Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2026**; 53(11): 55362
https://doi.org/10.31083/CEOG55362

Original Research

A Randomized, Double-Blind, Placebo-Controlled Study of Dendritic Cell Vaccine Maintenance Therapy in Patients With FIGO Stage III–IV Ovarian Cancer After First-Line Chemotherapy

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Academic Editor: Samir A. Farghaly
Submitted: 27 June 2026 Revised: 24 August 2026 Accepted: 8 September 2026 Published: 19 November 2026

Abstract

Background: Immune therapy for ovarian cancer faces numerous challenges because ovarian cancer is generally considered an immunologically "cold" tumor. One feasible approach to enhancing the antitumor activity of T cells is to improve antigen presentation by dendritic cells (DCs). However, few studies have focused on the use of this strategy as maintenance therapy after first-line chemotherapy in patients with ovarian cancer. This study aimed to evaluate safety, efficacy and immune response of personalized dendritic cell vaccine (DCVAC) as a first-line maintenance of ovarian cancer. **Methods:** This randomized, double-blind, placebo-controlled phase II trial included patients with the International Federation of Gynecology and Obstetrics (FIGO) stage III–IV ovarian cancer. Participants were randomly assigned to the dendritic cell vaccine or the placebo group at a 2:1 ratio. Patients with no disease progression after postoperative chemotherapy were administered the study drug for a maximum of 15 doses. 25 patients were randomized but 3 patients were excluded before study treatment due to chemotherapy-related adverse reactions. 22 participants (DCVAC, n = 15; placebo, n = 7) were included in the modified intention-to-treat (mITT) population. **Results:** (1) Safety: Most adverse events were graded 1–2 according to CTCAE version 5.0. (2) Efficacy: The median progression-free survival (PFS) was 22.6 months in the DCVAC group and 36.4 months in the placebo group (HR: 0.9746, 95% confidence interval [CI]: 0.3294–2.883, $p = 0.9629$). Thus, DCVAC did not significantly improve PFS in this study. Findings from the subgroup analyses, including breast cancer gene (*BRCA*) wild-type subgroup, were underpowered due to the small sample size and require further independent validation. (3) Immune reactivity: Exploratory immune cell analyses were limited to 4 paired samples, and baseline biomarker analyses included only 12 participants. Following DCVAC treatment, there was a potential trend toward increased numbers of antitumor immune cells, including T cells, B cells, natural killer (NK) cells, and conventional dendritic cells (cDCs), whereas plasmacytoid dendritic cells (pDCs) tended to decrease; however, these changes did not reach statistical significance. Patients with a higher proportion of $CD8^+$programmed cell death protein 1 $(PD\text{-}1)^+$ T cells and a lower proportion of senescent $CD8^+$ T cells in the peripheral blood before treatment might have longer PFS, suggesting that these populations may serve as potential biomarkers of a favorable response to DCVAC treatment. However, these findings still require validation in larger populations and independent studies. **Conclusion:** Maintenance therapy with DCVAC after first-line chemotherapy in patients with FIGO stage III–IV ovarian cancer had an acceptable safety profile in this exploratory trial. However, the primary mITT analysis did not demonstrate a PFS benefit. Larger prospective studies are warranted to assess efficacy and validate potential subgroup or biomarker signals. **Clinical Trial Registration:** The study has been registered at https://clinicaltrials.gov with the identifier NCT04834544 (https://clinicaltrials.gov/study/NCT04834544?cond=NCT04834544&viewType=Card&rank=1).

Keywords: dendritic cell vaccine; ovarian cancer; maintenance therapy; immune biomarkers

1. Introduction

Ovarian epithelial cancer (EOC) is the most fatal malignant tumor of the female reproductive system, with an overall 5-year survival rate of 48%. Nearly 75% of patients are already in the advanced stage when symptoms appear, with a 5-year survival rate of only 29% [1,2]. The initial treatment for ovarian cancer consists of surgery and postoperative platinum-based chemotherapy. Although most patients achieve complete or partial remission after initial treatment, approximately 75% of patients present with recurrence and eventually develop drug resistance [2,3]. Medication-based maintenance therapy after first-line treatment is an effective means of delaying recurrence. Currently, treatments widely used in the maintenance treatment of ovarian cancer include poly (ADP- ribose) polymerase (PARP) inhibitors and bevacizumab [4,5]. However, the

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population that benefits from these treatments is limited to those with *BRCA* mutations and homologous recombination deficiency (HRD). For patients who are HRD-negative, the benefit in terms of progression-free survival (PFS) is only 3–4 months [6,7].

Among the many maintenance treatment options, immunotherapy is a noteworthy area of research. The presence of tumor-infiltrating lymphocytes is highly correlated with a higher 5-year survival rate in patients with ovarian cancer [8]. There are numerous challenges in the application of single T-cell therapy for ovarian cancer, known as a "cold" tumor; these include low T-cell infiltration, poor antigen presentation, and immune tolerance to tumor antigens [9]. In the tumor microenvironment, dendritic cells (DCs) acquire and process tumor-associated antigens, which are presented via Major Histocompatibility Complex (MHC) I/II molecules to activate T cells [10,11]. One feasible approach to enhancing the antitumor effect of T cells is to augment the antigen presentation process of DCs.

The first clinical study of DC vaccines began in 1996 [12]. As of July 1, 2026, over 600 DC-related clinical trials on tumor treatment have been registered on the website (https://clinicaltrials.gov/) and studies in melanoma, prostate cancer, malignant glioma, and renal cell carcinoma have entered phase III clinical trials. In 2010, sipuleucel-T (PROVENGE), an autologous cellular immunotherapy, became the first FDA-approved therapeutic cancer vaccine for the treatment of asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer [13]. Clinical studies of sipuleucel-T have demonstrated treatment-associated immune responses and explored their relationships with survival outcomes [14]. Currently, some dendritic cell vaccines are undergoing clinical trials for ovarian cancer, where their safety has been verified, and some studies suggest benefits in terms of PFS and overall survival [15]. This study focused on the use of a DCVAC for maintenance therapy after first-line chemotherapy in ovarian cancer patients.

