A phase III, multicenter, randomized study of olvimulogene nanivacirepvec followed by platinum-doublet chemotherapy and bevacizumab compared with platinum-doublet chemotherapy and bevacizumab in women with platinum-resistant/refractory ovarian cancer

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ABSTRACT

Background Treatment options for patients with platinum-resistant/refractory ovarian cancers are limited and only marginally effective. The development of novel, more effective therapies addresses a critical unmet medical need. Olvimulogene nanivacirepvec (Olvi-Vec), with its strong immune modulating effect on the tumor microenvironment, may provide re-sensitization to platinum and clinically reverse platinum resistance or refractoriness in platinum-resistant/refractory ovarian cancer.

Primary Objective The primary objective is to evaluate the efficacy of intra-peritoneal Olvi-Vec followed by platinum-based chemotherapy and bevacizumab in patients with platinum-resistant/refractory ovarian cancer.

Study Hypothesis This phase III study investigates Olvi-Vec oncolytic immunotherapy followed by platinum-based chemotherapy and bevacizumab as an immunochemotherapy evaluating the hypothesis that such sequential combination therapy will prolong progression-free survival (PFS) and bring other clinical benefits compared with treatment with platinum-based chemotherapy and bevacizumab.

Trial Design This is a multicenter, prospective, randomized, and active-controlled phase III trial. Patients will be randomized 2:1 into the experimental arm treated with Olvi-Vec followed by platinum-doublet chemotherapy and bevacizumab or the control arm treated with platinum-doublet chemotherapy and bevacizumab.

Major Inclusion/Exclusion Criteria Eligible patients must have recurrent, platinum-resistant/refractory, non-resectable high-grade serous, endometrioid, or clear-cell ovarian, fallopian tube, or primary peritoneal cancer. Patients must have had ≥3 lines of prior chemotherapy.

Primary Endpoint The primary endpoint is PFS in the intention-to-treat population.

Sample Size Approximately 186 patients (approximately 124 patients randomized to the experimental arm and 62 to the control arm) will be enrolled to capture 127 PFS events.

Estimated Dates for Completing Accrual and Presenting Results Expected complete accrual in 2024 with presentation of primary endpoint results in 2025.

Trial Registration NCT05281471.

INTRODUCTION

Olvimulogene nanivacirepvec (abbreviated as Olvi-Vec; aka GL-ONC1; laboratory name: GLV-1h68) oncolytic viral immunotherapy has been studied extensively in many pre-clinical studies either as monotherapy or as combination therapies, demonstrating its robust oncolysis effect and immune modulating functions.[1–5] Olvi-Vec was further investigated clinically in a variety of cancers, including ovarian cancer.[6 7] A phase Ib study of intra-peritoneal Olvi-Vec monotherapy showed promising safety, clinical activities, and immune activation in patients with platinum-resistant/refractory ovarian cancer.[7] Subsequently, the phase II VIRO-15 study showed that intraperitoneally delivered Olvi-Vec followed by platinum-based chemotherapy±bevacizumab resulted in a promising response and survival outcomes in patients with heavily pre-treated platinum-resistant/refractory ovarian cancer with a median of four prior lines of therapy.[8 9] The phase II study met the pre-established primary endpoint of objective response rate (ORR)

at 54%, with duration of response of 7.6 months and median progression-free survival (PFS) of 11.0 months, which indicated clinical reversal of platinum resistance and refractoriness.

