Dendritic cell vaccine (DCVAC) combined with chemotherapy in patients with newly diagnosed epithelial ovarian carcinoma after primary debulking surgery: biomarker exploratory analysis of a phase 2, open-label, randomized, multicenter trial (SOV01, NCT02107937)

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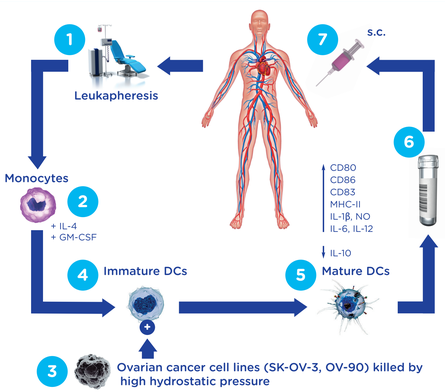
Background:

Most patients with epithelial ovarian cancer (EOC) relapse despite primary debulking surgery and subsequent chemotherapy. Autologous dendritic cell immunotherapy (DCVAC/OvCa) contains dendritic cells loaded with antigens derived from EOC cells. We hypothesized that the addition of DCVAC/OvCa to platinum-based chemotherapy (CMT) stimulates antitumor immunity and may prolong progression-free survival (PFS) and overall survival (OS).

DCVAC/OvCa manufacturing process:

1. Patient visits leukapheretic center
2. Monocytes are separated
3. Ovarian carcinoma cell lines are killed by high hydrostatic pressure to induce immunogenic cell death
4. Immature DCs were co-cultured with killed tumor cells and maturation of DCs is induced
5. Dendritic cells are activated
6. ~18 doses of DCVAC/OvCa are produced and frozen
7. Patient completes DCVAC treatment



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Primary objective:

- To compare the efficacy of DCVAC/OvCa + CMT in a parallel or sequential setting vs. CMT only in patients with FIGO stage III EOC, as measured by PFS

Key secondary, safety & exploratory objectives:

- OS
- To explore predictive and prognostic biomarkers
- To determine the safety profile of DCVAC/OvCa

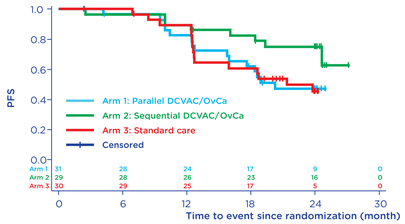
Methods:

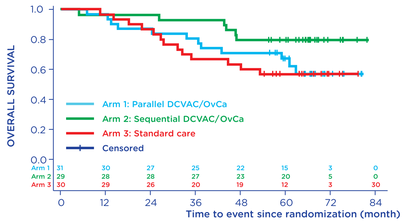
- Efficacy and safety of DCVAC/OvCa in newly diagnosed FIGO stage III EOC patients after cytoreductive surgery were investigated. Patients were randomized in a 1:1:1 ratio to one of the following groups:
  - Parallel DCVAC: DCVAC/OvCa concomitantly (in parallel) added to CMT
  - Sequential DCVAC: DCVAC/OvCa sequentially added to CMT
  - Standard of Care (SoC): CMT only
- All patients received SoC CMT: paclitaxel 175 mg/m^2, followed by carboplatin AUC 5–7: 6 cycles in total.
- Patients in the parallel and sequential DCVAC/OvCa groups underwent leukapheresis within 7 days of randomization and received ≤10 doses of DCVAC/OvCa: the initial 5 doses given q3 wks and the remaining 5 doses q6 wks. Each DCVAC/OvCa dose contained approximately 10M autologous dendritic cells.
- The presence of CD8$^+$ T cells in the tumor samples at baseline was determined by immunohistochemistry. CD8$^+$ T-cell density was quantified in whole tumor sections using Calopix® software (Tribvn Healthcare). Patients with CD8$^+$ T-cell counts ≤30 CD8$^+$ T cells/mm^2 are considered to show low tumor immunity (CD8^{Lo}) and are expected to have a worse prognosis compared to patients with CD8$^+$ T-cell counts of >30 CD8$^+$ T cells/mm^2 (CD8^{Hi}).

