#5577 Phase 1b Study of Oncolytic Vaccinia Virus GL-ONC1 in Recurrent Ovarian Cancer

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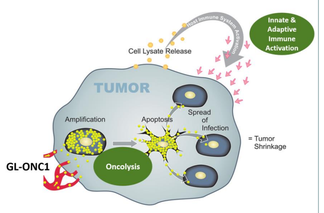
ABSTRACT

Background: Immunotherapy can trigger immune activation including tumor-infiltrating CD8+ T cells, leading to antitumor response and survival benefits. Immunotherapeutic GL-ONC1 (modified vaccinia virus (VACV)) causes oncolysis, immune activation and durable anti-cancer memory.

Methods: Intraperitoneal (i.pe.) infusion of GL-ONC1 monotherapy was given at high repeated doses in patients (pts) with platinum refractory/resistant disease. Primary endpoint: adverse events; Secondary endpoints: anti-tumor response by RECIST1.1 **&** survival. Eleven heavily pretreated pts with end-stage recurrent ovarian cancer (ROC) were enrolled: 3-4 prior lines (n=3), ≥ 5 lines (n=8), ECOG 0 (n=7) or 1 (n=4), ascites/pleural effusion (n=9) **&** progressive disease (PD) at baseline (n=10). There were two dose cohorts: 3 × 10^9 (**Cohort 1**: n=6) or 1 × 10^{10} (**Cohort 2**: n=5) plaque forming units/day on 2 consecutive days.

Results: ***(1)*** Adverse reactions included Grade 1-2 chills (n=7), nausea (7), fever (6), abdominal pain/distention (4), & vomiting (3). There were no differences in toxicity for the two dose levels. ***(2)*** GL-ONC1 colonized and replicated in the tumor, as indicated by a virus-encoded glucuronidase (GusA) assay. ***(3)*** Clearance of tumor cells in ascites with induction of lymphocyte infiltration was shown in 5 pts with ascites. ***(4)*** Reduction of circulating tumor cells (CTC) was identified in 6/8 (75%) pts who had baseline CTC, ranging 1-42 per 7.5 mL blood. ***(5)*** Enhanced infiltration of CD8+ T cells into tumor tissue was demonstrated by repeat biopsy. ***(6)*** A tumor-specific T cell response was absent at baseline but confirmed at Week-30 in patient with objective response (OR) by IFN-γ ELISPOT assay. ***(7)*** Disease Control Rate (DCR = OR + stable disease (SD) ≥ 15 weeks) was 6/11 (55%). ***(8)*** Extended progression-free survival (PFS) of 23, 35, 59 (with confirmed PR) & 71 weeks were observed in 4 pts, respectively. ***(9)*** More than doubling of PFS compared to the last chemotherapy regimen was recognized in 4/11 (36%) pts.

Conclusions: Promising safety data, anti-tumor activity, and immune activation mechanisms were documented in this Ph1b trial, and a Ph2 trial (VIRO-15) is currently enrolling. Future studies combining GL-ONC1 and other immune therapies and/or chemotherapy are under consideration.



Clinical trial design considerations:

- I.pe. route of drug delivery is relevant to ovarian cancer (OC)
- OCs are immunogenic → VACV is excellent adjuvant for tumor antigen presentation
- High tumor-infiltrating lymphocytes (TILs) favors survival → Oncolytic VACV stimulates TILs
- Oncolytic VACV may overcome chemo- and/or radiation-resistance
- For patients with chemo resistant ovarian cancer that would otherwise consider palliative care or use of drugs with poor Response Rate

OBJECTIVES

- **Primary**
  - Analysis of adverse events
- **Secondary**
  - Anti-tumor response by RECIST1.1 **&** survival (PFS/OS)
- **Translational**
  - Evaluate virus-encoded transgene expression, tumor biomarkers, circulating tumor cells (CTCs), TILs in tumor biopsy, tumor-specific T-cell response in peripheral blood, cytology in ascites, immunohistochemistry of PD-L1 expression in tumor biopsies pre- and post-GL-ONC1 Tx.