We hypothesize that the clinically meaningful improvements observed in the previous phase II VIRO-15 study was the result of virus-induced immunogenic cell death and priming of anti-tumor immunity through 'cross-presentation' of the tumor (neo)antigens, which was further boosted by subsequent cytotoxic chemotherapy via additional immunogenic cell death. Pre-clinical and clinical data support the staggered combination approach of viral immunotherapy, chemotherapy, and anti-angiogenic therapy.[10–12] Olvi-Vec converts immunologically 'cold' tumors to 'hot' tumors with induced tumor infiltrating lymphocytes (TILs), changes of tumor gene expression, relieves hypoxia and re-polarizes myeloid-derived suppressor cells from M2 to M1 type,[13] which led to favorable modulation of the tumor microenvironment. Influx of CD4+ and CD8+ TILs has been noted as a positive prognostic factor in ovarian cancer.[14] In addition to generating immunogenic cell death, cytotoxic chemotherapy may also reduce myeloid-derived suppressor cells/T-reg inhibitory signals. Anti-angiogenic therapy was noted to have immunomodulating functions to counteract tumor-induced immunosuppression.[15] It may also improve local perfusion in tumors to allow relief of hypoxia and, together with immune activating virotherapy, reverse the immunosuppressive state of the tumor. Taken together, the combination regimen may provide much needed anti-tumor synergy to enhance therapeutic outcomes.

In summary, previous pre-clinical and clinical data support the approach of Olvi-Vec-primed immunochemotherapy and provide a strong rationale for the design of the phase III OnPrime/GOG-3076 study. The primary objective is to evaluate the efficacy (by determination of PFS per RECIST 1.1) of Olvi-Vec followed by platinum-doublet chemotherapy and bevacizumab versus platinum-doublet chemotherapy and bevacizumab in all study patients as randomized in the intention-to-treat (ITT) population.

Box 1 Key inclusion and exclusion criteria

Inclusion criteria:

⇒ Histologically confirmed (from prior treatment) non-resectable ovarian, fallopian tube, or primary peritoneal cancer.
⇒ High-grade serous (including malignant mixed Mullerian tumor (MMMT) with metastasis that contains high-grade epithelial carcinoma, International Federation of Gynecology and Obstetrics (FIGO) grades 2 and 3 allowed), endometrioid, or clear-cell ovarian cancer.
⇒ Performance status Eastern Cooperative Oncology Group (ECOG) of 0 or 1.
⇒ Received a minimum of three prior lines (including the first line) of systemic therapy with no maximal limit.
⇒ Received prior bevacizumab (or biosimilar) treatment.
⇒ Have platinum-resistant or -refractory disease from the most recent platinum-based line of therapy.

Exclusion criteria:

⇒ Tumors of mucinous, low-grade serous, squamous cell, small cell neuroendocrine sub-types, MMMT tumors absent an epithelial component on recent biopsy, or non-epithelial ovarian cancers (eg, germ cell tumors, sex-cord tumors).
⇒ Known current central nervous system (CNS) metastasis.
⇒ Contra-indications for intra-peritoneal catheter placement: bowel obstruction with distended abdomen, rigid abdomen with bulky anterior wall carcinomatosis, abdominal wall hernia mesh that precludes laparoscopic entry to abdomen.
⇒ Active urinary tract infection, pneumonia, or other systemic infections.
⇒ Received prior virus-based gene therapy or therapy with cytolytic virus of any type.
⇒ Receiving concurrent anti-viral agent.
⇒ Prior malignancy of other histology active within previous 3 years except for locally curable cancers apparently cured such as basal/squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast, any other stage I/II local malignancies.

METHODS

Trial Design

OnPrime/GOG-3076 is a multicenter, prospective, randomized, and active-controlled phase III trial assessing the efficacy and safety of intra-peritoneal Olvi-Vec followed by platinum-doublet chemotherapy and bevacizumab compared with platinum-doublet chemotherapy and bevacizumab in women with platinum-resistant/refractory ovarian cancer. Patients eligible for the study must meet the key inclusion and exclusion criteria as summarized in box 1.

Patients will be randomized to one of two arms (figure 1): (1) experimental arm: Olvi-Vec+platinum-doublet chemotherapy and bevacizumab; or (2) active comparator arm: platinum-doublet chemotherapy and bevacizumab.

After platinum-doublet and bevacizumab, continued therapy with non-platinum chemotherapy and bevacizumab will be provided to clinically stable patients in both arms.

This study has two stratification factors, which include:

- Platinum-free interval after the most recent platinum-based therapy: <1 month versus 1–6 months.
- Baseline germline *BRCA1/2* mutation status: positive versus negative. Variants of unknown significance are considered as negative.