Comparison of efficacy (PFS and OS)

PFS	Parallel DCVAC	Sequential DCVAC	SoC
Patient count	31	29	30
Median time (months)	20.3	NA	21.4
Comparison vs. SoC arm			
HR estimate	0.98	0.39	
HR 95% CI	(0.48; 2.00)	(0.16; 0.96)	
Log-rank p-value	0.9483	0.0336	

OS	Parallel DCVAC	Sequential DCVAC	SoC
Patient count	31	29	30
Median time (months)	NA	NA	NA
Comparison vs. SoC arm			
HR estimate	0.84	0.40	
HR 95% CI	(0.38; 1.84)	(0.15; 1.06)	
Log-rank p-value	0.6631	0.0557	

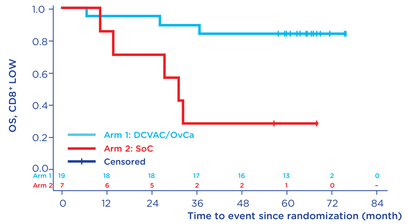


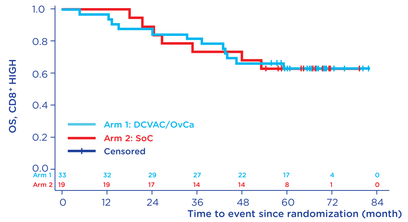


OS results in CD8^{Lo} and CD8^{Hi} patients

OS low CD8$^+$ T-cell levels	DCVAC	SoC
Patient count	19	7
Median time (months)	NA	31.2
Comparison vs. SoC arm		
HR estimate	0.15	
HR 95% CI	(0.04; 0.65)	
Log-rank p-value	0.0038	

OS high CD8$^+$ T-cell levels	DCVAC	SoC
Patient count	33	19
Median time (months)	NA	NA
Comparison vs. SoC arm		
HR estimate	0.99	
HR 95% CI	(0.39; 2.52)	
Log-rank p-value	0.9830	





Results:

- From November 2013 through March 2016, 99 patients were randomized. At the final analysis, the modified intention-to-treat (mITT) population (primary analysis population of all randomized patients except those in the DCVAC/OvCa groups who failed to receive ≥1 dose of DCVAC/OvCa) included: 31 patients in parallel DCVAC, 29 patients in sequential DCVAC, and 30 patients in SoC groups.
- Baseline characteristics and DCVAC/OvCa exposure were well-balanced between the groups.
- PFS benefit in the sequential DCVAC/OvCa group was statistically significant (p=0.034) compared to the SoC group, with a demonstrable trend in OS. Median OS was not reached in either group at the time of 66 mths median follow-up (34% of events).
- CD8^{Lo} patients in the parallel and sequential DCVAC/OvCa groups showed significantly improved clinical outcomes compared to patients in the CD8^{Lo} SoC group: a median PFS gain of 6 mths (19 vs. 13 mths) and a robust OS gain (median not reached vs. 31 mths) were observed, with minimal difference between the DCVAC/OvCa groups. This improvement with DCVAC/OvCa was not seen in CD8^{Hi} patients. The OS results were confirmed in the intention-to-treat population.
- DCVAC/OvCa showed a good safety profile with 8 DCVAC/OvCa-related adverse events (Grade 1-2) in a total of 4 patients, as per investigator's judgement.

Patients' baseline characteristics:

Characteristics, mITT population (all randomized patients except those in the DCVAC/OvCa groups who failed to receive at least 1 dose of DCVAC/OvCa; primary population)	Statistic	Parallel DCVAC (N=31)	Sequential DCVAC (N=29)	SoC (N=30)
Age at randomization (derived) [years]	n	31	29	30
	Mean (StD)	58.7 (12)	55.8 (11.4)	61.3 (7.5)
	Median	61.7	55.9	62.3
Type of epithelial ovarian cancer	n	31	29	30
Endometrioid	n (%)	2 (6.5%)	6 (20.7%)	1 (3.3%)
Mucinous	n (%)	1 (3.2%)	0	0
Serous	n (%)	28 (90.3%)	23 (79.3%)	29 (96.7%)
Post-surgery residual lesion	n	31	29	30
Maximal residuum <1 cm	n (%)	4 (12.9%)	5 (17.2%)	5 (16.7%)
Zero residuum	n (%)	27 (87.1%)	24 (82.8%)	25 (83.3%)
CD8$^+$ T-cell count/mm^2 in tumor tissue (collected as exploratory characteristic)	n	29	23	26
	Mean (StD)	91 (147.9)	198.6 (252.4)	117.4 (116)
	Median	40.4	110.5	85.5

Conclusions:

- Treatment with DCVAC/OvCa was shown to be safe and to significantly improve PFS in optimally debulked EOC patients.
- In a subset of patients with a low CD8$^+$ T-cell tumor tissue density, the treatment with DCVAC/OvCa led to a significantly improved OS and a gain of 6 mths in PFS compared to the SoC group.
- DCVAC/OvCa was shown to promote anticancer immunity, particularly in patients with cold tumors, as indicated by low CD8$^+$ T-cell density.

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