Phase I Trial of Intravenously Delivered Attenuated Vaccinia (GL-ONC1) with Chemoradiotherapy for Locoregionally Advanced Head/Neck Cancer

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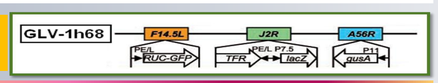
BACKGROUND

Oncolytic viruses represent a promising gene therapy strategy to treat malignancies. Vaccinia has been shown previously to have independent oncolytic activity, and due to its favorable safety profile, is a desirable vector for introducing a therapeutic payload. Multiple pre-clinical studies support the hypothesis that vaccinia is an effective chemo- and radio-sensitizer. Genetically modified and attenuated oncolytic vaccinia, GL-ONC1 (**see Figure 1**), has been clinically tested as a single agent, but has never been tested in combination with concurrent chemotherapy or radiotherapy.

Figure 1. Structure of GL-ONC1



SPECIFIC AIMS

- To determine the safety and tolerability of intravenous GL-ONC1 with concurrent definitive chemoradiotherapy in patients with locoregionally advanced (stage III-IVB) head and neck cancer.
- To analyze bodily fluids for the presence of viral shedding
- To analyze tissue for the presence of virus by a viral plaque assay (VPA)
- To analyze the susceptibility of tumor to viral infection in cell cultures.
- To analyze therapeutic outcomes including tumor response, time to recurrence, and progression-free-survival

METHODS

Population / Sample

- Unresected stage III-IVB carcinoma of the head/neck
- Excluding stage III-IVA HPV-positive oropharyngeal cancer
- Excluding patients w/ immunosuppression or severe comorbidity
- 14 patients treated at UCSD between May 2012 – Jan 2014

Design

- 3+3 phase I dose escalation trial
- ClinicalTrials.gov Identifier: NCT01584284

Chemoradiotherapy & Investigational Therapy

- IMRT 33-35 fractions of 2.00-2.12 Gy daily 5 fractions / week
- Concurrent cisplatin 100 mg/m^2 given days 1, 22, and 43
- Escalating doses of GL-ONC1:
  - -Cohort 1: 3x10^8 pfu given day 3
  - -Cohort 2: 1x10^9 pfu given day 3
  - -Cohort 3: 3x10^9 pfu given day 3
  - -Cohort 4: 3x10^9 pfu given days 3 and 8

Primary Event

- Dose-limiting toxicity (DLT), defined as:
  Grade ≥ 4 toxicity OR [grade ≥ 3 mucositis or skin reaction w/in RT port persisting > 6 weeks after CRT]

RESULTS

*Sample Characteristics - **See Tables 1-2***

- 18 patients consented (14 enrolled, 4 screen-failures (2 – ECOG PS > 2, 1 - HPV+ OPX, 1 – M1))
- Mean age 57. Disease site: HPX – 4, LX – 3, OPX – 2, CUP – 2, NPX – 1, SAL – 1, PNS - 1
- Stage IVA - 10 (71%), Stage IVB – 4 (29%). HPV-negative – 10 (71%), HPV-positive – 4 (29%)

Protocol Compliance

- 12 completed / 2 actively undergoing therapy
- 9 of 12 completed 3 cycles of cisplatin
- 1 patient required a treatment break longer than 7 days.

Adverse Events

- Treatment-Related (Probably or Definitely Related to GL-ONC1)
  - -Grade 2 fever, chills or rigors (6 (43%))
  - -Grade 1 rash (3 (21%)) – **See Figure 2**
  - -Grade 3 thrombocytopenia (2 (14%))
- Other Serious Adverse Events (Possibly or Unlikely Related to GL-ONC1)
  - - Acute Myocardial Infarction (deemed a DLT by FDA – later shown to have CAD) – Cohort 4
  - - DVT / Pulmonary Embolus (1) – Cohort 1
  - - Grade 3 emesis (1) – Cohort 4
  - - Grade 3 neutropenia (1) – Cohort 2
- No Viral Shedding observed in urine or oral swabs at days 4,5,9 or 10; 1 patient confirmed viral rash

*Tissue Analysis – **See Figure 3***

- Tumor Susceptibility to Viral Infection Confirmed in all 12 patients (2 pending)
  - - 6 to GL-ONC1 (culture / viral titer)
  - - 7 to GLV-2b372 (culture / viral titer)
  - - 8 confirmed by IHC for β-gluc (other 4 not tested)
  - - 11 confirmed by fluorescence (GFP or RFP)
- Viral presence in Mid-Treatment Biopsy for 3 patients confirmed by qPCR for A21L gene

Outcomes

- Median follow-up 10 months
- Best Overall Response on 4-month PET/CT: CR (8), PR (3), PD (1)
- 1-year PFS 74%, OS 100% - **See Figure 4**
- Failures – Local (1), Neck (2), Distant (1)