Treatment of chemotherapies and bevacizumab (or biosimilar) will be at the investigator's discretion within generally recognized clinical practice dosing standards. The platinum component will include either carboplatin (preferred) or cisplatin. The non-platinum component will be the physician's choice of gemcitabine, a taxane, or pegylated liposomal doxorubicin. Use of bevacizumab biosimilar is allowed. In both arms, continued therapy with non-platinum chemotherapy and bevacizumab is encouraged to clinically stable patients until they have iRECIST[16] confirmed progressive disease (ie, immune confirmed progressive disease determined by Blinded Independent Central Review (BICR)), if applicable, or who no longer tolerate therapy.

Because Olvi-Vec will be administered via an intra-peritoneal catheter only in patients randomized to the experimental arm, the study cannot be blinded to the medical staff involved in direct patient care. However, in order to ensure an unbiased radiological evaluation of tumor response, which is the critical assessment used in determination of PFS and ORR, imaging data will be reviewed by a BICR. All imaging scans (figure 2) will be submitted for BICR determination of response to treatment, disease progression per

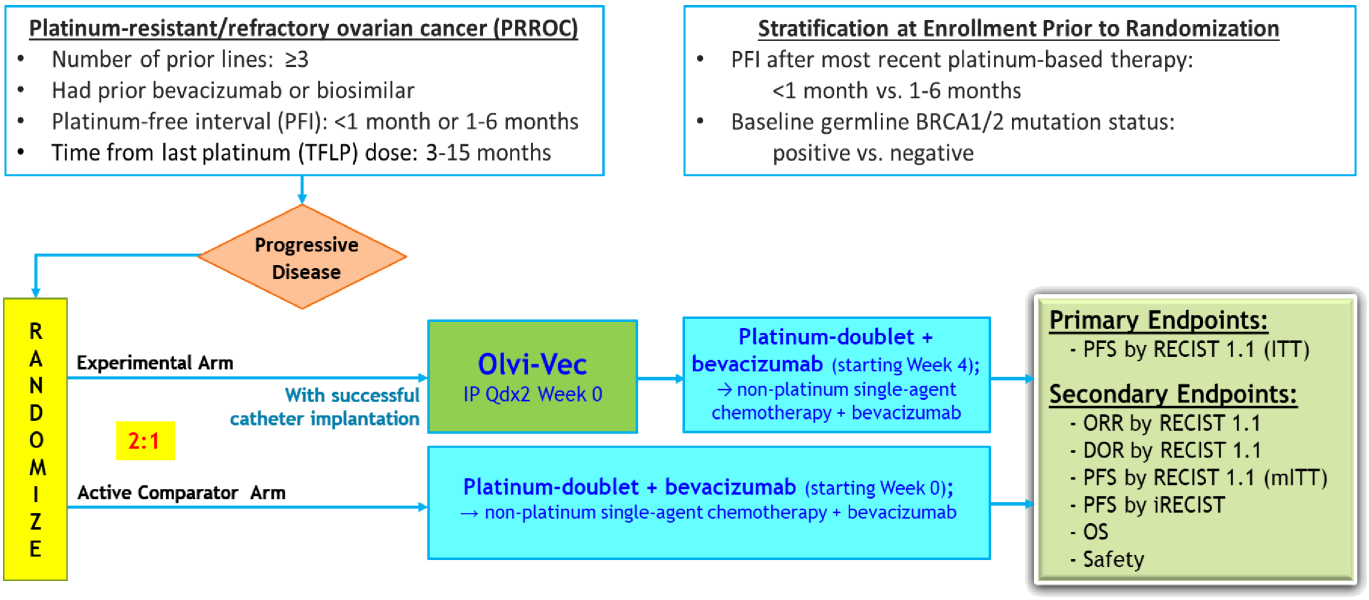

Figure 1 Investigation schema for phase III OnPrime/GOG-3076 trial for patients with platinum-resistant/refractory ovarian cancer. BRCA1/2, breast cancer gene 1/2; DOR, duration of response; IP, intra-peritoneal; ITT, intention-to-treat; mITT, modified intention-to-treat; ORR objective response rate; OS, overall survival; PFS, progression-free survival; Qdx2, 2 consecutive days.

