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

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BACKGROUND

Oncolytic viruses represent a novel and promising 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 patient samples for the presence of viral shedding by a viral plaque assay (VPA)
- To analyze tumor tissue for the presence of virus by quantitative polymerase chain reaction (qPCR)
- 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
- 19 patients treated at UCSD between May 2012 – Feb 2015

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
  - -Cohort 5: 3x10^9 pfu given days 3, 8, 15, and 22

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***
- 25 patients consented (19 enrolled, 6 screen-failures (2 – ECOG PS > 2, 1 - HPV+ OPX, 1 – M1, 1-abnormal lab value, 1- Trial no longer accepting patients))
- Mean age 56. Disease site: OC – 2, HPX – 3, LX – 4, OPX – 4, CUP – 3, NPX – 1, SAL – 1, PNS – 1
- Stage IVA - 14 (74%), Stage IVB – 5 (26%). HPV-negative – 14 (74%), HPV-positive – 5 (26%)

Protocol Compliance
- 19 completed
- 15 of 19 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 (10 (53%))
  - -Grade 1 rash (6 (32%)) – **See Figure 3**
  - -Grade 3 thrombocytopenia (1 (5%))
  - -Grade 3 dizziness (1 (5%))
  - -Grade 3 hypotension (1 (5%))
- Other Serious Adverse Events (Unlikely related to GL-ONC1)
  - - Acute Myocardial Infarction (a DLT determined to be unlikely related to GL-ONC1) – Cohort 4
  - - Abdominal infection (1) – Cohort 1
  - - Cellulitis (1) – Cohort 1
  - - Dehydration (1) – Cohort 4
  - - Grade 3 neutropenia (1) – Cohort 4
  - - DVT / Pulmonary Embolus (1) – Cohort 1
  - - Grade 3 emesis (1) – Cohort 4
  - - Syncope (1)- Cohort 5

- No Viral Shedding observed in urine or oral swabs at days 4,5,9 or 10; 3 patient confirmed transient viral rash

Ex Vivo Tissue Analysis
- Tumor Susceptibility to Viral Infection Confirmed in all 13 patients
  - - 6 to GL-ONC1 (culture / viral titer)
  - - 8 to GLV-2b372 (culture / viral titer)
  - - 9 confirmed by enzymatic assay for β-glucuronidase (other 4 not tested)
  - - 11 confirmed by fluorescence (GFP or RFP) – **See Figure 2**
- Viral presence in mid-treatment biopsy for 4 patients confirmed by qPCR for A21L gene

Outcomes
- Median follow-up 10 months
- Best Overall Response on 4-month PET/CT: CR (11), PR (3), PD (3)
  - - 2 PD prior to 4-month PET/CT
- 1-year PFS 66%, OS 78% (HPV-neg pts) - **See Figures 4 and 5**
- Failures – Locoregional (3), Distant (3)

Tables 1 & 2. Demographic Characteristics

SEX	
Male	18
Female	1
AGE	
Range	23-77
Median Age	57
RACE	
Caucasian	16
Black or African American	2
Other	1

TNM STAGE	
T0 N2b	3
T1 N2b	1
T2 N2b	1
T2 N3b	1
T3 N2a	1
T3 N2b	3
T3 N2c	2
T4a N0	1
T4a N2b	1
T4a N3	1
T4 N1	1
T4b N0	1
T4b N2b	1
T4b N2c	1

Figure 4. 1 and 2 year overall survival and progression-free survival in historical vs. GL-ONC1 treated HPV-neg patients