Tables 1 & 2. Demographic Characteristics

SEX	
Male	13
Female	1

AGE	
Range	23-77
Median Age	60

ETHNICITY	
Caucasian	12
Black or African American	2

TNM STAGE	
T0 N2b	2
T1 N2b	1
T2 N2b	1
T2 N3b	1
T3 N2a	1
T3 N2b	2
T3 N2c	2
T4a N0	1
T4a N3	1
T4b N0	1
T4b N2b	1

Figure 2. (A) Pox-like rash confirmed as viral in origin by VPA and fluorescence imaging. (B) Surface fluorescence imaging of tumor in man with salivary gland carcinoma

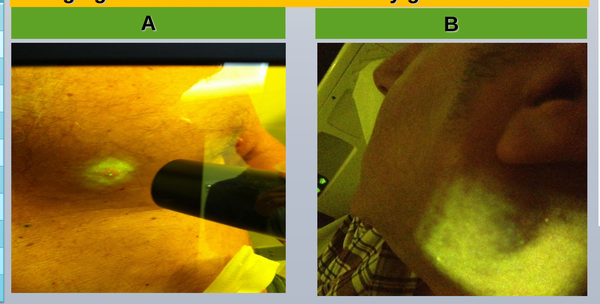


Figure3. Tumor biopsy specimens showing susceptibility to infection with GL-ONC1 (left) and a related vaccinia strain, GLV-2b372

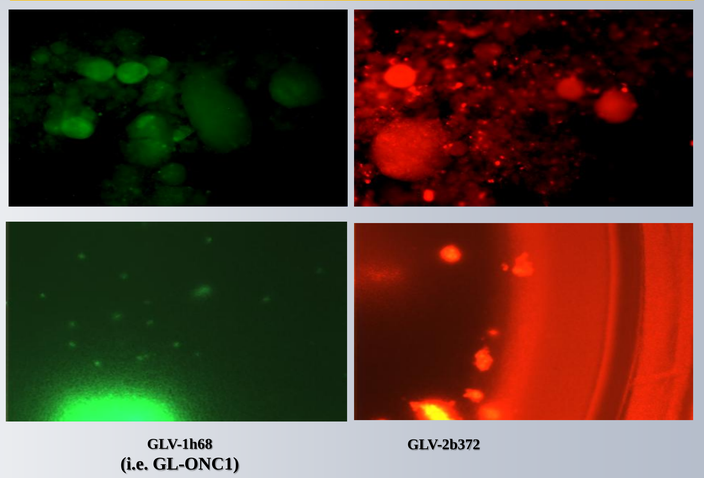
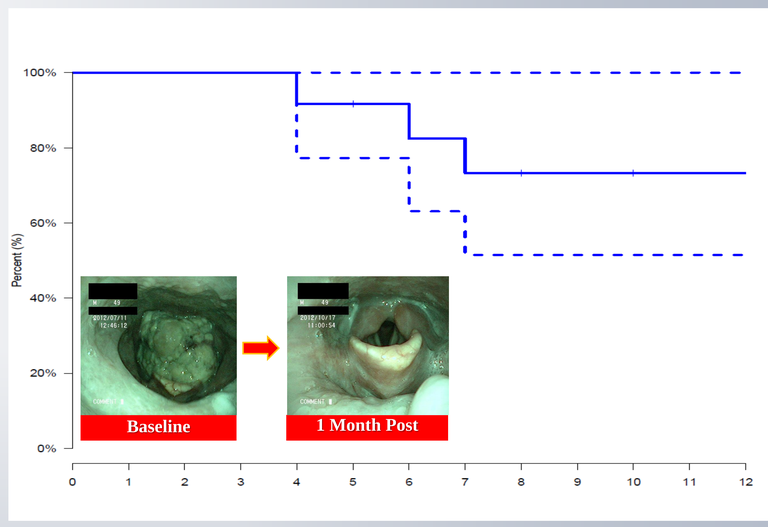


Figure 4. Kaplan-Meier Plot of Progression-Free Survival (bold) with 95% confidence intervals (dotted). [INSET: Favorable early response in HPV- T3 hypopharynx mass]



CONCLUSIONS

- IV GL-ONC1 with standard chemoradiotherapy is safe and feasible in patients with stage IV HNC
- Further study needed to determine the optimal dosing schedule
- Favorable toxicity profile indicates RT+GL-ONC1 is also feasible strategy
- Phase I will be extended to 4-6 treatments (cohorts 5 & 6)
- Next steps: multi-center phase II trial, endoscopic fluoroscopy

Trial Sponsored by:

Genelux Corporation