RECIST 1.1 and iRECIST during the study, and continued treatment as allowed per iRECIST.

Participants

Patients are eligible if they have a history of histologically confirmed (from prior treatment) non-resectable ovarian, fallopian tube, or primary peritoneal cancer who have either platinum-resistant or platinum-refractory disease based on the platinum-free interval (PFI) by radiological assessment from the most recent platinum-based line of therapy, with PFI of 1–6 months as platinum-resistant and PFI of <1 month as platinum-refractory. High-grade serous (including MMMT with metastasis that contains high-grade epithelial carcinoma; FIGO grades 2 and 3 allowed), endometrioid, or clear-cell ovarian cancer are included. Patients are eligible if they have received a minimum of three prior lines (including the first line) of systemic therapy with no maximal limit. Ineligible patients include those who have tumors of mucinous, low-grade serous, squamous cell, small cell neuroendocrine sub-types, MMMT tumors absent an epithelial component on recent biopsy, or non-epithelial ovarian cancers (eg, germ cell tumors, sex-cord tumors).

Outcomes/Statistical Methods

The primary efficacy endpoint is PFS as assessed by BICR in the intention-to-treat (ITT) population. ITT is defined as: all patients

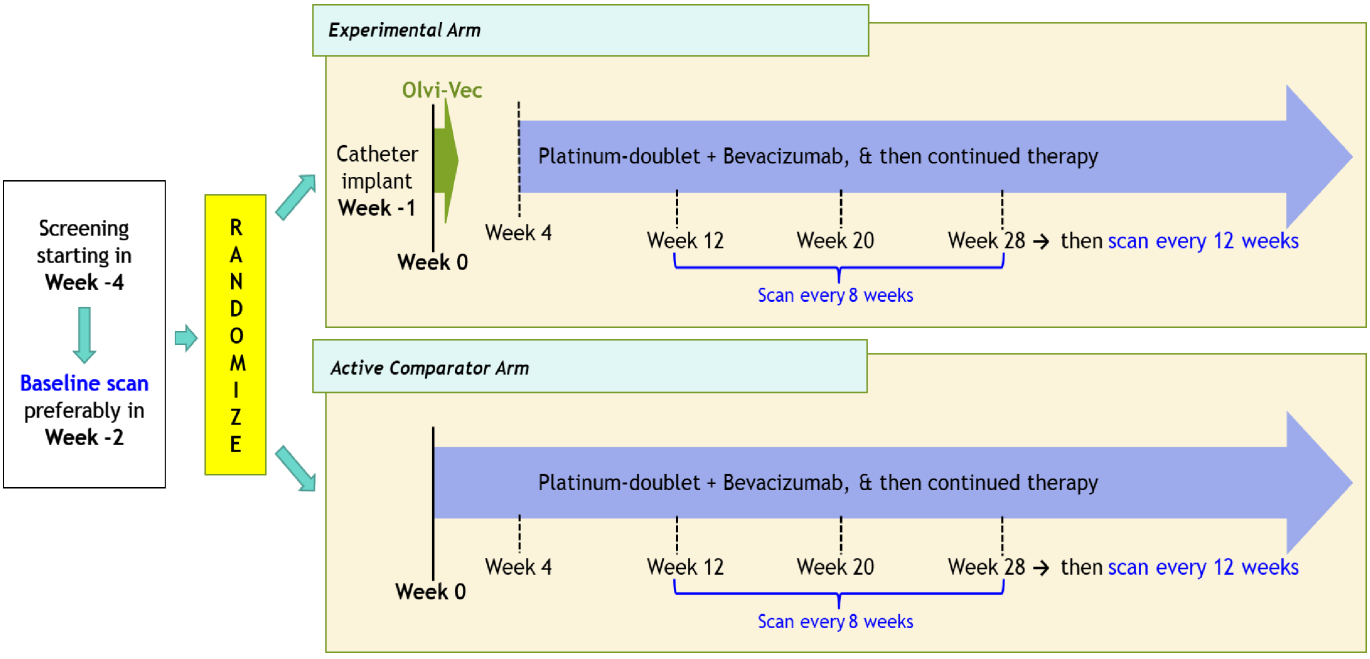

Figure 2 Screening, initiation of treatment, and imaging timepoints.