2. Materials and Methods

2.1 Study Design

This study is a phase II, randomized, double-blind, placebo-controlled study initiated by researchers. Patients were screened for inclusion in the study 2 days after undergoing initial or interval debulking surgery for tumors, and after signing an informed consent form, they were randomly assigned to the DCVAC group or the placebo group at a 2:1 ratio. Within one week of enrollment, leukapheresis was completed (at least 3 weeks after the last neoadjuvant chemotherapy). Adjuvant chemotherapy was initiated only at least 2 days after leukapheresis is completed, and after completing 6 cycles of platinum-based chemotherapy, chemotherapy response assessment was conducted. Patients with no disease progression entered the study drug treatment phase; the first 5 doses were administered at 3-week intervals (±3 days) and then at 6-week intervals (±3 days) for a maximum of 15 doses. The study design allowed for the concurrent use of other maintenance therapies, such as bevacizumab, PARP inhibitors (PARPi), and small-molecule tyrosine kinase inhibitors (TKIs). After a maximum of 15 drug infusions, patients entered the follow-up phase, with follow-ups conducted every 3 months until the end of the study or the patient's death. This study was approved by the Ethics Committee of the Peking University Third Hospital (Project ID: M202000, Approval No: 2020 027-02), and all methods were performed in accordance with the relevant guidelines and regulations. The study has been registered at https://clinicaltrials.gov with the identifier NCT04834544, and the initial release date is 03/29/2021.

2.2 Production of the DCVAC and Placebo

Autologous mononuclear cells obtained through leukapheresis were cultured with granulocyte–macrophage colony–stimulating factor and interleukin-4 (IL-4) to generate immature DCs from the collected monocytes. High hydrostatic pressure was then used to induce immunogenic cell death in the EOC cell lines OV-90 and SK-OV-3 (at a 2:1 ratio) to sensitize immature DCs [16]. Cell lines including OV-90 (catalog No. CRL-3585) and SK-OV3 (catalog No. HTB-77) were purchased from American Type Culture Collection (ATCC). Both cell lines were cultured in RPMI-1640 medium (Lonza, catalog No.BW12-918F) supplemented with 10% fetal bovine serum (Gibco, catalog No.A5256701) and incubated at 37 °C with 5% CO_2. Both cell lines were identified by STR profiling, and mycoplasma testing was negative for both cell lines. The immature DCs sensitized with tumor cells were subsequently activated using Toll-like receptor 3 ligands to transform into mature DCs. The mature DCs were cryopreserved in CryoStor CS10 freezing medium at a concentration of approximately 5×10^6 DCs and stored in liquid nitrogen. The placebo contained only a balanced electrolyte solution, CryoStor CS10 (which includes sugars, salts, and other components to buffer the pH, maintain osmotic pressure, scavenge free radicals, provide energy substrates), and 10% dimethyl sulfoxide (Fig. 1).

2.3 Transportation, Storage and Administration of the Treatment

The study drug was prepared in the central laboratory, transported to the hospital in a dry ice freezer filled with liquid nitrogen vapour (temperature below –150 °C), and stored in a liquid nitrogen tank. Both the study drug and the placebo were divided and stored in cycloolefin copolymer material AT-Closed Vials® or polypropylene cryotubes with internal thread polypropylene screw caps at a temperature below –150 °C. The tubes were packaged according to each dose of administration.

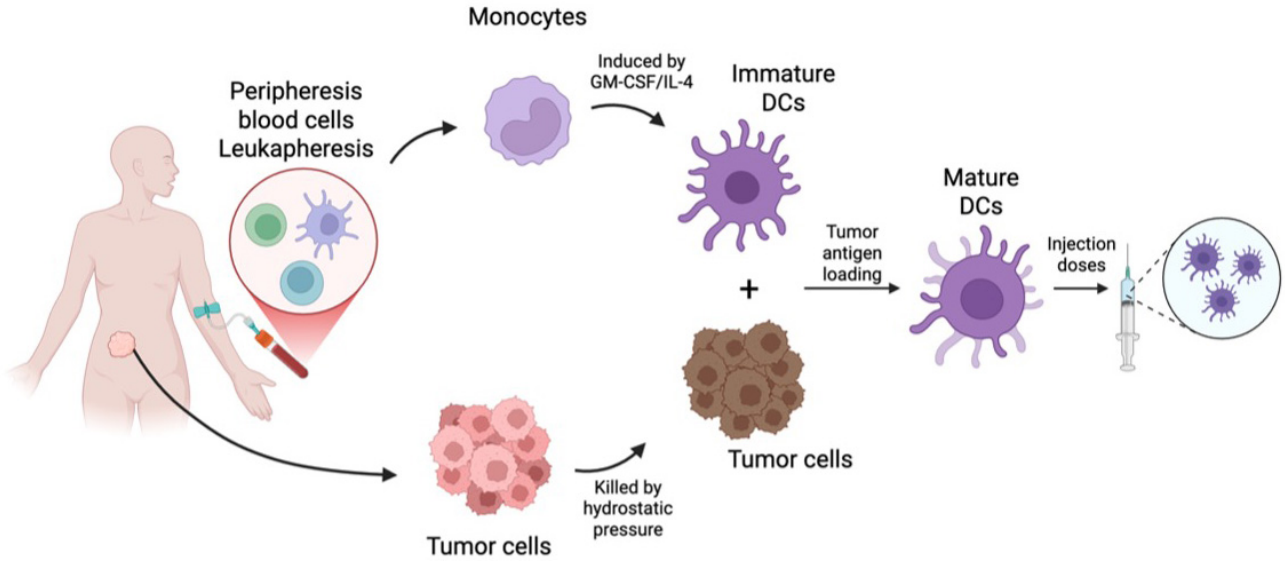


Fig. 1. Schematic of the study. Created in BioRender. Zhang, X. (2025) https://BioRender.com/0gx19s0. GM-CSF, granulocyte-macrophage colony stimulating factor; IL-4, interleukin-4; DCs, dendritic cells.

On the day of administration, a dose containing approximately 5×10^6 activated autologous DCs of DCVAC or a placebo was thawed and resuspended in 0.9% precooled saline, with a total volume of 5 mL, which was divided into two injections (each 2.5 mL). The two injections were administered subcutaneously to the axillary and contralateral inguinal lymph node areas. After injection, the patients were observed for at least 30 minutes, and vital signs were measured. For the next dosing cycle, the administration site was switched.

2.4 Inclusion Criteria

(1) Eighteen years of age or older at the time written informed consent was obtained.

(2) Newly diagnosed, histologically confirmed the International Federation of Gynecology and Obstetrics (FIGO) stage III or IV EOC (high-grade serous or high-grade endometrioid).

(3) Residual disease after surgery (primary debulking surgery or interval debulking surgery), with optimal resection defined as R0 or R1 (R0 was defined as no macroscopic residual disease, and R1 was defined as macroscopic residual disease with a maximal diameter of <1 cm).

(4) Known *BRCA* status or determination of *BRCA* status before randomization.

(5) Laboratory criteria:

a. White blood cells >4000/mm^3 (4.0×10^9/L).

b. Neutrophil count >1500/mm^3 (1.5×10^9/L).

c. Hemoglobin ≥8 g/dL (80 g/L).

d. Platelet count ≥100,000/mm^3 (100×10^9/L).

e. Total bilirubin <2 × upper limit of normal (ULN).

f. Serum alanine aminotransferase, aspartate aminotransferase, and creatinine <2 × ULN.

g. Blood urea nitrogen <2 × ULN.

h. Adequate coagulation parameters: activated partial thromboplastin time ≤1.5 × ULN; international normalized ratio ≤1.5.

