC1 when administered intrapleurally.
Methods: Pts with pleural effusion from malignant pleural mesothelioma (MPM), NSCLC, breast cancer, or other solid tumor, and a free pleural space were eligible. Single doses of $1x10^7$, $1x10^8$, $1x10^9$, or $3x10^9$ plaque forming units were administered, and escalation used a 3+3 design. Virus was infused with 500cc Ringer's Lactate as a bolus through a pleural catheter. Fluorescent-imaging guided, thoracoscopic pleural biopsies were performed 2-9 days later. Blood, sputum, urine, and pleural fluid were analyzed for viral titers by viral plaque assays (VPA). No chemotherapy or radiation was administered during the course of the study (-14 days to 60 days).
Results: 14 pts have been treated: MPM (11), NSCLC (2), breast (1). Among 13 evaluable pts (1pt with NSCLC was not evaluable due to the rapid development of brain metastases) no dose limiting toxicities occurred. The most common toxicities were fever (7 pts), chills (6), and flu-like symptoms (5), all grade 1/2 occurring mostly in the 24hr after infusion. One patient at dose level 4 had transient grade 3 AST/ALT elevation (days 2-4). 1/28 urine and 5/28 pleural fluid post-treatment samples had +VPA. Positive GL-ONC1 infection of tumor specimens was identified in 6 of 8 pts with epithelioid MPM based on VPA, IHC and GFP imaging. 5 of the 9 pts with epithelioid MPM had time to progression > 9 mo (18 mo in one pt). Pts with NSCLC and breast cancer progressed quickly at metastatic sites.
Conclusions: Single dose, intrapleural administration of GL-ONC1 is safe, but is best suited for patients with MPM whose disease is limited to the pleura. We are now exploring multi-day treatment, and also treatment in conjunction with pleurectomy for pts with MPM. Analysis of tumor specimens for viral infection using VPA, IHC, and beta-glucuronidase is ongoing. Supported by Genelux Corporation (NCT01766739).

BACKGROUND

- GL-ONC1 (laboratory name: GLV-1h68) is an attenuated vaccinia virus genetically engineered with the insertion of RUC (*Renilla* luciferase)-GFP, LacZ (beta-galactosidase), and gusA (beta-glucuronidase) genes. [1]



- GL-ONC1 successfully infected all six MPM cell lines tested (MSTO-211H, VAMT, JMN, H-2372, H-2452, and H-2052)
- All cell lines were sensitive to killing by GLV-1h68
- In an orthotopic model, GLV-1h68 effectively prevented development of cachexia and tumor-related morbidity, reduced tumor burden, and cured MPM in both early and late treatment groups.



Intraoperative fluorescence imaging within the pleural cavity in an orthotopic mouse model using MSTO-211H

OBJECTIVES

Primary
- To determine the recommended dose of GL-ONC1 given intrapleurally in patients with a malignant pleural effusion

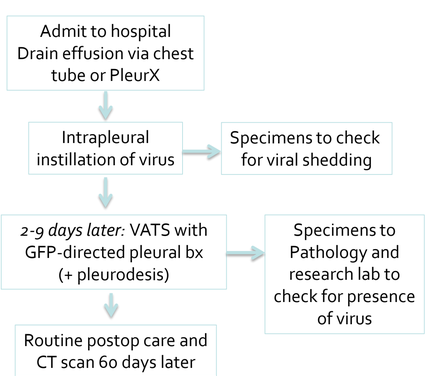
Secondary
- Feasibility, safety, and tolerability of intrapleural administration of GL-ONC1
- Detection of virus in body fluids
- Evaluation of viral appearance in tumor
- Evaluation of anti-vaccinia virus immune response

Cohort	Dose, Plaque Forming Units (pfu)
1	1×10^7
2	1×10^8
3	1×10^9
4	3×10^9

METHODS

Eligibility:
- Malignant pleural effusion from MPM, NSCLC, or breast cancer, with free pleural space
- ECOG/Zubrod performance status ≤ 2
- Chemotherapy, radiotherapy or immunotherapy must have stopped >14 days prior to receiving study drug; however, small field palliative radiotherapy, TKI therapies, and hormonal therapies are allowed.
- Adequate hematologic and biochemical laboratory studies
- No steroid use of more than 20 mg/day prednisone (or equivalent).