are analyzed as randomized regardless of the treatment actually received. Key secondary endpoints include ORR by RECIST 1.1, overall survival (OS), and safety. Survival analyses for PFS and OS will be performed using standard Kaplan–Meier analyses. PFS in the modified ITT (mITT) population will also be included in the secondary endpoints. mITT is defined as: All randomized patients who received at least one dose of treatment within the arm to which they were randomized (ie, experimental arm with one or more doses of virus and active comparator arm with one or more doses of chemotherapy).

Sample Size

Sample size was calculated with one-tail α of 0.025 and power of 90% to detect a hazard ratio (HR) of 0.55. Approximately 186 patients will be randomized in this trial in a 2:1 ratio to the two treatment arms to capture a total required 127 PFS events for the final analysis of the primary endpoint of PFS.

DISCUSSION

This phase III OnPrime/GOG-3076 trial builds on the efficacy and safety data reported in the previous phase II VIRO-15 trial,[9] with promising ORR and PFS observed in heavily pre-treated patients with platinum-resistant/refractory ovarian cancer. The phase II results also showed that the intra-peritoneal route of delivery was efficient in generating tumor cell killing and immune activation and led to clinical reversal of platinum resistance or refractoriness in this difficult-to-treat patient population. We expect that similar results will be observed in this phase III trial, which essentially follows the phase II trial design.

This phase III trial has an active comparator arm to receive platinum-doublet chemotherapy and bevacizumab, which is given in both arms. The only difference between the two arms is Olvi-Vec virotherapy in the experimental arm. Therefore, this stringent randomized phase III trial as proposed would clearly define the role of Olvi-Vec in the combination regimen of Olvi-Vec-primed immunochemotherapy.

BRCA1/2 mutations have been associated with increased sensitivity to platinum-based therapy.[17] However, in the phase II VIRO-15 trial, patients with *BRCA1/2* variants had ORR by RECIST of 29% versus 65% in those with wildtype *BRCA1/2*. Therefore, the response to platinum observed in the phase II trial cannot be attributed to *BRCA1/2* mutation carriers. Stratification based on *BRCA1/2* variants is included in the phase III OnPrime/GOG-3076 trial to further understand the relevance to response and other efficacy endpoints.

Olvi-Vec therapy is infused on two consecutive days by a temporary intra-peritoneal catheter. The intra-peritoneal route of delivery is relevant to ovarian cancer. Peritoneal metastases, especially the widespread and surgically difficult small nodules, may provide a large surface area to allow direct and efficient interaction between viral particles and tumor cells in the limited space of the peritoneal cavity. Only a portion of the tumor cells is needed to be infected by the virus to generate subsequent immune activation activities. Previous studies have shown that intra-peritoneal administration of Olvi-Vec was well tolerated with manageable safety profiles.[6 7 9] Hydration with intra-venous fluid during the days of and after virus treatment can help to alleviate symptoms and prevent dehydration.

