

Protocol 1101-1088

**Phase I study of intra-pleural
administration of GL-ONC1 in patients
with malignant pleural effusion:
primary, metastases and mesothelioma**

Principal Investigator:

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Malignant pleural mesothelioma (MPM)

- Approximately 3,000 cases /yr. in US
- Almost always a fatal disease
- Median survival 4-12 months
- 10% surgical candidates
- Resistant to chemotherapy and radiation therapy
- Only small incremental survival benefit with chemo + surgery +RT (MS 16 mos)

Malignant pleural mesothelioma (MPM)

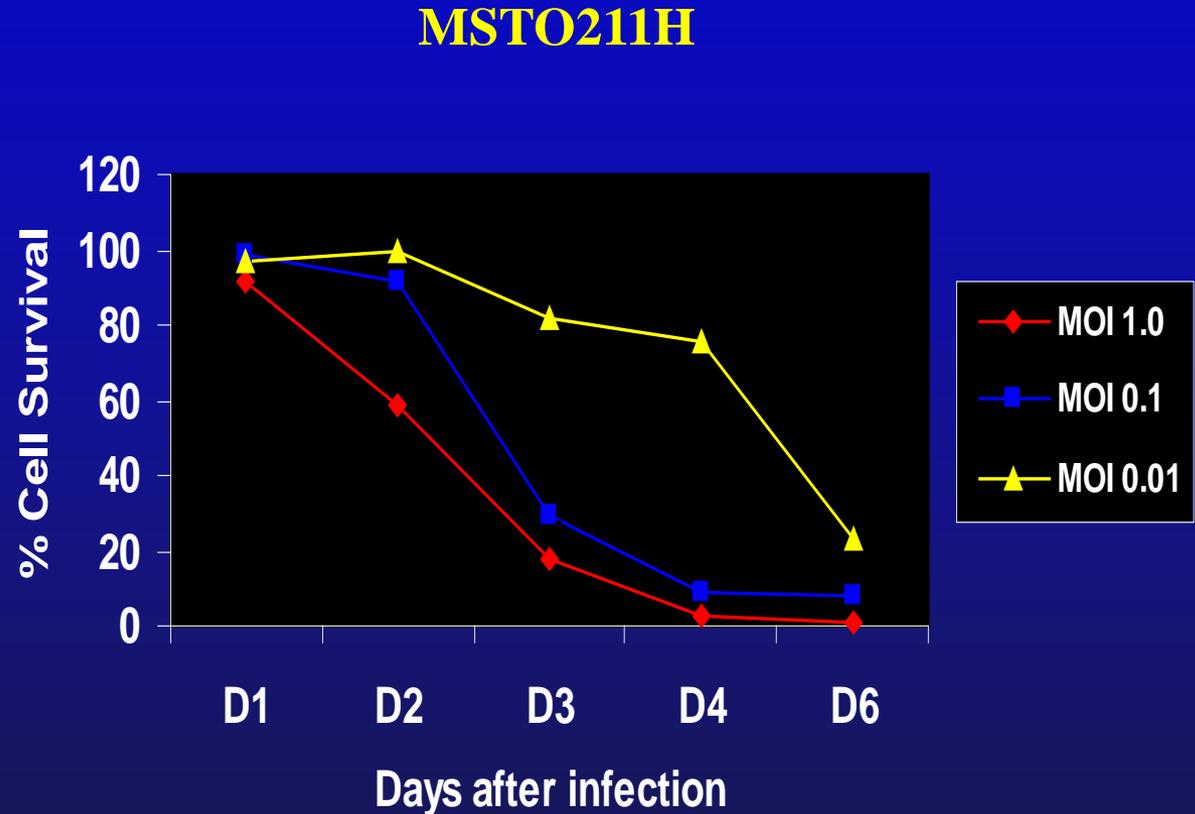
- We have maximized potential benefit of traditional Rx paradigms
- Novel therapies needed

