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Clinical Activity of Olvimulogene Nanivacirepvec–Primed Immunochemotherapy in Heavily Pretreated Patients With Platinum-Resistant or Platinum-Refractory Ovarian Cancer

The Nonrandomized Phase 2 VIRO-15 Clinical Trial

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IMPORTANCE Patients with platinum-resistant or platinum-refractory ovarian cancer (PRROC) have limited therapeutic options, representing a considerable unmet medical need.

OBJECTIVE To assess antitumor activity and safety of intraperitoneal (IP) olvimulogene nanivacirepvec (Olvi-Vec) virotherapy and platinum-based chemotherapy with or without bevacizumab in patients with PRROC.

DESIGN, SETTING, AND PARTICIPANTS This open-label, nonrandomized multisite phase 2 VIRO-15 clinical trial enrolled patients with PRROC with disease progression following their last prior line of therapy from September 2016 to September 2019. Data cutoff was on March 31, 2022, and data were analyzed between April 2022 and September 2022.

INTERVENTIONS Olvi-Vec was administered via a temporary IP dialysis catheter as 2 consecutive daily doses (3×10^9 pfu/d) followed by platinum-doublet chemotherapy with or without bevacizumab.

MAIN OUTCOMES AND MEASURES Primary outcomes were objective response rate (ORR) via Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) and cancer antigen 125 (CA-125) assay, and progression-free survival (PFS). Secondary outcomes included duration of response (DOR), disease control rate (DCR), safety, and overall survival (OS).

RESULTS Twenty-seven heavily pretreated patients with platinum-resistant (n = 14) or platinum-refractory (n = 13) ovarian cancer were enrolled. The median (range) age was 62 (35-78) years. The median (range) prior lines of therapy were 4 (2-9). All patients completed both Olvi-Vec infusions and chemotherapy. Median follow-up duration was 47.0 months (95% CI, 35.9 months to NA). Overall, ORR by RECIST 1.1 was 54% (95% CI, 33%-74%), with a DOR of 7.6 months (95% CI, 3.7-9.6 months). The DCR was 88% (21/24). The ORR by CA-125 was 85% (95% CI, 65%-96%). Median PFS by RECIST 1.1 was 11.0 months (95% CI, 6.7-13.0 months), and the PFS 6-month rate was 77%. Median PFS was 10.0 months (95% CI, 6.4-NA months) in the platinum-resistant group and 11.4 months (95% CI, 4.3-13.2 months) in the platinum-refractory group. The median OS was 15.7 months (95% CI, 12.3-23.8 months) in all patients, with a median OS of 18.5 months (95% CI, 11.3-23.8 months) in the platinum-resistant group and 14.7 months (95% CI, 10.8-33.6 months) in the platinum-refractory group. Most frequent treatment-related adverse events (TRAEs) (any grade, grade 3) were pyrexia (63.0%, 3.7%, respectively) and abdominal pain (51.9%, 7.4%, respectively). There were no grade 4 TRAEs, and no treatment-related discontinuations or deaths.

CONCLUSIONS AND RELEVANCE In this phase 2 nonrandomized clinical trial, Olvi-Vec followed by platinum-based chemotherapy with or without bevacizumab as immunochemotherapy demonstrated promising ORR and PFS with a manageable safety profile in patients with PRROC. These hypothesis-generating results warrant further evaluation in a confirmatory phase 3 trial.

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Patients with platinum-resistant or platinum-refractory ovarian cancer (PRROC) have limited treatment options.[1] Clinical management of PRROC in patients with up to 2 prior lines include the AURELIA regimens of bevacizumab and non-platinum-based single-agent chemotherapies.[2] Thereafter, patients typically receive physician's choice of a nonplatinum chemotherapy or enroll into clinical trials. The latest National Comprehensive Cancer Network Guidelines also include platinum-based regimens for platinum-resistant disease.[1] Single-agent therapy response rates, median progression-free survival (PFS), and median overall survival (OS) range from 10% to 15%, 3 to 4 months, and 9 to 12 months, respectively.[3] Hence, the development of novel, more effective therapies addresses a critical unmet medical need.