RESULTS

Patient Characteristics

Eleven heavily pretreated end-stage ROC pts were enrolled:

- Characteristics related to prior platinum Tx:
  - Platinum-resistant (n=9; 82%), Platinum-refractory (n=1; 9%), Intermediate platinum-sensitive (n=1; 9%)
- **# of prior lines therapy:** 3-4 (n=3; 27%), **≥ 5 (n=8; 73%)**
- ECOG 0 (n=7; 64%) or 1 (n=4; 36%)
- **With ascites/pleural effusion at baseline (n=9; 82%)**
- **Progressive disease (PD) at baseline (n=10; 91%)**
- **Cohort 1:** 3 × 10^9 pfu (n=6); **Cohort 2:** 1 × 10^{10} pfu (n=5)

Safety

Adverse Events	# of Pts (n=11)
Grades 1 & 2 AEs (occurred in ≥ 3 patients)	
Chills	7 (63.6%)
Nausea	7 (63.6%)
Fever	6 (54.5%)
Abdominal distention	4 (36.4%)
Abdominal pain	4 (36.4%)
Vomiting	3 (27.3%)
Grade 3 AEs (occurred in the same patient)	
Nausea	1 (9.1%)
Vomiting	1 (9.1%)
No Grade 4 AEs	

Summary:
GL-ONC1 Tx is well tolerated.

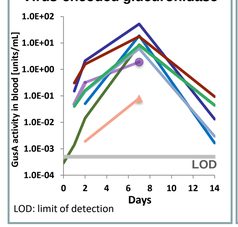
No DLT; MTD not reached

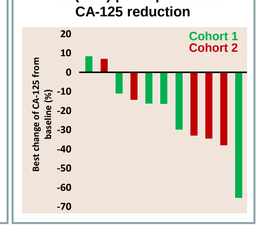
Flu-like symptoms in general; lasting a few hours overnight post each Tx

No discontinuation due to treatment-related AEs

Prophylactic hydrations given daily to avoid dehydration, and to reduce symptoms

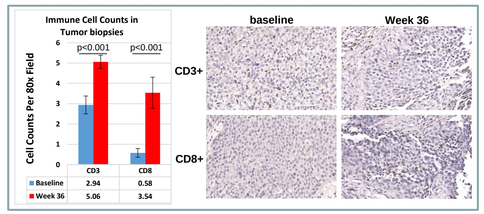
Biomarkers



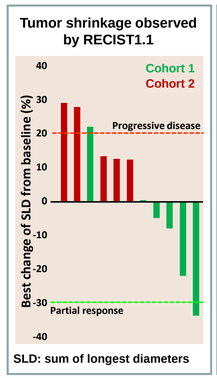


Tumor Infiltrating Lymphocytes (TILs)

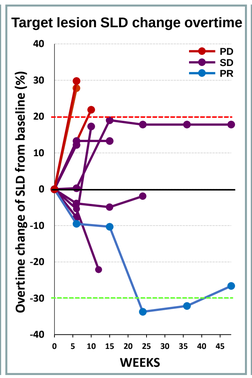
Exemplary IHC analysis - pt.#15A-06, with PFS of 71 weeks:
Significant infiltration of CD8+ cytotoxic T cells into tumors after virus treatment indicates activation of immunosurveillance