Platinum-resistant/refractory ovarian cancer is typically considered as a 'cold' tumor with low intra-epithelial infiltration of CD8+ T-lymphocytes,[18] which could explain the poor efficacy of immune checkpoint inhibitors as monotherapy.[19 20] The main challenge for immune checkpoint inhibitors in platinum-resistant ovarian cancer is to turn this 'cold' tumor into 'inflamed' by favoring infiltration of functional cytotoxic T-cells. Combination therapies have been investigated in platinum-resistant/refractory ovarian cancer in various studies.[21–24] However, no combination regimen of immunotherapy has been approved so far in platinum-resistant/refractory ovarian cancer. The potential reasons for the lack of significant clinical progress may be due to insufficient immune priming and activation of effector T-cells and/or lack of T-cell trafficking into tumors. Therefore, alternative strategies are needed to overcome such challenges in the platinum-resistant/refractory ovarian cancer setting. Olvi-Vec oncolytic immunotherapy is an ideal immune modulating agent to induce an inflamed tumor immune microenvironment by induction of pro-inflammatory cytokines/chemokines and to drive the intra-epithelial infiltration of effector T-cells.[6–9] In addition, Olvi-Vec as an oncolytic virus has its intrinsic tumor cell killing effect with immunogenic cell death. The combination of virus-mediated immune priming with immunogenic cell death and further boost by subsequent platinum-doublet chemotherapy together with anti-angiogenic therapy may generate significantly enhanced anti-tumor activity in platinum-resistant/refractory ovarian cancer.

Platinum-based chemotherapy has been the cornerstone of the clinical management of ovarian cancer. However, once platinum resistance or refractoriness develop, expected response rates to subsequent therapies are less than 20% and the median PFS is only 3–4 months.[25 26] Platinum re-challenge may still be a reasonable therapeutic option in some patients who have platinum-resistant disease and maintain a good performance status.[27–29] For example, oxaliplatin and gemcitabine showed ORR by RECIST of 24%; however, all responses with a median duration of 5 months were in platinum-resistant patients, with none in platinum-refractory patients.[28] Therefore, identifying a platinum re-sensitizing agent is an ideal strategy to allow platinum re-challenge to be deep and durable. Historically, hypomethylating agents such as guadecitabine have been investigated as potential platinum re-sensitizing agents.[30] The task of identifying an effective re-sensitizing agent to platinum is considered as one of the ultimate challenges in the effective management of recurrent ovarian cancer, especially in the platinum-resistant/refractory ovarian cancer setting. Olvi-Vec may provide re-sensitization to platinum and meet the critical need.

In summary, we believe that the OnPrime/GOG-3076 trial has the potential to transform the current practice of treating platinum-resistant/refractory ovarian cancer by providing clinicians with a new treatment approach of the uniquely positioned immune modulating agent Olvi-Vec as oncolytic immunotherapy and a platinum re-sensitizing agent.