Olvimulogene nanivacirepvec (Olvi-Vec; aka GL-ONC1; laboratory name: GLV-1h68) is a modified oncolytic vaccinia virus that selectively infects malignant cells and replicates especially well in ovarian and lung cancers.[4] Because ovarian cancer usually metastasizes throughout the peritoneal cavity, it is amenable to intraperitoneal (IP) virotherapy given the large peritoneal surface area of carcinomatosis.[5] Olvi-Vec activates both innate immunity via proinflammatory response and adaptive immunity, which modify the tumor microenvironment and promote a condition wherein reversal of platinum resistance is potentially realized.[6]

This study investigated Olvi-Vec followed by platinum-doublet chemotherapy with or without bevacizumab, evaluating the hypothesis that such sequential therapy produces significant antitumor activity with manageable toxic effects for patients with PRROC.

Key Points

Question What is the clinical activity of olvimulogene nanivacirepvec oncolytic immunotherapy and subsequent platinum-doublet chemotherapy with or without bevacizumab in women with platinum-resistant or platinum-refractory ovarian cancer (PRROC)?

Findings In this phase 2 nonrandomized clinical trial of 27 patients with PRROC and a median of 4 prior lines of therapy, 13 of 24 (54%) evaluable by Response Evaluation Criteria in Solid Tumors version 1.1 experienced an objective response, with a median progression-free survival of 11.0 months and a manageable safety profile.

Meaning These hypothesis-generating results exceed historically expected outcomes from standard therapies or platinum rechallenge, warranting further clinical evaluation in a larger confirmatory phase 3 clinical trial.

Methods

Study Design and Participants

The trial protocol is available in Supplement 1 and the analysis plan is in Supplement 2. The primary end points were objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) and cancer antigen 125 (CA-125) assay,[7] and PFS. The secondary end points comprised safety, duration of response (DOR), disease control rate (DCR), and OS. The baseline for ORR and PFS evaluation was the assessment time point immediately prior to starting subsequent platinum-based therapy to allow direct comparison with historical data. The study was approved by the central Quorum (now Advarra) institutional review board, and all patients provided written informed consent.

Eligible patients included those with primary or acquired histologically confirmed PRROC, Eastern Cooperative Oncology Group performance status of 0 or 1, and documented progressive disease at screening. Patients with mucinous carcinoma, nonepithelial ovarian cancers, and unresolved bowel obstruction were excluded. Participant PRROC status was determined by platinum-free interval, defined as the time from last dose of most recent platinum-based regimen to disease progression, with progression of less than 6 months as platinum-resistant, and lack of response or progression earlier than 1 month as platinum-refractory.

Procedures

All patients received Olvi-Vec at 3×10^9 plaque-forming units (pfu)/d on 2 consecutive days through a temporary IP catheter placed laparoscopically approximately 5 days before. Immediately prior to the first dose of Olvi-Vec, patients underwent an IP instillation and drainage of 1 L lactated Ringer's to reduce IP complement and facilitate viral replication. Chemotherapy was recommended to start approximately 6 weeks following Olvi-Vec. Platinum doublet was at the discretion of investigators, selected from gemcitabine, taxane, or pegylated liposomal doxorubicin (PLD) coupled with carboplatin or cisplatin. If patients developed undue toxic effects associated with platinum therapy, continued nonplatinum single-agent therapy was encouraged. Bevacizumab was allowed with platinum-doublet or single-agent therapies. Treatment continued until disease progression or unacceptable toxic effects.

Statistical Analysis

The study had 90% power using a 1-sided 5% significance level to detect an improvement in ORR by RECIST 1.1 from 27% (ie, null hypothesis based on the AURELIA study[2]) to 54% in 28 evaluable patients. This study had a Simon 2-stage design, with stage 1 proceeding to stage 2 after achieving 5 or more responders in up to 15 evaluable participants; and stage 2: the null was rejected if there were 12 or more responders of up to 28 evaluable patients. The DOR, PFS, and OS were summarized using the Kaplan-Meier method. Statistical analyses were conducted using R software (version 4.0.2, R Foundation). Data analyses were conducted between April 2022 and September 2022.

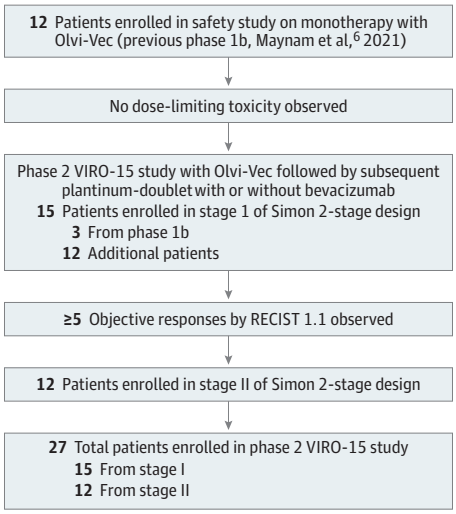
Results

Antitumor Activity

Twenty-seven patients with platinum-resistant (n = 14) or platinum-refractory (n = 13) ovarian cancer (**Figure 1**; eTable 1