Viral Therapies for Mesothelioma

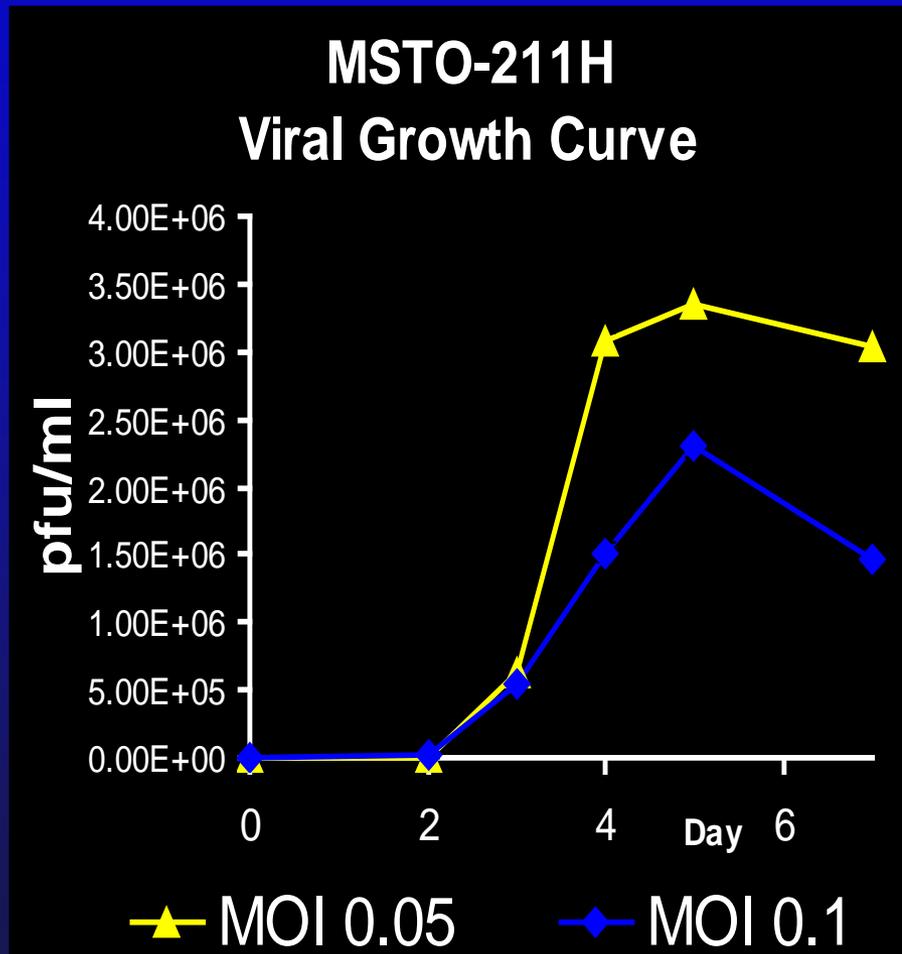
- Phase I trial of an HSV-tk-transduced ovarian cancer cell line (PA1-STK cells) infused ip followed by administration of ganciclovir
 - LSU
 - *Hum Gene Therapy 9:2641, 1998*
- Phase 1 adenovirus delivery of herpes simplex thymidine kinase followed by ganciclovir as suicide gene therapy
 - Univ Penn
 - *Clin Cancer Res 11:7444, 2005*
- A phase I trial of repeated intrapleural adenoviral-mediated interferon-beta gene transfer for mesothelioma and metastatic pleural effusions
 - Univ Penn
 - *Mol. Ther. 18: 852, 2010*
- A phase I Trial of Oncolytic Measles Virotherapy with NIS reporter in Malignant Pleural Mesothelioma
 - Mayo Clinic
 - *RAC protocol 1003-1033*