(6) Eastern Cooperative Oncology Group (ECOG) performance status 0–2.

(7) Consent to the use of 2 highly effective forms of contraception (included on the consent form) until 6 months after the last/final dose of first-line Pt-based adjuvant chemotherapy or DCVAC treatment or placebo (for patients with child-bearing potential and their partners who are sexually active).

(8) Signed informed consent and ability to comprehend the content of the consent form.

2.5 Exclusion Criteria

(1) Nonepithelial ovarian carcinoma or mixed epithelial histology.

(2) Borderline tumors (tumors of low malignant potential).

(3) First-line Pt-based adjuvant chemotherapy has already started after surgery.

(4) Intention to treat with intraperitoneal chemotherapy.

(5) Previous or concurrent radiotherapy to the abdomen and pelvis.

(6) Major surgery (except debulking surgery) within 3 weeks before providing informed consent or lack of a full recovery from any major surgery.

(7) Malignancy other than EOC, except for a malignancy that has been in complete remission for a minimum of 3 years and except carcinoma *in situ* of the cervix or nonmelanoma skin carcinomas that have been definitively treated.

(8) Use of any immunotherapy in the past (e.g., anti-PD-1/Programmed Cell Death Ligand-1 (PD-L1) or other immune checkpoint inhibitors, therapeutic vaccines, adoptive cell therapy, cytokines); in case of uncertainty, this criterion was discussed with the medical monitor.

(9) Symptomatic uncontrolled brain or leptomeningeal metastases. A scan to confirm the absence of brain metastases was not required. Patients with spinal cord compression were considered if they received definitive treatment for this condition and had evidence of clinically stable disease for 28 days.

(10) Comorbidities: human immunodeficiency virus (HIV), active hepatitis B (HBV) and/or hepatitis C virus (HCV), active syphilis, evidence of active bacterial, viral, or fungal infection requiring systemic treatment; clinically significant cardiovascular disease, including symptomatic congestive heart failure, unstable angina pectoris, severe cardiac arrhythmia requiring medication, uncontrolled hypertension, myocardial infarction or ventricular arrhythmia or stroke within a 6-month period before inclusion, ejection fraction <40% or serious cardiac conduction system disorders, if a pacemaker is not present; pericardial effusion of any CTCAE grade; severe chronic obstructive pulmonary disease defined as grade C or D according to the Global Initiative for Obstructive Lung Disease.

(11) High medical risk due to other serious, uncontrolled medical disorders; nonmalignant systemic diseases; or active, uncontrolled infections.

(12) History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study treatment, or is not in the best interest of the patient to participate.

(13) Active autoimmune disease requiring treatment.

(14) History of severe forms of primary immune deficiencies.

(15) History of anaphylaxis or other severe reactions following vaccination.

(16) Psychiatric or social conditions that, in the investigator's opinion, would prevent participation in the study.

(17) Known hypersensitivity to any constituent of DCVAC treatment or placebo.

(18) Systemic immunosuppressive therapy for any reason (except inhaled/intranasal steroids and short-term systemic steroids <30 days duration and ≤10 mg prednisone-equivalent per day are allowed).

(19) Participation in a clinical trial involving experimental therapy within the last 4 weeks before providing informed consent.

(20) Pregnant or breastfeeding, or expecting to conceive children within the projected duration of the study treatment.

(21) Refusal to provide informed consent.

2.6 Outcomes

PFS was defined as the time from randomization to the earlier date of assessment of objective progression or death from any cause in the absence of progression. Overall survival (OS) was defined as the time from randomization to the date of cancer-related death. Disease progression was assessed by the investigator per Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. Participants were followed for approximately 2 years or longer when continued follow-up was available.

2.7 Randomization and Blinding

Eligible patients underwent randomization centrally through a central randomization system within 5 days of signing the informed consent form (ICF) and were randomized in a 2:1 ratio to receive either DCVAC or placebo. Patients, investigators, and staff for assessment, monitoring and data validation remained blinded to study-treatment assignments from the time of randomization until the database lock. The type of treatment was concealed by the use of leukapheresis in both treatment groups, identical packaging, labeling, and identical dosing schedules. Placebo syringes should be sufficiently masked to prevent patients and blinded staff from being aware of the type of treatment.

2.8 Flow Cytometry

(1) Cell suspension preparation: Peripheral blood samples were collected before treatment and after 6 doses of treatment. Single-cell suspensions containing (1–5) × 10^6 cells were aliquoted.

(2) Antibody Staining: The antibodies from Biolegend were used (**Supplementary Table 1**). The antibody solutions were mixed thoroughly by pipetting and incubated in the dark at room temperature for 15 minutes.

(3) Washing: After staining, 200 µL of phosphate buffer saline (PBS) was added. The samples were centrifuged at 500 g for 5 minutes at 4 °C using a horizontal rotor centrifuge.

(4) Fixation: The supernatant was discarded, and the cells were resuspended in 100 µL of 1% paraformaldehyde for fixation.

(5) Filtration and Detection: Before analysis, the sample was filtered through a 300-mesh nylon mesh. The samples were analyzed via a Beckman CytoFLEX S flow cytometer.

(6) Data Analysis (**Supplementary Fig. 1**): The data were analyzed via Beckman Kaluza software (version 2.3.1, Beckman Coulter, Inc., Brea, CA, USA). First, we gated on $CD45^+$ leukocytes on the basis of CD45 expression. $CD45^+$ leukocytes were first identified on CD45-versus-side-scatter (SSC) plots. Mononuclear cells, including lymphocytes, were subsequently gated according to their size and granularity, as reflected by forward-scatter (FSC) and SSC characteristics. In both analytical branches, doublets and cellular aggregates were excluded using FSC

area (FSC-A) versus FSC width (FSC-W), thereby retaining singlet cells. In the monocyte branch, lineage-negative human leukocyte antigen DR isotype (HLA-DR)$^+$ cells were selected and further divided into CD14$^+$ and CD14$^-$ populations according to CD14 expression. Within the CD14$^-$ population, CD11c$^+$ conventional dendritic cells (cDCs) and CD123$^+$ plasmacytoid dendritic cells (pDCs) were identified based on CD11c and CD123 expression, respectively. In the lymphocyte branch, CD3 and CD19 expression were used to identify CD19$^+$ B cells, CD3$^+$ T cells, and CD3$^-$CD19$^-$ natural killer (NK) cells. NK cells were further classified as CD16$^-$CD56^{hi} or CD16$^+$CD56^{dim} subsets according to CD16 and CD56 expression. CD3$^+$ T cells were subdivided into CD4$^+$ and CD8$^+$ T-cell populations, and regulatory T cells (Tregs) were identified within the CD4$^+$ T-cell compartment based on high CD25 and low CD127 expression. PD-1 expression was also assessed in T cells. Finally, based on CD57 and CD28 expression, senescent T cells were identified (Tsen; CD57$^+$CD28$^-$).