in Supplement 3) were enrolled and received Olvi-Vec. A median 6 cycles (range, 1-17) of platinum-based therapy was given to all patients, which was initiated at a median of 6 weeks following Olvi-Vec. All patients received carboplatin-doublet therapy, except for 1 who had oxaliplatin-doublet therapy. The nonplatinum agents included gemcitabine (44%), docetaxel (26%), paclitaxel (15%), and PLD (15%). Bevacizumab was initiated with platinum-based therapies in 23 of 27 patients; however, the remaining 4 patients also received bevacizumab with delay. Six patients received oral cyclophosphamide with bevacizumab as continued therapy after platinum-based therapy.

Figure 1. Study Flow Diagram



RECIST 1.1 indicates Response Evaluation Criteria in Solid Tumors (version 1.1); Olvi-Vec, olvimulogene nanivacirepvec.

Twenty-four RECIST-evaluable patients with measurable disease had an ORR of 54% (13/24; 95% CI, 33%-74%; confirmed ORR, 42%; **Table**). The 13 responders exceeded the Simon stage 2 requirement by rejecting the null when there were 12 or more responders as planned; therefore, enrollment was terminated early. Four patients (16.7%) had 100% reduction in target lesions (2 with confirmed complete response), including 2 patients with platinum-refractory disease (**Figure 2**A-B). The median time to RECIST response was 4.0 months (95% CI, 2.0-4.9 months). The DOR was 7.6 months (95% CI, 3.7-9.6 months). The DCR was 88% (8 stable disease and 13 responders). Overall, 19 of 22 patients (86%) showed tumor shrinkage.

The ORR by CA-125 was 85% (95% CI, 65%-96%) in all patients, and 25 of 26 patients (96%) exhibited decreased CA-125 levels (Figure 2C-D). The median PFS was 11.0 (95% CI, 6.7-13.0) months, with 77% achieving a 6-month PFS, and the median OS was 15.7 (95% CI, 12.3-23.8) months (Table; eFigure in Supplement 3).

Safety

Most frequent TRAEs (any grade) included pyrexia (n = 18; 63%), abdominal pain (n = 14; 51.9%), and nausea (n = 13; 48.1%) (eTable 2A in Supplement 3). Toxic effects were manageable; however, nonsteroidal anti-inflammatory agents were avoided for up to 3 weeks following Olvi-Vec to minimize inhibition of viral activities. Flu-like symptoms, including fever, chills, and myalgia, were primarily transient in hours or overnight. Hydration was administered prophylactically or as needed during and immediately following treatment with Olvi-Vec to reduce symptoms.

Discussion

In this nonrandomized phase 2 clinical trial, we documented 54% ORR by RECIST in all evaluable patients with a median

Table. Outcomes of Antitumor Activity

Variable	All	Platinum resistant	Platinum refractory
Response by RECIST 1.1			
Evaluable patients, No.	24[a]	11	13
ORR, % (95% CI)	54 (33-74)[b]	55 (26-84)	54 (27-81)
DOR, median (95% CI), mo	7.6 (3.7-9.6)	7.6 (3.7-NA)	8.0 (3.7-NA)
DCR, % (95% CI)	88 (68-97)	100 (72-100)	77 (46-95)
Response by CA-125			
Evaluable patients, No.	26[c]	13	13
ORR, % (95% CI)	85 (65-96)	85 (55-98)	85 (55-98)
Survival			
Evaluable patients, No.	27	14	13
PFS, median (95% CI), mo	11.0 (6.7-13.0)	10.0 (6.4-NA)	11.4 (4.3-13.2)
OS, median (95% CI), mo	15.7 (12.3-23.8)	18.5 (11.3-23.8)	14.7 (10.8-33.6)

Abbreviations: CA-125, cancer antigen 125 assay; DCR, disease control rate; DOR, duration of response; NA, not applicable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria in Solid Tumors (version 1.1).

[a] Three of 27 patients were not evaluable as defined by RECIST 1.1 criteria due to no measurable disease. However, these 3 patients were evaluable by the Gynecological Cancer InterGroup (GCIG) CA-125 criteria, showing 2 partial responses and 1 complete response as best response.

[b] Including 3 unconfirmed; 2 in resistant and 1 in refractory groups.