Treatment of Mesothelioma by Vaccinia Virus

- MSTO211H
- JMN
- H2373
- VAMT
- H2052
- H2452



Infected Cells Support Viral Replication

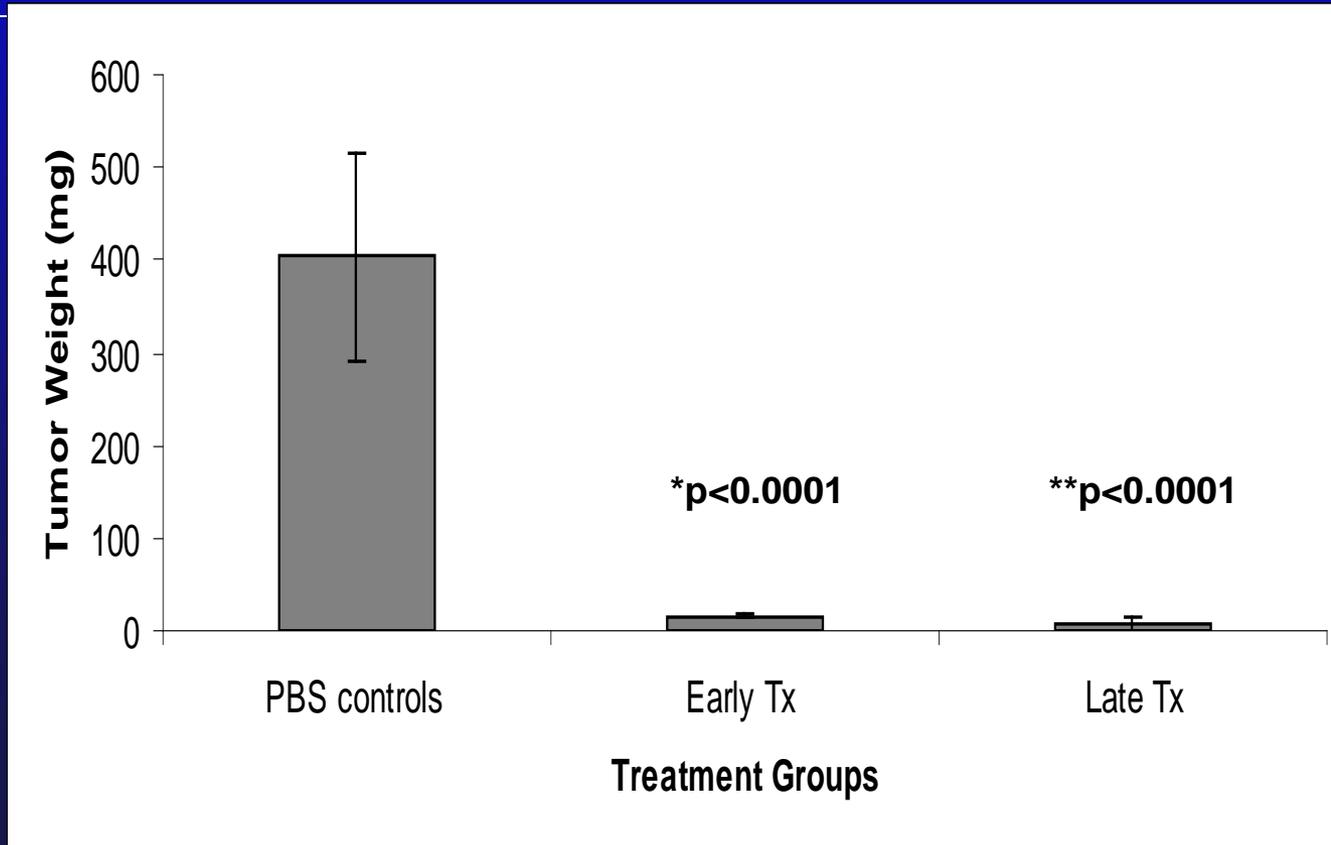


• Cell Line Fold-increase

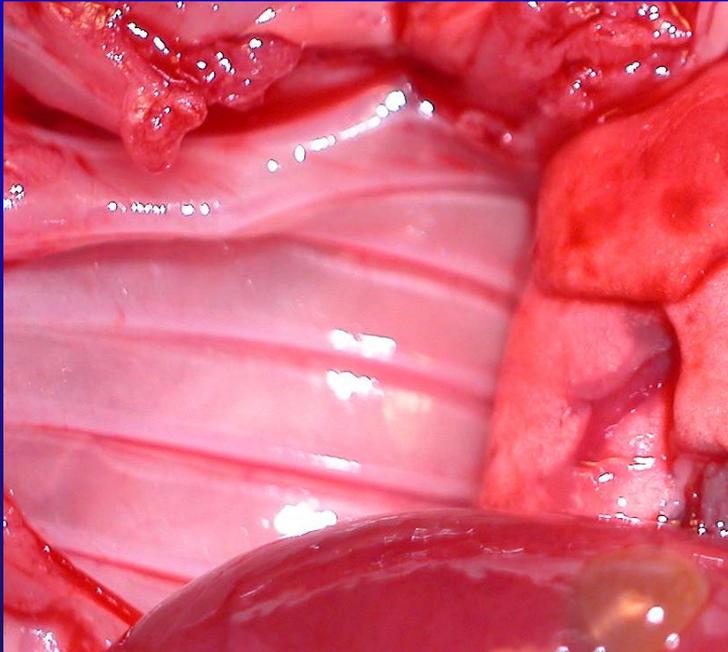
- MSTO-211H 3556