2.9 Statistical Analysis

GraphPad Prism version 10.1.1 was used for the statistical analysis. The modified intention-to-treat (mITT) population is used for the primary safety and efficacy analysis, which included participants who experienced randomization and received at least 1 dose of treatment and was the primary population for the efficacy analysis. Participants were analyzed according to randomized group. The per-protocol (PP) population excluded the DCVAC participant who received only one dose of treatment due to the weak effect of a single dose, and was used only for a supportive sensitivity analysis. Categorical data are described using frequencies and rates, and intergroup comparisons were made using Fisher's exact test. The data normality was assessed based on Shapiro-Wilk test. Comparisons between groups of normally distributed quantitative data were made using the *t* test or analysis of variance; comparisons between groups for non-normally distributed data were made using the Wilcoxon signed-rank test; and correlations between two variables were assessed via Spearman's correlation analysis. PFS was estimated using the Kaplan-Meier method and compared using the log-rank test; hazard ratios (HR) with 95% confidence intervals (CI) were estimated using Cox proportional-hazards models. All subgroup and immune-biomarker analyses were exploratory. A p-value ≤ 0.05 was considered to indicate statistical significance. In multiple comparisons, Bonferroni correction or Holm-Bonferroni correction was applied to control the false positive rate when necessary, especially in the subgroup analysis and immune marker analysis.

3. Results

3.1 Patient Enrollment

Between April 2021 and February 2022, a total of 32 newly diagnosed patients with FIGO stage III–IV ovarian or fallopian tube cancer were admitted to our hospital and provided informed consent to enter the screening phase. Five patients withdrew from the study for personal reasons before randomization, and two patients were excluded before leukapheresis because they did not meet the inclusion criteria. A total of 25 participants were randomized in a 2:1 ratio to DCVAC (n = 17) or placebo (n = 8). However, three patients presented chemotherapy-related severe adverse reactions and did not proceed to the drug treatment phase. Two of them had myelosuppression and one of them had peripheral nerve toxicity. Therefore, the three patients were excluded from the primary safety and efficacy analysis. Eventually, a total of 22 participants were randomized in a 2:1 ratio to DCVAC (n = 15) or placebo (n = 7) and constituted the mITT population (Fig. 2). One participant assigned to DCVAC received only one infusion due to an individual decision and was excluded from the PP population because a single dose may lead to weak effect; therefore, the PP population comprised 14 DCVAC and 7 placebo participants. The follow-up of these patients is updated to Aug, 1, 2026. Baseline characteristics are summarized descriptively by randomized group in Table 1 (mITT group) and **Supplementary Table 2** (PP group). Concurrent treatment with PARPi or small molecule TKI is also shown in Table 1, and none of the patients received Bevacizumab as maintenance therapy.

3.2 Safety of the DCVAC

Adverse events during the treatment period in both the DCVAC group and the placebo group were primarily graded as 1–2 according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) grade (Fig. 3). A total of 4 grade 1 and 8 grade 2 adverse events were recorded in the DCVAC group, compared with 2 grade 1 and 1 grade 2 adverse events in the control group. The only recorded grade 3 adverse event was lymphopenia; the patient's absolute lymphocyte count decreased to a minimum of 0.31×10^9/L during treatment. The patient exhibited no signs of infection, such as fever, chills, cough, or sputum production, and the absolute lymphocyte count recovered to 0.67×10^9/L after two weeks. The most frequently reported grade 2 adverse events were neutropenia and lymphopenia, which occurred in three patients in the DCVAC group. Other grade 2 adverse events included abdominal pain and bloating, whereas grade 1 adverse events mainly consisted of elevated thyroid-stimulating hormone (TSH) levels, although the free T3 and free T4 levels of these patients were generally normal. During the enrollment period, two serious events were reported, both of which were deemed unrelated to the study drug. One was a localized skin allergic reaction without a clear cause before leukapheresis, which was alleviated with oral antihistamines and topical medication. The other was a proliferative reaction at the surgical incision site; a hard subcutaneous mass at the abdominal incision was removed and