[c] One of 27 patents was not evaluable by GCIG CA-125 criteria. However, this patient was evaluable by RECIST 1.1, showing stable disease as best response.

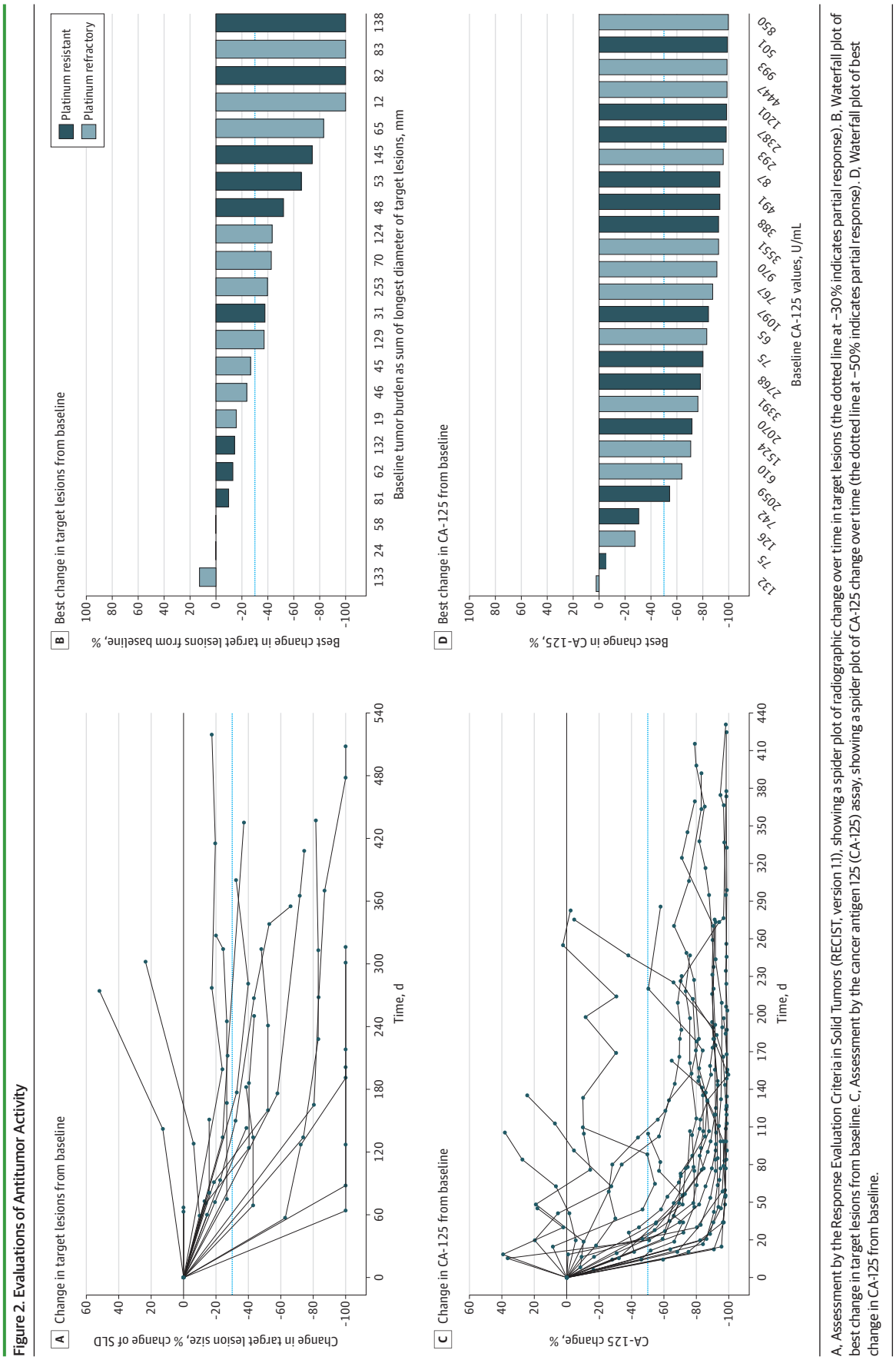


Figure 2. Evaluations of Antitumor Activity

A, Assessment by the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1), showing a spider plot of radiographic change over time in target lesions (the dotted line at −30% indicates partial response). B, Waterfall plot of best change in target lesions from baseline. C, Assessment by the cancer antigen 125 (CA-125) assay, showing a spider plot of CA-125 change over time (the dotted line at −50% indicates partial response). D, Waterfall plot of best change in CA-125 from baseline.

of 4 prior lines of therapy (22 of 27 [81%] had >2 prior lines). The results exceed the 27.3% ORR in the AURELIA study,[2] which excluded patients with more than 2 prior lines of therapy and platinum-refractory disease. Of note, only 7% (vs 81% in our study) of patients in the AURELIA study had prior treatment with bevacizumab. Furthermore, only 1 of 13 (8%) patients with platinum-refractory disease had transient response to prior platinum-based therapy, yet the same patients achieved 54% RECIST response and a median DOR of 8.0 months in this study, suggesting reversal of platinum refractoriness by treatment with Olvi-Vec.