- H-2052 1914
- H-2373 1120
- H-2452 749
- VAMT 350
- H-Meso 202
- H-28 5

GLV-1h68 Treatment of Mesothelioma

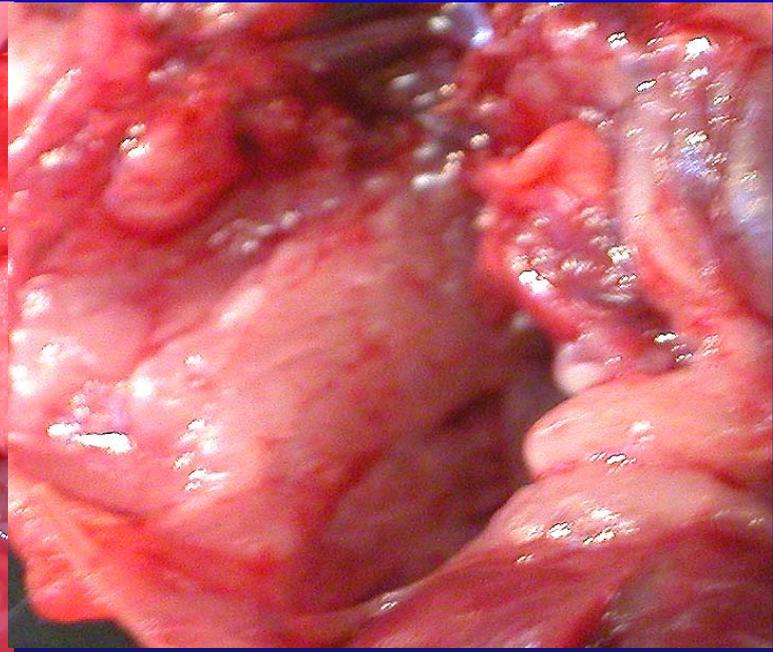
- Intrapleural implantation of MSTO-211H cells
- Treatment ip with 1×10^7 PFU
 - At 5 days (early) or 10 days (late)