Treatment:
- Virus was infused with 500cc Ringer's Lactate as a bolus through a pleural catheter.
- Fluorescent-imaging guided, thoracoscopic pleural biopsies were performed 2-9 days later.
- Blood, sputum, urine, and pleural fluid were analyzed for viral titers by viral plaque assays (VPA).
- No chemotherapy or radiation was administered during the course of the study (-14 days to 60 days).



RESULTS

Pt	Cohort	Pathology	Prior Treatment	Time to Progression (weeks)	Viral Detection in Tumor			Subsequent Treatment	Survival (weeks)
					GFP	IHC	VPA		
1	1	MPM epithelioid	None	39	-	+	+	P/D, chemo, RT, vaccine trial	119+
2	1	NSCLC, squamous	Chemo	1	-	-	-	Craniotomy, brain RT	38
3	1	MPM epithelioid	None	77	-	+	-	Chemo, RT	111+
4	1	MPM epithelioid	None	8	-	+	-	Chemo, RT	100+
5	2	MPM epithelioid	None	37	-	-	-	P/D, chemo, RT	98+
6	2	MPM epithelioid	None	42	+	-	-	P/D, Chemo, RT, vaccine trial	95+
7	2	NSCLC, adeno*	Chemo, RT	1	N/A	N/A	N/A	None	2
8	3	MPM epithelioid	None	16	-	-	+	Chemo, RT	77
9	3	MPM epithelioid	None	10	+	+	-	Chemo	58
10	3	MPM epithelioid	Chemo	39	+	+	-	P/D	78+
11	4	MPM, sarcomatoid	None	9	-	-	-	Chemo	13
12	4	Breast Ca	Chemo, surgery	1	-	-	-	Craniotomy, brain RT, chemo	13
13	4	MPM, biphasic	None	9	+	-	-	Chemo	24
14	4	MPM, epithelioid	None	9	-	+	+	Chemo	37+

Toxicities (Definitely, Probably, or Possibly Related)	G1	G2	G3	G4
Alanine aminotransferase increased	1		1	
Alkaline phosphatase increased	1	1		
Anemia		2		
Aspartate aminotransferase increased	1			
Aspartate aminotransferase increased	1		1	
Blood bilirubin increased	2			
Chills	6			
Dyspnea	1			
Fatigue	2			
Fever	4	4		
Flu like symptoms	5			
Headache	3			
Lymphocyte count decreased			2	
Myalgia	2			
Nausea	3			
Pain	1	1		
Platelet count decreased	1			
Rash macoulo-papular	1			
Sinus tachycardia	2	1		
Sweating	3			
White blood cell decreased	1			

MPM = malignant pleural mesothelioma
NSCLC = non-small cell lung cancer
P/D = pleurectomy/decortication
* Not evaluable for response
GFP = Green fluorescent protein
IHC = immunohistochemistry
VPA = viral plaque assay
+ Still alive

CONCLUSIONS

- Single dose, intrapleural administration of GL-ONC1 is safe. No dose limiting toxicities have been observed. No significant virus shedding was found.
- Because of the distant progression noted in patients with NSCLC and breast cancer, this regional therapy seems best suited for patients with MPM whose disease is mostly involving the pleura.
- Analysis of tumor specimens for viral infection using GFP, IHC, and VPA showed evidence of infection in 9/13 evaluable patients.
- We are now exploring multi-day treatment, and also treatment in conjunction with pleurectomy for pts with MPM.

REFERENCES

1. Zhang *et al.* 2007, *Cancer Research,* 67:10038-46
2. Kelly *et al. 2008, Human Gene Therapy,* 19:774-782