Prior studies have shown that *BRCA1/2* variants are associated with increased sensitivity to platinum-based therapy.[8] However, in this study, ORR by RECIST was 29% (2/7) in patients with *BRCA1/2* variants vs 65% (11/17) in those with wild-type *BRCA*, indicating response was not driven by *BRCA1/2* variation. Prior poly(ADP-ribose) polymerase (PARP) inhibitor exposure may induce platinum resistance.[9] However, in this study, 11 of 20 patients (55%) who received previous PARP inhibitors achieved RECIST response, further suggesting virus-induced reversal of platinum resistance and/or immune response.

Previous data support the staggered approach of viral immunotherapy and chemotherapy.[10-12] Virus-mediated tumor cell lysis may induce immune priming by increasing T-cell response through cross-presentation of the tumor (neo) antigens, and being further boosted by subsequent cytotoxic chemotherapy.[13] In this population, Olvi-Vec was associated with an influx of CD4-positive and CD8-positive tumor-infiltrating lymphocytes in paired tumor biopsy samples,[14] which was a positive prognostic factor in patients with ovarian cancer.[15] Overall, Olvi-Vec may convert immunologically "cold" to "hot" tumors by modifying the tumor microenvironment and abrogate platinum resistance.[16,17]

Limitations

One limitation of this single-arm nonrandomized clinical trial is the small number of participants.

Conclusions

The findings of this nonrandomized clinical trial suggest that Olvi-Vec and platinum-based chemotherapy with or without bevacizumab demonstrated promising ORR and PFS, and clinical reversal of platinum resistance and refractoriness, with manageable toxic effects among patients with PRROC. These hypothesis-generating results warrant further evaluation in a larger confirmatory study. The prospective phase 3 OnPrime/GOG-3076 study is currently enrolling (NCT05281471).

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Concept and design: Holloway, McKenzie.
Acquisition, analysis, or interpretation of data: Holloway, Mendivil, Kendrick, Abaid, Brown, LeBlanc, Mori, Ahmad.
Drafting of the manuscript: Holloway, Abaid, Brown, LeBlanc, Ahmad.
Critical revision of the manuscript for important intellectual content: Holloway, Mendivil, Kendrick, McKenzie, Mori, Ahmad.
Administrative, technical, or material support: Holloway, Mendivil, Kendrick, LeBlanc, McKenzie, Ahmad.
Supervision: Holloway, Brown.

Conflict of Interest Disclosures: Dr Holloway reported advisory board membership for a phase 3 protocol development from Genelux, Inc; and stock options given in lieu of hourly advisory fees during the conduct of the study. Dr McKenzie reported speakers bureau fees from Merck, Immunogen, and Seagen. She is also a Diversity, Inclusion, and Health Equity in Clinical Trials for GlaxoSmithKline advisory board member. No other disclosures were reported.

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Data Sharing Statement: See Supplement 4.

REFERENCES

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Ovarian Cancer Continue Including Fallopian Tube Cancer and Primary Peritoneal Cancer. Version 1. 2023. Accessed December 22, 2023. https://www.nccn.org/guidelines/category_1

2. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. [published correction appears in J Clin Oncol. 2014;32(35):4025]. *J Clin Oncol*. 2014;32(13):1302-1308. doi:10.1200/JCO.2013.51.4489

3. Davis A, Tinker AV, Friedlander M. "Platinum resistant" ovarian cancer: what is it, who to treat and how to measure benefit? *Gynecol Oncol*. 2014;133(3):624-631. doi:10.1016/j.ygyno.2014.02.038

4. Ascierto ML, Worschech A, Yu Z, et al. Permissivity of the NCI-60 cancer cell lines to oncolytic vaccinia virus GLV-1h68. *BMC Cancer*. 2011;11:451. doi:10.1186/1471-2407-11-451