GLV-1h68 Effectively Treats Pleural Mesothelioma

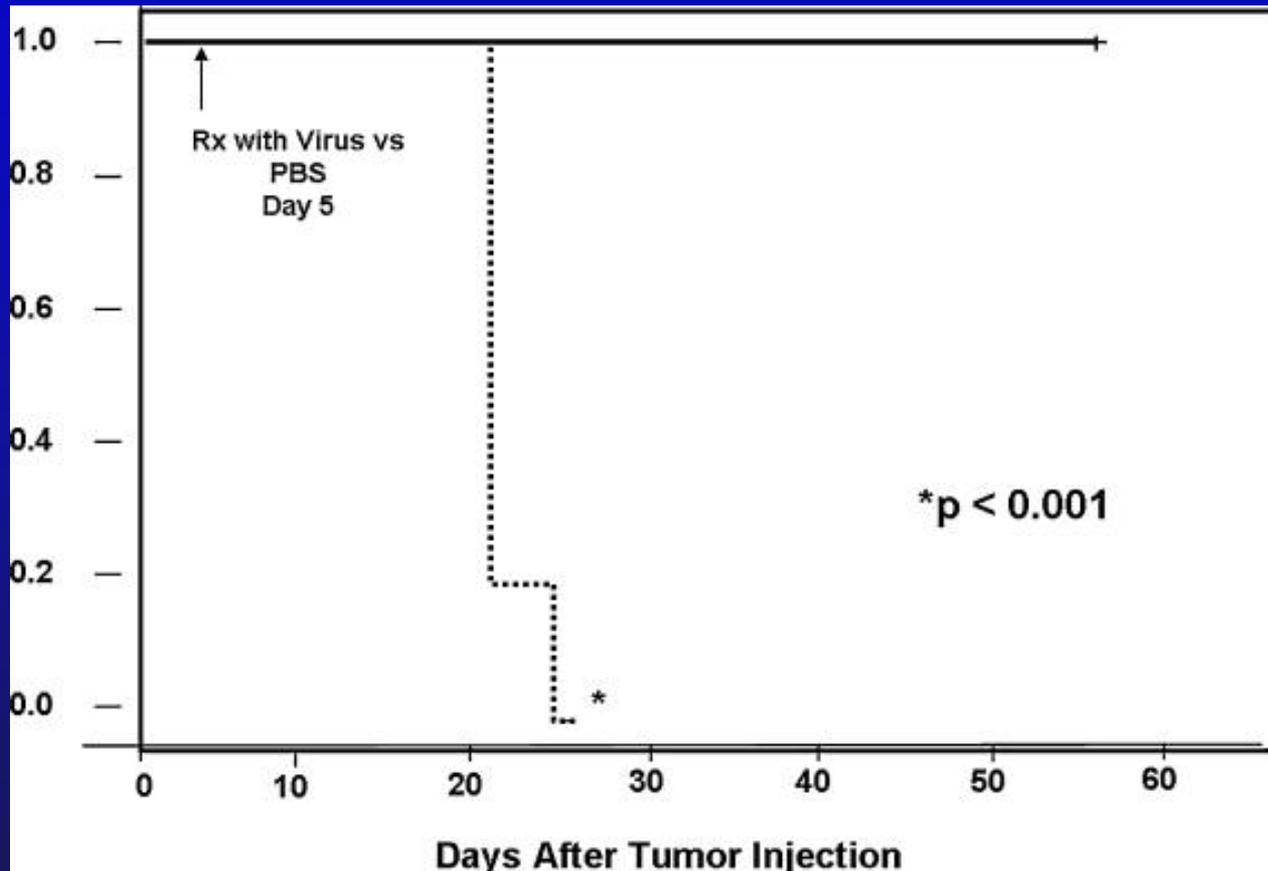


GLV-1h68 Treated

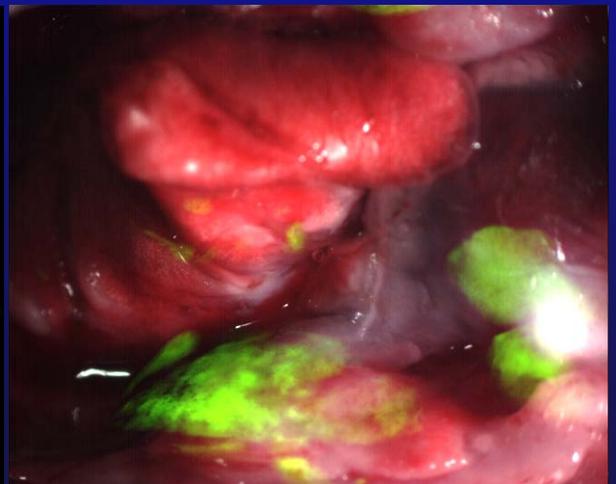
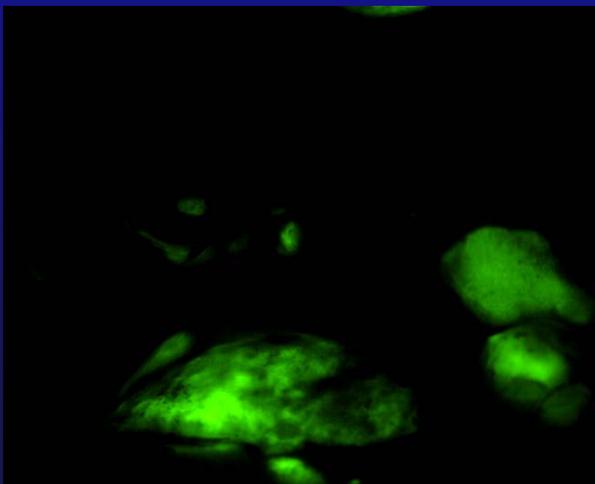
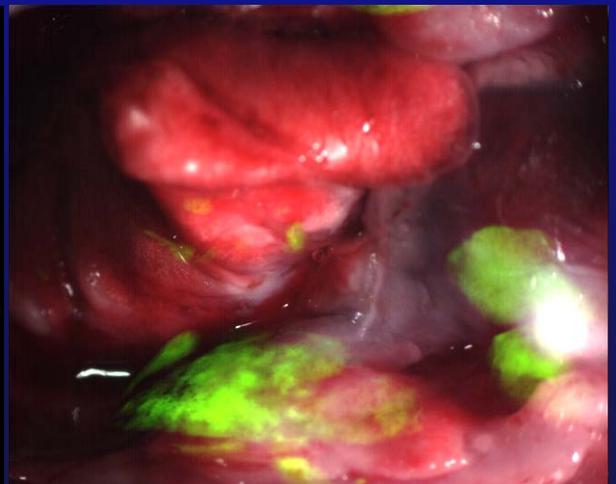
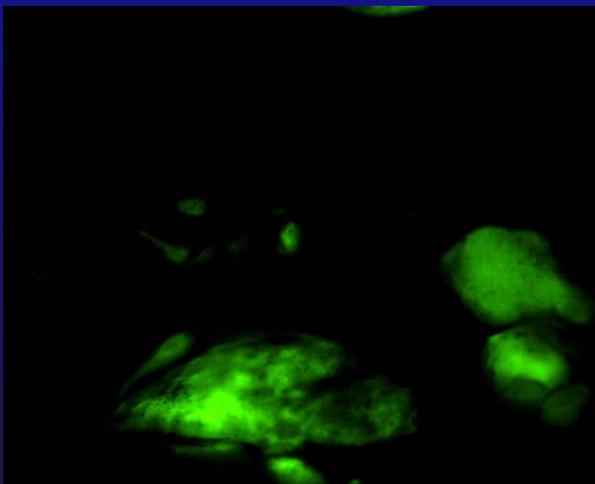
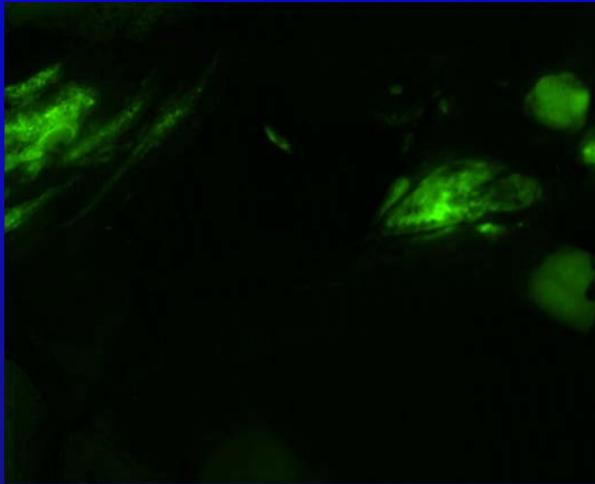


PBS Control

Survival after Treatment with GLV-1h68



Virally-mediated GFP Expression Localizes Tumor Deposits on Chest Wall, Lung, and Diaphragm



Phase I Study:

Intra-pleural administration of
GL-ONC1 in patients with
malignant pleural effusion:
primary, metastases and
mesothelioma

Inclusion Criteria

- *Pathologically proven malignant pleural effusions (MPM, met. NSCLC, other histologies)*
- *Free pleural space (partial or total) that permits the intrapleural drug instillation*
- Age ≥ 18 years
- Acute toxicities of prior RT, chemoRx, or surgery must have resolved to Grade ≤ 1
- Chemotherapy, radiotherapy or immunotherapy must have stopped more than 14 days
- ECOG PS 0-1
- No prior viral therapy

Study Schema

Enrollment

**Administration
of virus**

**Biopsies of
GFP positive
and negative
areas**

**Presentation
with malignant
pleural effusion**

**Drainage of
pleural fluid
with chest tube**

**VATS for
pleurodesis**

Evaluation for Toxicity

Dose level by cohort

Cohort	Dose **	Number of doses	Total volume of each injection
-1*	1×10^6	1	Final volume of preparation will be 100 mL, to be administered as a bolus.
+1	1×10^7	1	
+2	1×10^8	1	
+3	1×10^9	1	
+4	3×10^9	1	

* Necessary only if toxicity is encountered at the initial dose level.