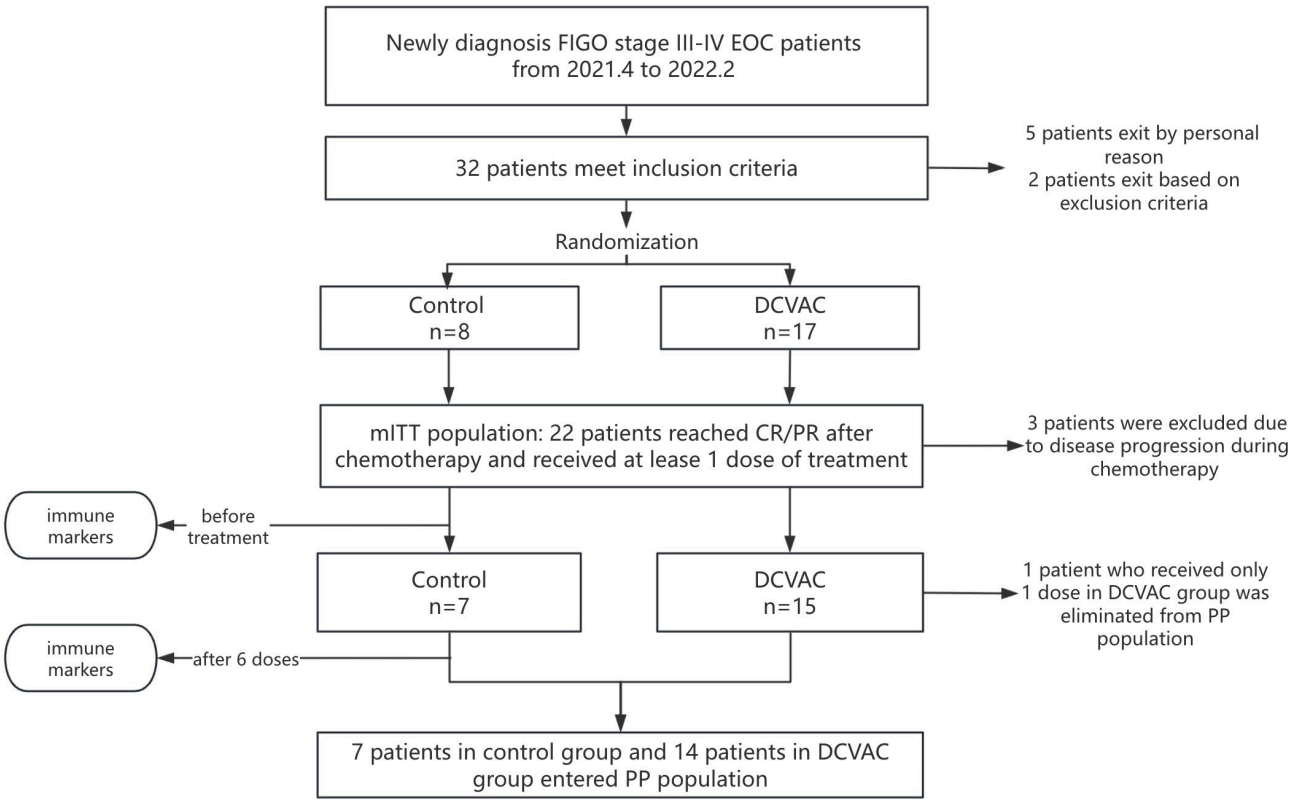


Fig. 2. Participant flow through the trial. FIGO, The International Federation of Gynecology and Obstetrics; EOC, ovarian epithelial cancer; CR/PR, complete response/ partial response; AEs, adverse events; DCVAC, dendritic cell vaccine.

Table 1. Clinical characteristics of the mITT group.

			DCVAC treatment (n = 15) (%)	Control (n = 7) (%)	*p* value
Age	≥65 years		5 (33.3)	1 (14.3)	0.6158
	<65 years		10 (66.7)	6 (85.7)	
Stage	III	IIIC	8 (53.3)	2 (28.6)	0.3808
	IV	IVA	2 (13.3)	2 (28.6)	
		IVB	5 (33.3)	3 (42.9)	
Debulking surgery type	Primary		9 (60.0)	4 (57.1)	0.9999
	Interval		6 (40.0)	3 (42.9)	
Surgery	R0		5 (33.3)	3 (42.9)	0.9999
	R1/R2*		10 (66.7)	4 (57.1)	
Chemotherapy	CR		11 (73.3)	6 (85.7)	0.9999
	PR		4 (26.7)	1 (14.3)	
BRCA status	*BRCA*m		4 (26.7)	4 (57.1)	0.3426
	*BRCA*w	HRD+	4 (26.7)	1 (14.3)	0.9999
		HRD-	1 (6.7)	0 (0.0)	
		Unknown	6 (40.0)	2 (28.6)	
Concurrent maintenance therapy	PARPi		11 (73.3)	6 (85.7)	0.9999
	Small molecule TKIs		2 (13.3)	1 (14.3)	0.9999

* R2 resection occurred in 2 patients in the DCVAC group and in none of the control group; the R2 resection were recorded as deviations of protocol. *BRCA*m, *BRCA* mutation; *BRCA*w, *BRCA* wild type; mITT, modified intention-to-treat; HRD, homologous recombination deficiency; PARPi, PARP inhibitor; TKI, tyrosine kinase inhibitors.

Table 2. Analyses stratified by risk factors.

Relapse/Total		DCVAC (n = 15)	Control (n = 7)	Hazard ratio for progression (95% CI)	*p* value
Surgery type	Primary	5/9	2/4	0.848 (0.203–3.224)	0.8208
	Secondary	4/6	1/3	1.080 (0.197–5.926)	0.9292
Surgery satisfaction	R0	1/5	1/3	0.292 (0.028–3.034)	0.7143
	R1/R2	8/10	2/4	1.364 (0.378–4.929)	0.6357
BRCA status	*BRCA*m	0/4	1/4	0.089 (0.009–0.897)	0.0401
	*BRCA*w	9/11	2/3	0.982 (0.207–4.655)	0.9818

pathologically examined, revealing fibrofatty connective tissue. In summary, the safety of DCVAC has been confirmed.

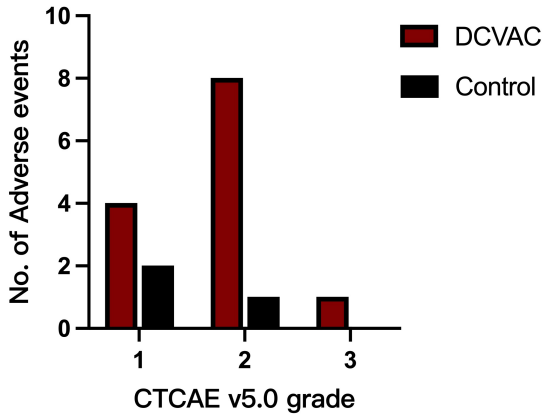


Fig. 3. Distribution of adverse events by CTCAE v5.0 grade in the DCVAC and control group of mITT population.

3.3 Efficacy of the DCVAC

The planned analysis time for PFS in this study was when all randomly assigned patients had been followed up for at least two years or all patients had experienced disease progression; the overall study endpoint was when the OS reached at least 50%. The three patients who discontinued the study due to chemotherapy related adverse events before receiving study treatment, therefore they were not included in the PFS analysis. As of the analysis time, the median PFS of DCVAC versus control was 22.6 months versus 36.4 months in mITT group, whereas it was 23.4 months versus 36.4 months in PP group. The number of progression events in DCVAC group and control group is 10 versus 5. The Median follow-up duration is 52.3 months. The number of censored observations is 5 in DCVAC group and is 2 in control group. The survival analysis of mITT group revealed no significant difference in PFS between the treatment and control groups (DCVAC vs. control, HR 0.9746, 95% CI 0.3294–2.883, $p = 0.9629$; Fig. 4), and a similar result in PP group (DCVAC vs. control, HR 0.9061, 95% CI 0.2971–2.764, $p = 0.8624$; **Supplementary Fig. 2**).

Exploratory subgroup analyses were conducted according to *BRCA* status, type of debulking surgery, and residual disease after surgery (Table 2). In the *BRCA*-mutation-type subgroup, the HR was 0.089 (95% CI 0.009–0.897; $p = 0.0401$). This finding did not meet the Bonferroni-adjusted significance threshold (adjusted alpha = 0.016), and produced an unstable effect estimate. It should therefore be considered hypothesis-generating only. No significant subgroup differences were observed according to primary versus interval debulking surgery or R0 versus R1/R2 residual disease.

3.4 Special Cases

The clinical courses of three DCVAC-treated participants who did not achieve a complete response after surgery and first-line chemotherapy are reported descriptively. Their observed PFS durations were 11.8, 24.2, and 29.6 months. These individual observations were not prespecified efficacy analyses.

One particular case from the DCVAC group involved a patient with stage IIIC high-grade serous ovarian cancer. Preoperative enhanced computed tomography (CT) of the abdomen and pelvis revealed masses in both adnexal regions measuring only 1 cm. Positron emission tomography/(PET)/CT revealed multiple enlarged lymph nodes in the retroperitoneal, para-aortic, and iliac artery regions, with heterogeneous enhancement and partial fusion. These lymph nodes encased the abdominal aorta and inferior vena cava, causing narrowing of the latter. Lymph node biopsy confirmed high-grade serous carcinoma of female reproductive system origin.