5. Lauer UM, Schell M, Beil J, et al. Phase I study of oncolytic vaccinia virus GL-ONC1 in patients with peritoneal carcinomatosis. *Clin Cancer Res*. 2018;24(18):4388-4398. doi:10.1158/1078-0432.CCR-18-0244

6. Manyam M, Stephens AJ, Kennard JA, et al. A phase 1b study of intraperitoneal oncolytic viral immunotherapy in platinum-resistant or refractory ovarian cancer. [published correction appears in *Gynecol Oncol*. 2022;165(2):401]. *Gynecol Oncol*. 2021;163(3):481-489. doi:10.1016/j.ygyno.2021.10.069

7. Rustin GJ, Vergote I, Eisenhauer E, et al; Gynecological Cancer Intergroup. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). *Int J Gynecol Cancer*. 2011;21(2):419-423. doi:10.1097/IGC.0b013e3182070f17

8. Mylavarapu S, Das A, Roy M. Role of BRCA mutations in the modulation of response to platinum therapy. *Front Oncol*. 2018;8:16. doi:10.3389/fonc.2018.00016

9. Rose PG. Ovarian cancer recurrence: is the definition of platinum sensitivity modified by PARPi, bevacizumab or other intervening treatments? a clinical perspective. *Cancer Drug Resist*. 2022;5(2):415-423. doi:10.20517/cdr.2022.01

10. Song CK, Han HD, Noh KH, et al. Chemotherapy enhances CD8(+) T cell-mediated antitumor immunity induced by vaccination with vaccinia virus. *Mol Ther*. 2007;15(8):1558-1563. doi:10.1038/sj.mt.6300221

11. Wennier ST, Liu J, McFadden G. Bugs and drugs: oncolytic virotherapy in combination with

chemotherapy. *Curr Pharm Biotechnol*. 2012;13(9):1817-1833. doi:10.2174/138920112800958850

12. Russell L, Peng KW, Russell SJ, Diaz RM. Oncolytic viruses: Priming time for cancer immunotherapy. *BioDrugs*. 2019;33(5):485-501. doi:10.1007/s40259-019-00367-0

13. Emens LA, Middleton G. The interplay of immunotherapy and chemotherapy: harnessing potential synergies. *Cancer Immunol Res*. 2015;3(5):436-443. doi:10.1158/2326-6066.CIR-15-0064

14. Holloway R, Mendivil A, Kendrick J, et al. Oncolytic vaccinia (Olvi-Vec) primed immunochemotherapy in platinum-resistant/refractory ovarian cancer. *Int J Gynecol Cancer*. 2020;30:A9-A10. doi:10.1136/ijgc-2020-IGCS.12

15. Pinto MP, Balmaceda C, Bravo ML, et al. Patient inflammatory status and CD4+/CD8+ intraepithelial tumor lymphocyte infiltration are predictors of outcomes in high-grade serous ovarian cancer. *Gynecol Oncol*. 2018;151(1):10-17. doi:10.1016/j.ygyno.2018.07.025

16. Wang W, Kryczek I, Dostál L, et al. Effector T-cells abrogate stroma-mediated chemoresistance in ovarian cancer. *Cell*. 2016;165(5):1092-1105. doi:10.1016/j.cell.2016.04.009

17. Ochoa de Olza M, Navarro Rodrigo B, Zimmermann S, Coukos G. Turning up the heat on non-immunoreactive tumours: opportunities for clinical development. *Lancet Oncol*. 2020;21(9):e419-e430. doi:10.1016/S1470-2045(20)30234-5

Supplemental Online Content

Holloway RW, Mendivil AA, Kendrick JE, et al. Clinical activity of olvimulogene nanivacirepvec–primed immunochemotherapy in heavily pretreated patients with platinum-resistant or platinum-refractory ovarian cancer: the nonrandomized phase 2 VIRO-15 clinical trial. *JAMA Oncol*. Published online May 25, 2023. doi:10.1001/jamaoncol.2023.1007