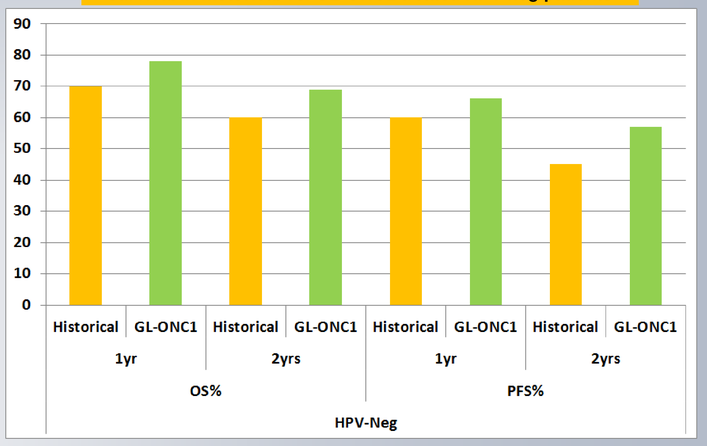


Figure 5. Kaplan-Meier Plot of Progression-Free Survival (bold) with 95% confidence intervals (dotted). [INSET: Favorable early response in HPV- T3 hypopharynx mass]

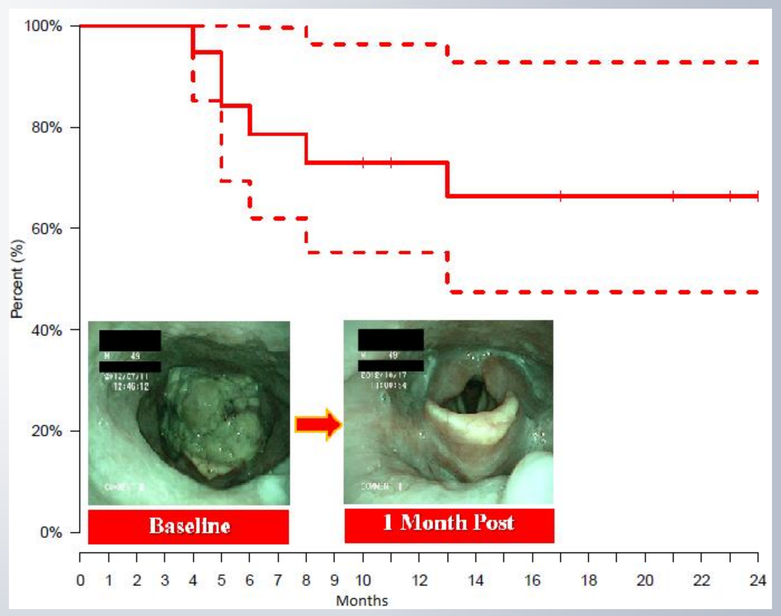


Figure2. Tumor biopsy specimens showing susceptibility to *ex vivo* infection with GL-ONC1 (left) and a related vaccinia strain, GLV-2b372

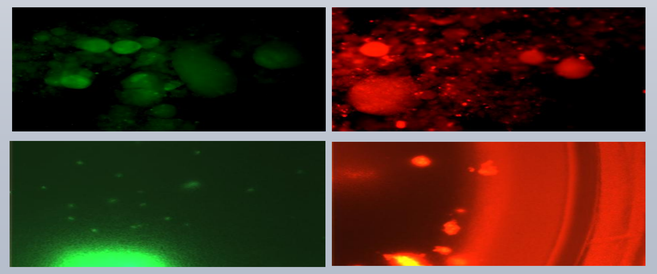
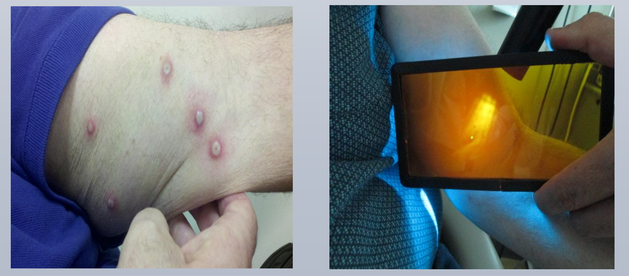


Figure 3. (A) Transient and self-limiting pox-like rash confirming systemic viral delivery (B) Rash confirmed as viral in origin by VPA and fluorescence imaging.



CONCLUSIONS

- IV GL-ONC1 with standard chemoradiotherapy is safe and feasible in patients with stage IV HNC
- Favorable safety profile indicates RT+GL-ONC1 is also feasible strategy
- Favorable trend of survival benefit in HPV-negative patients
- Next steps: multi-center phase II trial

Trial Sponsored by: Genelux Corporation