Dendritic Cell Vaccine With Chemotherapy In Patients With Epithelial Ovarian Carcinoma After Primary Debulking Surgery

Interim Analysis Of A Phase 2, Open-label, Randomized, Multicenter Trial

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Ovarian Cancer: Introduction

22,400 NEW CASES
14,070 DEATHS
UNITED STATES 2018¹

44,784 NEW CASES
31,504 DEATHS
EUROPEAN UNION (EU28) 2018²

~70% of Stage III/IV patients will relapse despite optimal surgery and CHT

¹ American Cancer Society: Cancer Facts and Figures 2018. Atlanta, Ga: American Cancer Society, 2018
² ECIS - European Cancer Information System; From https://ecis.jrc.ec.europa.eu, accessed on 24/05/2018 © European union, 2018
Patient visits leukapheresis centre

Monocytes are separated

Ovarian carcinoma cell lines are killed by high hydrostatic pressure to induce immunogenic cell death

Immature DCs are mixed with killed tumor cells and maturation of DCs is induced

Kloudova et al., Oncotarget, 2016; 7(29):46120-46126
Fucikova et al., J Transl Med., 2011; 9:223

Ovarian cancer cell lines (SK-OV-3, OV-90) killed by high hydrostatic pressure
Fucikova et al., Int. J. Cancer, 135, 2014: 1165-1177
Adkins et al., OncoImmunology, 2014: 3:12
Tumor Cell Lines Were Selected To Match The Antigen Profile in Primary Tumors

RELATIVE mRNA EXPRESSION OF 21 TAAS IN CANCER CELL LINES, PRIMARY TUMOR CELLS AND CONTROL OVCA TISSUE

qPCR results

Relative mRNA expression

Publication: Kloudova et al., Oncotarget, 2016
Matured DCs are prepared

~18 doses of DCVAC/OvCa are produced and frozen

Patient completes DCVAC treatment

Kloudova et al., Oncotarget, 2016; 7(29):46120-46126
Fucikova et al., J Transl Med., 2011; 9:223

Ovarian cancer cell lines (SK-OV-3, OV-90) killed by high hydrostatic pressure
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Adkins et al., OncoImmunology, 2014: 3:12
Study Design in First-Line Setting

Epithelial cancer of the ovary, fallopian tube and peritoneum:
- FIGO stage III
- Serous, endometrioid, or mucinous
- PS 0 - 2
- <1 cm max. residuum
- No prior systemic therapy

Randomization 1:1:1
Stratification: 0 vs <1 cm

Treatment Arm A:
- Chemotherapy +
- Concomitant DCVAC/OvCa

Treatment Arm B:
- Chemotherapy +
- Maintenance DCVAC/OvCa

Treatment Arm C:
- Chemotherapy

Endpoints:
- Primary: PFS at 2 years after randomization
- Secondary: OS, PFI BIO CA-125, AEs

Study Treatments:
- 6 Cycles: Carboplatin (AUC 5-7) + Paclitaxel (175mg/m²)
- 10 Doses: DCVAC/OvCa (1 x 10⁷ DCs/dose)

R=randomization; PFI=progression-free interval
Hypothesis For The Study Design

RATIONALE FOR CONCOMITANT

Concomitant chemotherapy targets tumor-induced immune suppression.

Immune system partially recovered after each chemotherapy cycle

RATIONALE FOR MAINTENANCE

Minimal tumor burden after chemotherapy sets the optimal conditions for immune stimulation.

Immune system fully recovered after completing cytotoxic therapy
Analysis Populations