eFigure. Kaplan-Meier Estimate of Overall Survival

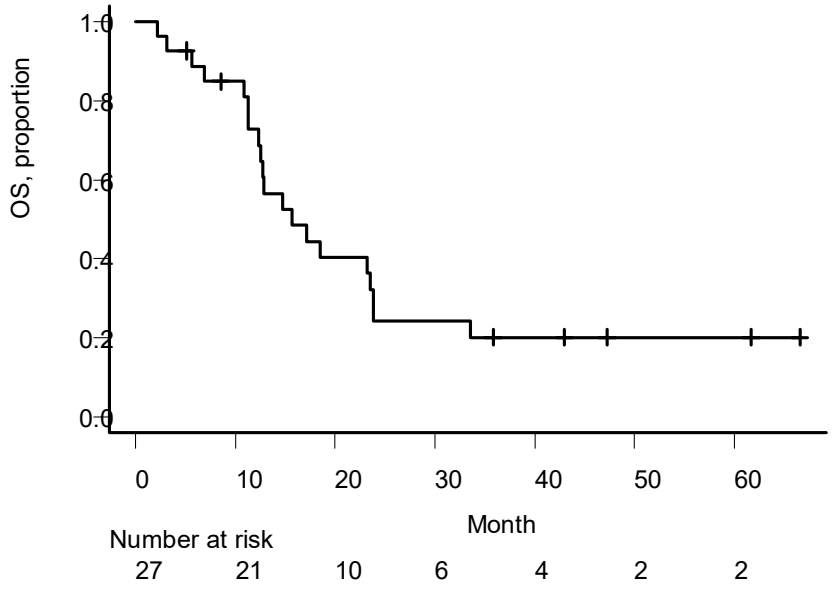
eTable 1. Patient Demographic and Clinical Characteristics

eTable 2. Adverse Events

This supplemental material has been provided by the authors to give readers additional information about their work.

Oncolytic Viral Immunochemotherapy in Ovarian Cancer

eFigure 1. Kaplan-Meier Estimate of Overall Survival (OS)



eTable 1. Patient Demographic and Clinical Characteristics

Baseline Characteristics	Patients (n = 27)
Age, median (range), year	62 (35-78)
Histology	
High-grade serous	25 (92%)
Intermediate-grade serous	1 (4%)
Mixed	1 (4%)
Clinical stage	
III	1 (4%)
IIIA	1 (4%)
IIIB	4 (15%)
IIIC	17 (62%)
IV	4 (15%)
ECOG performance status	
0	17 (63%)
1	10 (37%)
BMI[a], median (range), kg/m^2	23.3 (18.6-47.6)
PNI[a,b], median (range)	43.8 (32.0-56.8)
Prior number of lines, median (range)	4 (2-9)
Prior platinum lines, median (range)	2 (1-5)
Time from the last dose of the most recent platinum regimen to initiation of platinum-based therapy in this study, median (range), [95% CI], mo	9.9 (2.4-45.1), [9.2-17.0]
Platinum status at enrollment	
Platinum-resistant	14 (52%)
Platinum-refractory	13 (48%)
Prior therapy with bevacizumab	
Yes	22 (81%)
No	5 (19%)
Prior PARP inhibitor therapy	
Yes	20 (74%)
No	7 (26%)
Prior radiation therapy	
Yes	5 (19%)
No	22 (81%)
Baseline genetic profiles	
Tumor PD-L1 expression	
Positive	1 (4%)
Negative	25 (92%)
Unknown	1 (4%)
Germline or somatic BRCA1/2 mutations	
Germline	4 (15%)
Somatic	4 (15%)
Negative	19 (70%)
Microsatellite instability (MSI) status	
Stable	19 (70%)
Unknown	8 (30%)
Tumor mutational load	
Low	13 (48%)

Intermediate	4 (15%)
Unknown	10 (37%)

Abbreviations: BMI, body mass index; BRCA, BReast CAncer gene; CA, cancer antigen; CI, confidence interval; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; months (mo); ORR, objective response rate; PARP, poly-adenosine diphosphate-ribose polymerase; PFS, progression-free survival; PNI, prognostic nutritional index; PD-L1, programmed death ligand-1.
[a]BMI and PNI were recorded to provide insight on nutritional and immune status.
[b]PNI was calculated using the formula: PNI = 10 × serum albumin value (g/dL) + 0.005 × absolute lymphocyte count (per mm^3).

eTable 2.