** Intermediate dose levels may be evaluated if indicated.

Responses to Queries

Ornelles Question 3

- *Given that a strong selective pressure has been shown to silence transgene expression, could this not affect conclusions drawn from imaging patient tumors and non-tumor tissue at late times of therapy? ...The viral progeny produced by multiple rounds of replication will have had a greater opportunity to silence reporter gene expression and detection by imaging methods alone could lead to a false negative conclusion.*
- We will be assessing by VATS on days 2-7. We anticipate that the virus will have replicated no more than 3 cycles. We should be able to use the GFP marker gene for assessment of viral infection.
- Random pleural biopsies and GFP-directed biopsies will be performed to allow for assessment of viral presence.
- Viral plaque assays (VPA) will be performed to confirm presence of virus.

Strome Question 1

- *Why are 3 CT Scans necessary?*
- **RESPONSE:** As an assessment of eligibility and for patient safety, the amount of free pleural space to permit infusion of treatment drug needs to be ascertained by CT scan during the screening has to determine if drainage is needed.

Strome Question 3

- *It is of interest to me from a company perspective and not this trial that immunosuppressive therapy is an exclusion criteria, yet in trial 1089, using the same viral construct giving combined chemo radiation therapy with this product is considered acceptable. Also in this study appropriately no chemotherapy or large field radiation therapy is being allowed.*
- **RESPONSE:** As the route of intrapleural administration of GL-ONC1 has not been investigated in a phase I trial, clinical protocol 1101-1088 was designed as a single agent treatment in order to determine the safety of this type of administration route. As such, chemotherapy, large field radiation therapy, or any other type of anti-cancer treatment is not allowed so as not to confound the results.

Strome: Consent Form

- Immune response further explained
- Risk of CT scan
- Chest tube further explained
- VATS (video assisted thoracoscopic surgery) further explained
- Treatment of generalized vaccinia infection further explained
- Thromboembolic event in Marsden trial added

Consent Form

- **Chest tube and VATS standard therapy for this population**
- **Vaccinia treatment will be according to SOP in appendix**
- **Treatment of complications not covered by sponsor is standard for most phase 1 trials**

Roizman Question 3

- *The clinical plan envisions testing GL-ONC1 by pleural drainage at days 2 and 3 after treatment. Implicit in this scheme is that the investigators do not think that the virus will persist and spread following initial infection. What is the rationale for testing patients after days 2 and 3 but not at later time to determine just how long does the infectious virus persist in the thoracic cavity?*
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- **RESPONSE:** The patients will also be tested on the day of pleurodesis, which is sometime between days 3-7. After that, we will no longer have easy access to the pleural cavity since the chest tube will be removed. Thus, we will stop assaying for virus not because we believe the virus will no longer persist, but because the pleural cavity will no longer be accessible.

Roizman Question 4

- ***Please clarify whether VATS will be done for clinical indications or will VATS be required for this protocol***

- **RESPONSE:** As stated in the Study Synopsis in section 'Assessment of Viral Appearance in Tumor', unless medically contraindicated, patients will under VATS
 - ❖ **This is done for:**
 - **1) comfort and functional status of patient**
 - **2) to facilitate future chemotherapy**

Roizman Question 4

- *It can be expected that the side effects of the treatment (fever, flu like symptoms, etc) will occur in patients in whom the virus replicated to a high level? Will these patients be selected for thoracic surgery?*
- **RESPONSE:** VATS is a standard medical practice to reduce the potential for a recurrence of pleural fluid in this patient population. Fever or flu-like symptoms would not be a determining factor in delaying thoracic surgery except in cases of sepsis.