Given the complexity of the disease and the difficulty in achieving complete surgical resection, the patient underwent exploratory laparotomy for ovarian cancer debulking. Intraoperatively, multiple enlarged and fused lymph nodes were found in the retroperitoneal and pelvic regions. Owing to the hardness and extensive fusion of some lymph nodes, complete resection was not possible; R2 surgical resection was achieved, with residual disease located in the para-aortic lymph nodes. Although the patient with R2 surgical resection was a deviation from the protocol, due to the patient's request, the enrollment conditions were relaxed after assessment by the principal investigator.

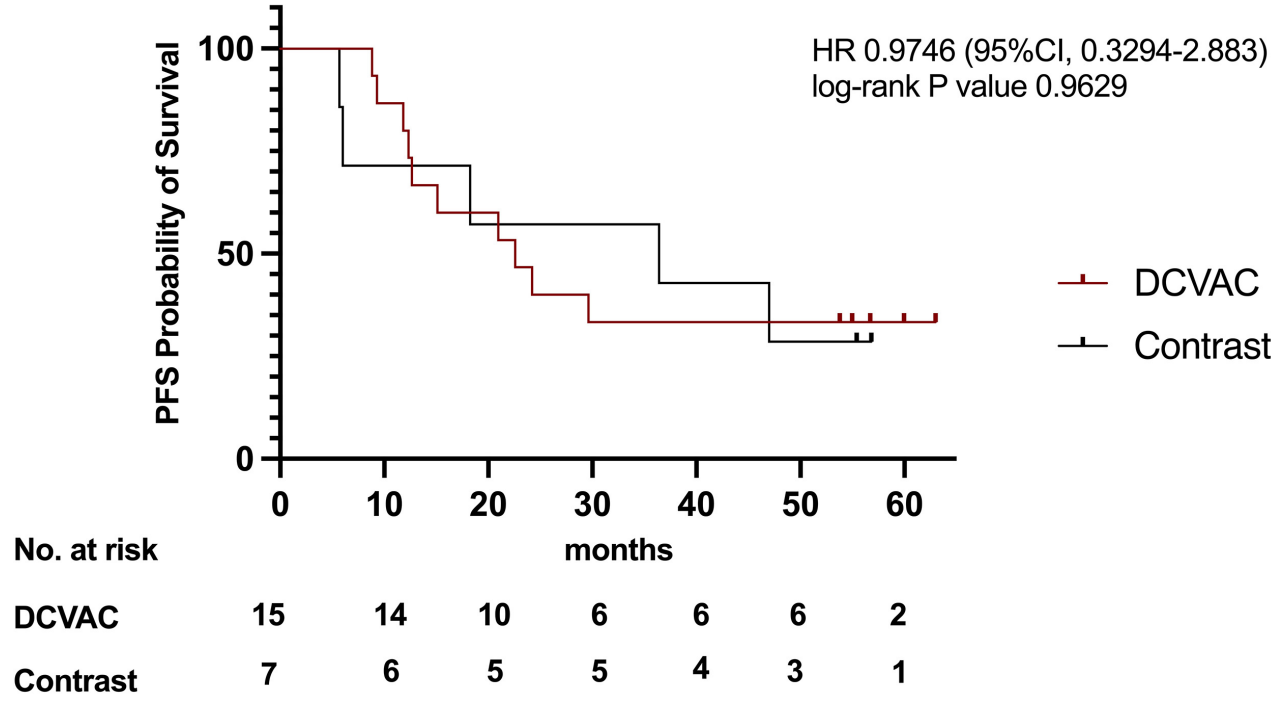


Fig. 4. Progression-free survival of mITT group.

Table 3. Changes in immune cell composition before and after DCVAC treatment (n = 4).

	Pre-treatment	Post-treatment	*p* value
$CD3^+/CD45^+$	13.09 (4.86, 33.70)	37.11 (11.83, 46.29)	0.073
$CD19^+/CD45^+$	2.15 (0.09, 2.71)	3.27 (1.30, 4.80)	0.011
$CD16^-CD56^{hi}/CD45^+$	0.07 (0.04, 0.07)	0.15 (0.03, 0.22)	0.144
$CD16^+CD56^{dim}/CD45^+$	5.14 (1.14, 27.89)	10.84 (1.38, 26.22)	0.599
$CD14^+/CD45^+$	0.40 (0.20, 0.82)	0.12 (0.03, 0.26)	0.042
$cDC/CD45^+$	0.07 (0.06, 0.23)	0.24 (0.01, 0.90)	0.215
$pDC/CD45^+$	0.10 (0.05, 0.11)	0.05 (0.03, 0.1)	0.191

Postoperatively, the patient received four cycles of the paclitaxel plus carboplatin (TC) chemotherapy regimen, which normalized CA125 levels. A total of six chemotherapy cycles were administered. Genetic testing revealed wild-type *BRCA* and HRD positivity, and the patient did not receive PARP inhibitor (PARPi) maintenance therapy postoperatively. During the maintenance treatment period, the patient received 15 doses of the study drug. Throughout the treatment, CA125 levels remained within the normal range. Imaging follow-up revealed stable and slightly reduced lymph node lesions. The largest retroperitoneal lymph node measured 41 × 23 mm preoperatively, 30 × 6 mm before DCVAC treatment initiation after chemotherapy, and 24 × 10 mm after DCVAC treatment completion (Fig. 5), with a PFS of 29.6 months.

However, six months after the infusions were discontinued, CA125 levels rose to 43.9 U/mL, and the lymph nodes began to slowly enlarge, indicating tumor progression. This temporal observation is not able to establish that DCVAC caused the preceding disease stability.

3.5 The Alteration of Immune Cells

Flow cytometry was used to assess major peripheral-blood immune-cell populations and subsets, including T cells, B cells, natural killer cells, monocytes, and dendritic cells. Only four participants had paired pre- and post-treatment samples. After DCVAC treatment, numerical increases were observed in T cells, B cells, natural killer cells, and conventional dendritic cells, whereas plasmacytoid dendritic cells numerically decreased (Table 3). None of these changes met the Holm-Bonferroni-adjusted significance threshold (first adjusted alpha = 0.007). Given the very small paired sample, these findings are descriptive and hypothesis-generating.