**ITT**
All patients randomized

n = 99

**mITT**
Patients who received ≥1 dose of therapy with post-baseline endpoint assessment

n = 92

**PP**
Patients who received ≥8 doses of DCVAC/OvCa and/or ≥3 cycles of chemotherapy

n = 87
## Treatment Exposure

### No Difference in Treatment Exposure in All Arms

<table>
<thead>
<tr>
<th>INDICATOR</th>
<th>ARM A n = 31</th>
<th>ARM B n = 30</th>
<th>ARM C n = 31</th>
</tr>
</thead>
<tbody>
<tr>
<td>N of 1st-line CHT cycles: mean ± SD, median (min - max)</td>
<td>5.90 ± 0.40, 6 (4-6)</td>
<td>5.80 ± 0.76, 6 (3-6)</td>
<td>5.68 ± 1.14, 6 (0-6)</td>
</tr>
<tr>
<td>N of 1st-line CHT non-responders: n (%)</td>
<td>1 (3.23%)</td>
<td>1 (3.33%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>N of DCVAC/OvCa doses: mean ± SD, median (min - max)</td>
<td>9.61 ± 1.43, 10 (3-10)</td>
<td>9.47 ± 2.03, 10 (2-10)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>N of pts with DCVAC/OvCa continued beyond progression and administered together with 2nd-line CHT: n (%)</td>
<td>3 (9.68%)</td>
<td>3 (10.00%)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Types of 2nd-line CHT started before completion of DCVAC/OvCa1</td>
<td>1 patient: doxorubicin &amp; liposomal doxorubicin 1 patient: doxorubicin &amp; gemcitabine 1 patient: topotecan</td>
<td>1 patient: doxorubicin &amp; carboplatin 1 patient: cisplatin &amp; doxorubicin &amp; endoxan 1 patient: gemcitabine monotherapy</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

1 The number provided to each second-line therapy listed shows the number of patients with the particular treatment.
Baseline Characteristics in ITT

Known Prognostic Factors Are Balanced in All Arms (Also Comparable in mITT and PP)

<table>
<thead>
<tr>
<th>INDICATOR GROUP</th>
<th>INDICATOR</th>
<th>ARM A (n = 34)</th>
<th>ARM B (n = 34)</th>
<th>ARM C (n = 31)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>Median age (years)</td>
<td>61.5</td>
<td>57.5</td>
<td>62.0</td>
<td>0.49</td>
</tr>
<tr>
<td>RESIDUAL DISEASE</td>
<td>R0 (n, %)</td>
<td>29 (85%)</td>
<td>29 (85%)</td>
<td>26 (84%)</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>R1 (n, %)</td>
<td>5 (15%)</td>
<td>5 (15%)</td>
<td>5 (16%)</td>
<td></td>
</tr>
<tr>
<td>HISTOLOGY GRADE</td>
<td>High-grade tumors (n, %)</td>
<td>23 (74%)</td>
<td>22 (81%)</td>
<td>21 (87%)</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td>Lower-grade tumors (n, %)</td>
<td>8 (26%)</td>
<td>5 (19%)</td>
<td>3 (13%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Collection in progress (n)</td>
<td>3</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>HISTOLOGY TYPE</td>
<td>Endometrioid (n, %)</td>
<td>2 (6%)</td>
<td>6 (18%)</td>
<td>1 (3%)</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Serous (n, %)</td>
<td>31 (91%)</td>
<td>28 (82%)</td>
<td>30 (97%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mucinous (n, %)</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>CA 125</td>
<td>CA-125 baseline median (kU/L)</td>
<td>73.5</td>
<td>86.9</td>
<td>99.2</td>
<td>0.33</td>
</tr>
<tr>
<td>ECOG</td>
<td>0 (n, %)</td>
<td>17 (50%)</td>
<td>18 (53%)</td>
<td>20 (64%)</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>1 (n, %)</td>
<td>12 (35%)</td>
<td>12 (35%)</td>
<td>8 (26%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (n, %)</td>
<td>5 (15%)</td>
<td>4 (12%)</td>
<td>3 (10%)</td>
<td></td>
</tr>
</tbody>
</table>
PFS

~ 6-month Benefit in mPFS and 57% Decrease in The Hazard of Progression in Arm B

**2-Year PFS Rate (%)**

- **mITT**
  - Arm A: 51.6
  - Arm B: 30
  - Arm C: 45.2

- **PP**
  - Arm A: 51.7
  - Arm B: 25
  - Arm C: 46.7

**Median (months)**

- **mITT**
  - Arm A: 18.3
  - Arm B: 24.3
  - Arm C: 18.6

- **PP**
  - Arm A: 20
  - Arm B: NE
  - Arm C: 18.6

**Arms Comparison**

- **Arm B vs. Arm C**
  - **mITT**: 0.43 (0.18-1.03) 0.05
  - **PP**: 0.32 (0.12-0.83) 0.01