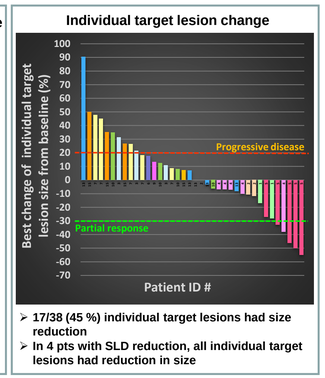


Anti-Tumor Response & Disease Control Observed



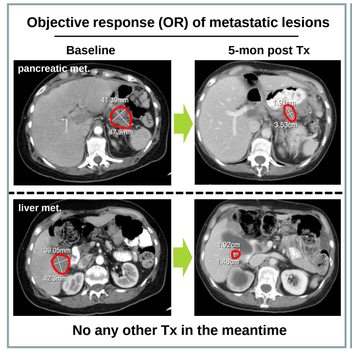
SLD: sum of longest diameters



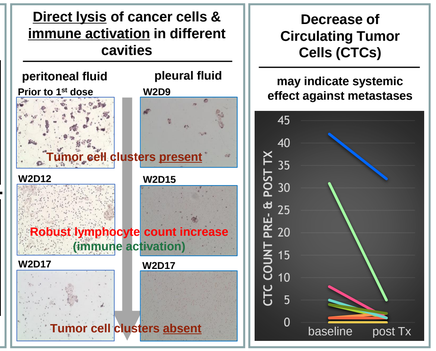


- 17/38 (45 %) individual target lesions had size reduction
- In 4 pts with SLD reduction, all individual target lesions had reduction in size

Distal Anti-tumor Effects from i.pe. Route of Delivery

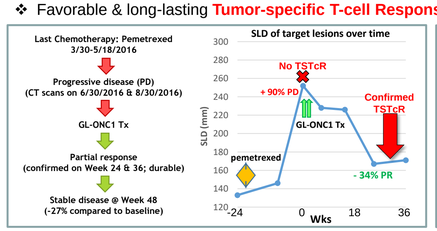


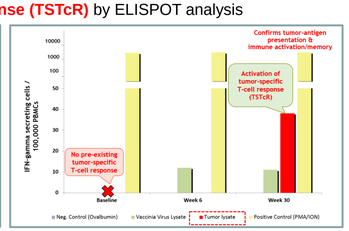
No any other Tx in the meantime



Case Report (Ch1: #15A-05): OR & Tumor-specific T-cell Response

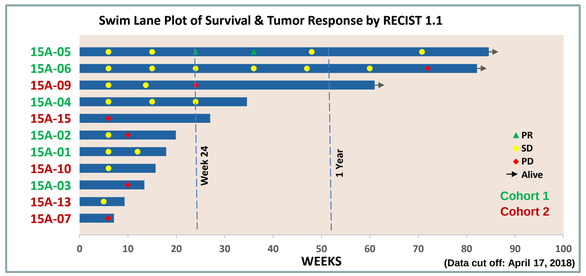
- **Heavily treated w/ 9 prior regimens of chemo; no Tumor-specific T-cell response at baseline**
- **Documented Objective Response (OR) from GL-ONC1 Tx** after Failure of Last Chemotherapy
- Favorable & long-lasting **Tumor-specific T-cell Response (TSTcR)** by ELISPOT analysis





Clinically Significant Results

- **Disease Control Rate** (DCR = OR + SD≥15 wks) = **55 % in 6/11** evaluable pts (4 in Ch1, 2 in Ch2).
- **Extended PFS** of **23, 35, 59 (with confirmed PR) & 71 wks** observed in **4 pts** (3 in Ch1, 1 in Ch2).
- **More than doubling of PFS** compared to the last chemotherapy regimen was recognized **in 4/11 (36%) pts** (2 in Ch1, 2 in Ch2).



Immune Modulation

Acute inflammatory responses and **PD-L1 upregulation** in tumors by oncolytic virus GL-ONC1 can **sensitize tumors to PD-1/PD-L1 blockade.**

CONCLUSIONS

- **GL-ONC1 treatments are well tolerated, with transient overnight flu-like symptoms. Daily i.v. hydration during treatment relieved symptoms and prevented dehydration.**
- **Mechanisms of Action are demonstrated:**
  - ***Direct lysis:*** **Virus colonized and replicated in the tumor, killing of tumor cells in ascites, and reduced circulating tumor cells.**
  - ***Immunotherapy:*** **Virus-induced immune activation with enhanced tumor infiltration of CD8+ T cells and generation of tumor-specific T-cell response were observed.**
- **Clinical significant disease control (including objective response) and extended PFS were documented at both dose levels.**
- **Phase 2 trial (VIRO-15) in ROC pts with adequate nutritional & immune status is currently enrolling at Cohort 1 dose level.**

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Protocol #: GL-ONC1-015; ClinicalTrials.gov Identifier: NCT02759588;