We further explored associations between baseline immune-cell composition and PFS in 12 DCVAC-treated participants. Baseline regulatory T cells, activated $CD8^+PD\text{-}1^+$ T cells, and senescent $CD8^+CD28\text{-}CD57^+$ T cells were evaluated using univariate Cox models. A higher proportion of $CD8^+PD\text{-}1^+$ T cells was nominally associated with longer PFS, whereas a higher proportion of senescent



Fig. 5. Imaging changes in the illustrative DCVAC-treated case. (A) Preoperative CT on 2022-02-19. Multiple enlarged and fused lymph nodes were observed in the retroperitoneum, with the largest lymph nodes measuring 41 × 23 mm, 27 × 19 mm, 35 × 26 mm, 20 × 17 mm, 29 × 21 mm, and 23 × 19 mm. (B) Post-chemotherapy, pre-DCVAC treatment CT on 2022-08-17. The largest lymph nodes measured 30 × 6 mm, 13 × 10 mm, 10 × 9 mm, 15 × 8 mm, 11 × 6 mm, and 18 × 8 mm. (C) Post-DCVAC treatment CT on 2024-01-23. The largest lymph nodes measured 24 × 10 mm, 16 × 10 mm, 12 × 8 mm, 14 × 8 mm, 11 × 6 mm, and 10 × 9 mm. CT, computed tomography. Red arrow: enlarged and fused lymph nodes.

Table 4. Correlations between baseline peripheral blood immune cell composition and the PFS in the treatment group (n = 12).

	Ratio	Sig.	HR (95% CI)
$CD3^+/CD45^+$	28.92 (4.86, 40.28)	0.159	0.937 (0.856, 1.026)
$CD4^+/CD3^+$	48.65 (28.54, 75.57)	0.182	0.948 (0.877, 1.025)
$Treg/CD4^+$	5.26 (0.47, 10.84)	0.362	1.137 (0.863, 1.498)
$CD8^+/CD3^+$	44.11 (38.87, 49.35)	0.589	0.981 (0.917, 1.050)
$PD\text{-}1^+/CD8^+$	29.83 (6.96, 67.17)	0.044	0.954 (0.911, 0.999)
$Tsen/CD8^+$	29.09 (14.05, 60.71)	0.047	1.076 (1.001, 1.158)
$CD19^+/CD45^+$	2.67 (0.09, 10.87)	0.351	0.831 (0.563, 1.226)
$CD16^-CD56^{hi}/CD45^+$	0.15 (0.04, 0.38)	0.4	0.030 (0.000, 106.074)
$CD16^+CD56^{dim}/CD45^+$	3.94 (0.05, 27.89)	0.273	1.068 (0.949, 1.202)
$CD14^+/CD45^+$	0.37 (0.02, 0.82)	0.856	0.724 (0.022, 23.783)
$cDC/CD45^+$	0.22 (0.18, 0.26)	0.695	0.685 (0.104, 4.524)
$pDC/CD45^+$	0.11 (0.00, 0.22)	0.628	13.168 (0.000, 441,304.246)

PFS, progression-free survival.

$CD8^+$ T cells was nominally associated with shorter PFS (Table 4). Neither association met the Bonferroni-adjusted significance threshold (adjusted alpha = 0.007). Because of the small sample, multiple comparisons, and wide confidence intervals, these analyses are exploratory and cannot establish predictive biomarkers.

Further analysis using the maximum selection test to determine the cut-off values for these two cell populations and Kaplan–Meier analysis revealed that patients with a high proportion of $CD8^+PD\text{-}1^+$ T cells (>40.47%) in the peripheral blood before treatment had longer PFS (p = 0.011, Fig. 6A). In contrast, patients with a high proportion of senescent $CD8^+$ T cells (>40.46%) had shorter PFS (p = 0.001, Fig. 6B). Because the cutoffs were selected from the same small dataset (n = 12), these estimates are highly susceptible to overfitting and false-positive findings. They should be considered hypothesis-generating and require prospective validation in an independent cohort; they do not demonstrate that either cell population predicts benefit from DCVAC.

4. Discussion

The tumor microenvironment of ovarian epithelial cancer is characterized by a scarcity of immune cells, which limits the efficacy of immunotherapy [17]. Tumor-infiltrating DCs in ovarian cancer remain inadequately activated [18]. Studies have suggested that type I DCs in lymph nodes can recruit T cells that are truly capable of mounting an immune response into the tumor microenvironment. However, as tumors progress, these type I DCs are gradually depleted [19]. Therefore, enhancing dendritic cell function through DCVACs holds promise for improving T-cell reactivity via antigen presentation, thereby strengthening antitumor immunity. In this study, DC maturation was

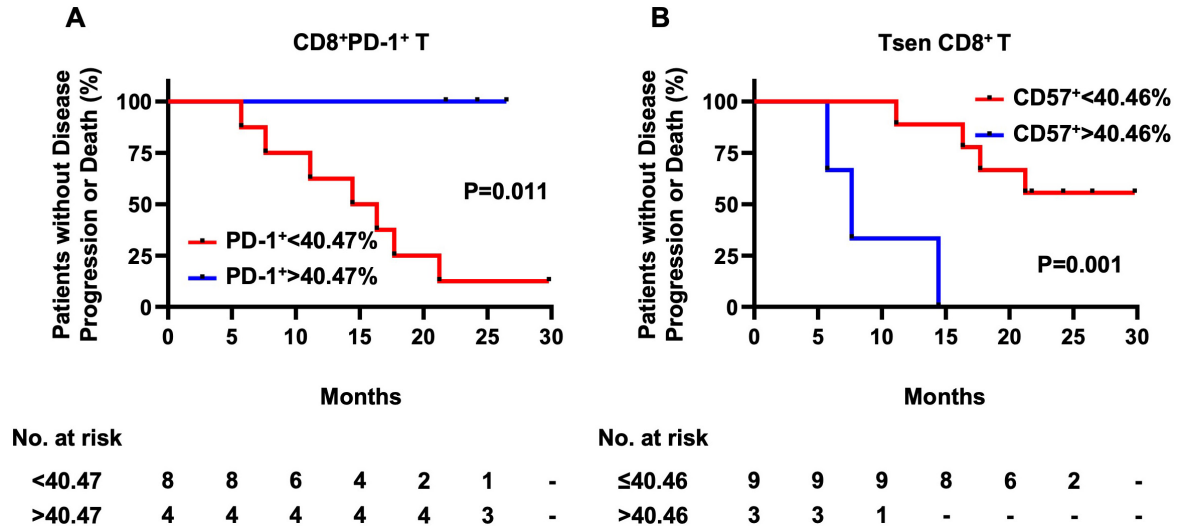


Fig. 6. Survival analysis for patients grouped according to the proportions of $CD8^+PD\text{-}1^+$ T cells and senescent $CD8^+$ T cells. (A) PFS of patients according to the proportion of $CD8^+PD\text{-}1^+$ T cells. (B) PFS of patients according to the proportion of Tsen $CD8^+$ T cells.

induced *in vitro* using whole tumor antigens. The advantage of this approach is that DCs can recognize and present antigens characteristic of ovarian cancer. However, the limitation is that these cells cannot target individualized cancer cell antigens in patients. Since there are differences in neoantigens on the surface of tumor cells among different patients, the effects of DCVACs may not be the same across a population. This is also the reason why current clinical trials are being performed to facilitate the design of personalized tumor neoantigen vaccines.