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REFERENCES

1 Worschech A, Chen N, Yu YA, *et al*. Systemic treatment of xenografts with vaccinia virus GLV-1H68 reveals the immunologic facet of oncolytic therapy. *BMC Genomics* 2009;10:301.
2 Yu YA, Galanis C, Woo Y, *et al*. Regression of human pancreatic tumor xenografts in mice after a single systemic injection of recombinant vaccinia virus GLV-1H68. *Mol Cancer Ther* 2009;8:141–51.
3 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.
4 Weibel S, Raab V, Yu YA, *et al*. Viral-mediated oncolysis is the most critical factor in the late-phase of the tumor regression process upon vaccinia virus infection. *BMC Cancer* 2011;11:68.
5 Weibel S, Basse-Luesebrink TC, Hess M, *et al*. Imaging of intratumoral inflammation during oncolytic virotherapy of tumors by 19F-magnetic resonance imaging (MRI). *PLoS One* 2013;8:e56317.
6 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;24:4388–98.
7 Manyam M, Stephens AJ, Kennard JA, *et al*. A phase 1B study of intraperitoneal oncolytic viral immunotherapy in platinum-resistant or refractory ovarian cancer. *Gynecol Oncol* 2021;163:481–9.
8 Holloway R, Mendivil A, Kendrick J, *et al*. 12 Oncolytic vaccinia (Olvi-Vec) primed immunochemotherapy in platinum-resistant/refractory ovarian cancer. IGCS 2020 Annual Meeting Abstracts; November 2020:A9–10
9 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* 2023;9:903–8.
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;15:1558–63.
11 Frentzen A, Yu YA, Chen N, *et al*. Anti-VEGF single-chain antibody GLAF-1 encoded by oncolytic vaccinia virus significantly enhances antitumor therapy. *Proc Natl Acad Sci U S A* 2009;106:12915–20.
12 Russell L, Peng KW, Russell SJ, *et al*. Oncolytic viruses: priming time for cancer immunotherapy. *BioDrugs* 2019;33:485–501.
13 Kilinc MO, Ehrig K, Pessian M, *et al*. Colonization of xenograft tumors by oncolytic vaccinia virus (VACV) results in enhanced tumor killing due to the involvement of myeloid cells. *J Transl Med* 2016;14:340.
14 Ovarian Tumor Tissue Analysis (OTTA) Consortium, Goode EL, Block MS, *et al*. Dose-response association of CD8+ tumor-infiltrating lymphocytes and survival time in high-grade serous ovarian cancer. *JAMA Oncol* 2017;3:e173290.
15 Voron T, Marcheteau E, Pernot S, *et al*. Control of the immune response by pro-angiogenic factors. *Front Oncol* 2014;4:70.
16 Seymour L, Bogaerts J, Perrone A, *et al*. iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol* 2017;18:e143–52.
17 Mylavarapu S, Das A, Roy M. Role of BRCA mutations in the modulation of response to platinum therapy. *Front Oncol* 2018;8:16.
18 Mariya T, Hirohashi Y, Torigoe T, *et al*. Prognostic impact of human leukocyte antigen class I expression and association of platinum resistance with immunologic profiles in epithelial ovarian cancer. *Cancer Immunol Res* 2014;2:1220–9.
19 Matulonis UA, Shapira-Frommer R, Santin AD, *et al*. Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: results from the phase II KEYNOTE-100 study. *Ann Oncol* 2019;30:1080–7.
20 Hamanishi J, Takeshima N, Katsumata N, *et al*. Nivolumab versus gemcitabine or pegylated liposomal doxorubicin for patients with platinum-resistant ovarian cancer: open-label, randomized trial in Japan (NINJA). *J Clin Oncol* 2021;39:3671–81.
21 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. *J Clin Oncol* 2014;32:1302–8.
22 Konstantinopoulos PA, Waggoner S, Vidal GA, *et al*. Single-arm phases 1 and 2 trial of niraparib in combination with pembrolizumab in patients with recurrent platinum-resistant ovarian carcinoma. *JAMA Oncol* 2019;5:1141–9.
23 Liu JF, Herold C, Gray KP, *et al*. Assessment of combined nivolumab and bevacizumab in relapsed ovarian cancer: a phase 2 clinical trial. *JAMA Oncol* 2019;5:1731–8.
24 Pujade-Lauraine E, Fujiwara K, Ledermann JA, *et al*. Avelumab alone or in combination with chemotherapy versus chemotherapy alone in platinum-resistant or platinum-refractory

ovarian cancer (JAVELIN Ovarian 200): an open-label, three-arm, randomised, phase 3 study. *Lancet Oncol* 2021;22:1034–46.
25 Pujade-Lauraine E, Banerjee S, Pignata S. Management of platinum-resistant, relapsed epithelial ovarian cancer and new drug perspectives. *JCO* 2019;37:2437–48.
26 Davis A, Tinker AV, Friedlander M. “Platinum resistant" ovarian cancer: what is it, who to treat and how to measure benefit? *Gynecol Oncol* 2014;133:624–31.
27 Nagourney RA, Brewer CA, Radecki S, *et al*. Phase II trial of gemcitabine plus cisplatin repeating doublet therapy in previously treated, relapsed ovarian cancer patients. *Gynecol Oncol* 2003;88:35–9.
28 Germano D, Rosati G, Manzione L. Gemcitabine combined with oxaliplatin (GEMOX) as salvage treatment in elderly patients with advanced ovarian cancer refractory or resistant to platinum: a single institution experience. *J Chemother* 2007;19:577–81.
29 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. Available: https://www2.tri-kobe.org/nccn/guideline/gynecological/english/ovarian.pdf
30 Oza AM, Matulonis UA, Alvarez Secord A, *et al*. A randomized phase II trial of epigenetic priming with guadecitabine and carboplatin in platinum-resistant, recurrent ovarian cancer. *Clin Cancer Res* 2020;26:1009–16.