A. Treatment-Related Adverse Events (TRAEs) Related to Olvi-Vec

Incidence of TRAEs Occurring in ≥ 2 patients, n (%)				
TRAEs[1]	**Any Grade**	**Grade 1-2**	**Grade 3**	**Grade 4**
Any TRAEs	26 (96.3)	26 (96.3)	4 (14.8)	0 (0)
Pyrexia	17 (63.0)	16 (59.3)	1 (3.7)	0 (0)
Abdominal Pain	14 (51.9)	12 (44.4)	2 (7.4)[2]	0 (0)
Nausea	13 (48.1)	13 (48.1)	0 (0)	0 (0)
Abdominal Distension	11 (40.7)	11 (40.7)	0 (0)	0 (0)
Rigors	10 (37.0)	10 (37.0)	0 (0)	0 (0)
Fatigue	10 (37.0)	9 (33.3)	1 (3.7)[2]	0 (0)
Muscular Weakness	7 (25.9)	7 (25.9)	0 (0)	0 (0)
Vomiting	7 (25.9)	7 (25.9)	0 (0)	0 (0)
Generalized Pain	6 (22.2)	6 (22.2)	0 (0)	0 (0)
Anorexia	4 (14.8)	3 (11.1)	1 (3.7)[2]	0 (0)
Headache	4 (14.8)	4 (14.8)	0 (0)	0 (0)
Dehydration	3 (11.1)	3 (11.1)	0 (0)	0 (0)

[1] All adverse events (AEs) were classified using the MedDRA v19, and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. TRAEs were defined as AEs determined to have a degree of attribution to Olvi-Vec, with an onset date on or after the date of first Olvi-Vec dose until 28 days after the second Olvi-Vec dose. Patients with multiple reports of same adverse event, most severe included. No deaths related to Olvi-Vec treatment; No discontinuation due to TRAEs.

[2] One patient experienced a serious adverse event.

B. Adverse Events (AEs) Related to Subsequent Platinum-based Chemotherapy ± Bevacizumab

Incidence of AEs Occurring in ≥ 2 Patients				
Patients, n (%): N=27	**Any Grade**	**Grade 1-2**	**Grade 3**	**Grade 4**
Any AEs	**23 (85.1)**	**23 (85.1)**	**7 (25.9)**	**2 (7.4)**
Nausea	9 (33.3)	8 (29.6)	1 (3.7)	0 (0.0)
Vomiting	8 (29.6)	8 (29.6)	0 (0.0)	0 (0.0)
Fatigue	7 (25.9)	7 (25.9)	0 (0.0)	0 (0.0)
Diarrhea	6 (22.2)	6 (22.2)	0 (0.0)	0 (0.0)
Hypertension	6 (22.2)	4 (14.8)	2 (7.4)	0 (0.0)
Platelet count decreased	6 (22.2)	3 (11.1)	1 (3.7)	2 (7.4)
Anemia	5 (18.5)	2 (7.4)	3 (11.1)	0 (0.0)
Headache	5 (18.5)	5 (18.5)	0 (0.0)	0 (0.0)
Asthenia	3 (11.1)	3 (11.1)	0 (0.0)	0 (0.0)
Constipation	3 (11.1)	3 (11.1)	0 (0.0)	0 (0.0)
Dehydration	3 (11.1)	2 (7.4)	1 (3.7)	0 (0.0)
Hypomagnesemia	3 (11.1)	3 (11.1)	0 (0.0)	0 (0.0)
Infusion related reaction	3 (11.1)	3 (11.1)	0 (0.0)	0 (0.0)
Alopecia	2 (7.4)	2 (7.4)	0 (0.0)	0 (0.0)

Arthralgia	2 (7.4)	2 (7.4)	0 (0.0)	0 (0.0)
Decreased Appetite	2 (7.4)	2 (7.4)	0 (0.0)	0 (0.0)
Dizziness	2 (7.4)	2 (7.4)	0 (0.0)	0 (0.0)
Dysgeusia	2 (7.4)	2 (7.4)	0 (0.0)	0 (0.0)
Epistaxis	2 (7.4)	2 (7.4)	0 (0.0)	0 (0.0)
Hypokalemia	2 (7.4)	2 (7.4)	0 (0.0)	0 (0.0)
Hyponatremia	2 (7.4)	2 (7.4)	0 (0.0)	0 (0.0)
Neuropathy	2 (7.4)	2 (7.4)	0 (0.0)	0 (0.0)
Rhinorrhea	2 (7.4)	2 (7.4)	0 (0.0)	0 (0.0)
***All AEs reported with any grade based on worst grade per patient.**				

Data Sharing Statement

Holloway. Phase 2 VIRO-15 Trial of Olvi-Vec-Primed Immunochemotherapy in Heavily Pretreated Patients with Platinum-Resistant or -Refractory Ovarian Cancer. *JAMA Oncol*. Published xx. Doi:xxx

Data

Data available: Yes

Data types: Deidentified participant data

How to access data: robhollowaymd@gmail.com

When available: With publication

Supporting Documents

Document types: None

Additional Information

Who can access the data: Researchers whose proposed use of the data has been approved

Types of analyses: For a specified approved purpose

Mechanisms of data availability: After approval of a proposal