This exploratory study demonstrated an acceptable safety profile of DCVACs as maintenance therapy after first-line chemotherapy in patients with ovarian cancer. The main adverse events reported were abdominal pain, bloating, elevated TSH levels, and lymphopenia, most of which were graded as 1–2 according to CTCAE v5.0 grade. These findings are consistent with the safety conclusions from other clinical trials of DCVACs in solid tumors [20,21,22], including ovarian cancer [23,24].

The primary mITT analysis did not demonstrate a PFS benefit with DCVAC compared with placebo (HR 0.9746, 95% CI 0.3294–2.883; $p = 0.9629$). Total treatment exposure was not analyzed in relation to PFS because participants had to remain progression-free and clinically eligible to receive additional doses; a naive comparison by dose count would therefore be vulnerable to guarantee-time (immortal-time) bias. No landmark analysis or time-dependent Cox model was prespecified or performed, and no dose-response interpretation is made.

The participant with unresectable fused para-aortic lymph nodes had radiographically stable residual disease during study treatment and an observed PFS of 29.6 months. Disease progression occurred approximately 6 months after the final infusion. This single clinical course is presented only as an illustrative observation. It cannot establish causality or efficacy, is susceptible to selection and survivorship bias, and should not be generalized to other patients.

The immune analyses were intended to describe pharmacodynamic changes and generate hypotheses regarding candidate biomarkers. Numerical changes in circulating immune-cell populations were based on only four paired samples and were not statistically significant after multiplicity correction. The baseline biomarker analysis included 12 DCVAC-treated participants, and the data-driven cutoff analyses were performed in the same small dataset. Accordingly, the observed associations involving $CD8^+PD\text{-}1^+$ and senescent $CD8^+$ T cells may reflect sparse-data bias, overfitting, or chance. These findings do not establish a mechanism of action, predictive value, or a population likely to benefit from DCVAC and require independent prospective validation.

Previous clinical studies on DCVACs have focused primarily on two aspects of vaccine reactivity: (1) the immune response of the human body after the application of DCVACs and (2) the identification of immune biomarkers of the DCVAC response, which are used for monitoring vaccine efficacy or selecting the most suitable population [25]. In addition to detecting well-recognized antitumor immune cells such as T cells, DCs, and NK cells in the enrolled patients, we also analyzed different T-cell subtypes. The purpose of this study was to describe the immunoreactivity of DCVACs and explore potential immune biomarkers. Tumors induce T-cell exhaustion to achieve immune evasion, and exhausted T cells express a variety of immune checkpoint molecules, including PD-1. Tumor immune checkpoint inhibitors can block this process to exert antitumor effects. T-cell senescence is distinct from T-cell exhaustion and is characterized by the downregulation of the costimulatory molecules CD27 and CD28 and the upregulation

of CD57, KLRG-1, and CD45RA [26]. Our previous research revealed that ovarian cancer primary lesions and ascites exhibit a senescent T-cell phenotype and that patients with higher levels of senescent T cells tend to have poorer survival outcomes [27]. This study suggest that the high proportion of $CD8^+PD\text{-}1^+$ T cells and a low proportion of senescent $CD8^+$ T cells in the peripheral blood before treatment might be a potential biomarker to better response to DC vaccine therapy, which still requires prospective validation in an independent cohort. These findings further potentially support the conclusions of basic research, indicating that DCVACs may enhance the antitumor function of exhausted T cells to exert antitumor effects. In contrast, patients with a significant senescent T-cell phenotype have a limited response to treatment, and there is currently a lack of therapeutic strategies to combat T-cell senescence. Therefore, activated and senescent T-cell subsets are promising immune biomarkers for selecting the most suitable population for DCVAC therapy.

Limitations

Although this study explored the safety, efficacy, and immunoreactivity of DCVACs in ovarian cancer, the following limitations still exist: (1) Due to the small sample size of the enrolled patients, nearly half of the patients received the drug 2–7 times, and the treatment duration was less than half a year; (2) the study did not stipulate that PARPi, bevacizumab, or other small molecule antiangiogenic drugs could not be used during the treatment with the study drug, which may have introduced confounding factors; (3) during the study period, the number of paired blood samples collected from patients before and after treatment was insufficient, resulting in a small number of samples for immunological analysis; and (4) all enrolled patients underwent tumor debulking surgery, with most achieving R0 resection, making it difficult to detect changes in immune cells in the tumor tissue lesions. Therefore, this study only assessed changes in immune biomarkers in the peripheral blood of patients, which is not sufficient to verify a stable correlation between changes in immune cells in the peripheral blood and those in the tissue.

5. Conclusions

The DCVAC in this study has a good safety profile as maintenance therapy after first-line chemotherapy in patients with ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. The adverse events, graded according to the CTCAE _5.0, are mainly at levels 1–2 and include abdominal pain, leukopenia, and elevated TSH.

The primary mITT analysis did not demonstrate a significant PFS difference between DCVAC and placebo (HR 0.9746, 95% CI 0.3294–2.883; $p = 0.9629$). The *BRCA*-mutation-type subgroup result was based on sparse data, did not remain statistically significant after the prespecified multiplicity correction, and must not be interpreted as evidence of treatment benefit.

Exploratory immune analyses showed numerical changes in circulating immune-cell populations, but the paired analysis included only four participants and no change remained statistically significant after multiplicity correction. Associations between baseline $CD8^+PD\text{-}1^+$ or senescent $CD8^+$ T-cell proportions and PFS were evaluated in only 12 participants using data-driven cutoffs. These findings are hypothesis-generating, are not validated predictive biomarkers, and require confirmation in larger prospective studies.

Availability of Data and Materials

Core data for this study are provided in the main figures and tables. Extra data can be accessed by contacting the corresponding authors with a reasonable inquiry.

Author Contributions

YL and HG designed the clinical study. XZ, YG, ZW, QH and CH performed the research. TH performed the experiments. XZ and TH analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All participants provided written informed consent before entering the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Peking University Third Hospital (Project ID: M2020002, Approval No: 2020 027-02), and all methods were performed in accordance with the relevant guidelines and regulations.

Acknowledgment

We appreciate research assistant Nan Wang for her efforts to collect data. We thank all individuals who participated in this study.

Funding

This study was supported by the National Natural Science Foundation of China (82372888), Capital's Funds for Health Improvement and Research (No.2020-2-4098), Beijing Natural Science Foundation (L248051), and the Key Clinical Project of Peking University Third Hospital (BYSYZD2021006).

Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/CEOG55362.

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