- **Arm A vs. Arm C**
  - **mITT**: 0.64 (0.20-2.04) 0.45
  - **PP**: 1.01 (0.49-2.09) 0.98

**Median Follow-up**: 26.8 months
**PFI\textsubscript{BIO} (Based on CA-125 Elevations)**

**PFI\textsubscript{BIO} Supporting PFS Benefit**

<table>
<thead>
<tr>
<th>PFI\textsubscript{BIO}</th>
<th>ARM A</th>
<th>ARM B</th>
<th>ARM C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient count</strong></td>
<td>31</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>(\cdot) \text{mITT}</td>
<td>29</td>
<td>28</td>
<td>30</td>
</tr>
<tr>
<td>(\cdot) \text{PP}</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Events**             |       |       |       |
| \(\cdot\) \text{mITT} | 16    | 9     | 14    |
| \(\cdot\) \text{PP}   | 15    | 7     | 14    |

| **Median (months)**    |       |       |       |
| \(\cdot\) \text{mITT} | 18.3  | \text{NE} | \text{NE} |
| \(\cdot\) \text{PP}   | 20    | \text{NE} | \text{NE} |

| **INDICATOR**          | HR    | 95% CI | p-value |
| B vs. C                | 0.48  | 0.21-1.12 | 0.08   |
| \(\cdot\) \text{mITT} | 0.37  | 0.15-0.93 | 0.03   |
| \(\cdot\) \text{PP}   | 1.06  | 0.52-2.17 | 0.88   |
| A vs. C                |       |       |       |
| \(\cdot\) \text{mITT} | 0.99  | 0.48-2.06 | 0.98   |
| \(\cdot\) \text{PP}   |       |       |       |

**MEDIAN FOLLOW-UP:** 26.8 months

- **ARM A:** chemotherapy + concomitant DCVAC/OvCa
- **ARM B:** chemotherapy + maintenance DCVAC/OvCa
- **ARM C:** chemotherapy only
- Censored

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Presented at: 2018 ASCO Annual Meeting
Presented by: Lukas Rob
A Trend Towards Improved OS in Arm B

**Patient count**
- mITT: ARM A: 31, ARM B: 30, ARM C: 31
- PP: ARM A: 29, ARM B: 28, ARM C: 30

**Events**
- mITT: ARM A: 5, ARM B: 1, ARM C: 7
- PP: ARM A: 4, ARM B: 0, ARM C: 7

**Median (months)**
- mITT: NE, NE, NE
- PP: NE, NE, NE

**INDICATOR**
<table>
<thead>
<tr>
<th>B vs. C</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mITT</td>
<td>0.13</td>
<td>0.02-1.08</td>
<td>0.03</td>
</tr>
<tr>
<td>PP</td>
<td>0.00</td>
<td>0-NE</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**A vs. C**
- mITT: 0.64 | 0.20-2.04 | 0.45
- PP: 0.51 | 0.15-1.76 | 0.28
## Adverse Events Causally-Related to DCVAC/OvCa (Per Investigator)

### DCVAC/OvCa Has A Favorable Safety Profile

<table>
<thead>
<tr>
<th>AE PREFERRED TERM</th>
<th>Severity (CTCAE grade v4.03)</th>
<th>ARM A Parallel DCVAC/OvCa (N=34)</th>
<th>ARM B Sequential DCVAC/OvCa (N=32)</th>
<th>ARM C Standard of Care (N=30)</th>
<th>Total (N=96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation</td>
<td>Grade 1</td>
<td>1 (2.9%)</td>
<td>-</td>
<td>N/A</td>
<td>1 (1.0%)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>Grade 1</td>
<td>-</td>
<td>1 (3.1%)</td>
<td>N/A</td>
<td>1 (1.0%)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>Grade 1</td>
<td>-</td>
<td>1 (3.1%)</td>
<td>N/A</td>
<td>1 (1.0%)</td>
</tr>
<tr>
<td>Drug hypersensitivity</td>
<td>Grade 2</td>
<td>-</td>
<td>1 (3.1%)</td>
<td>N/A</td>
<td>1 (1.0%)</td>
</tr>
<tr>
<td>Erythema</td>
<td>Grade 1</td>
<td>1 (2.9%)</td>
<td>-</td>
<td>N/A</td>
<td>1 (1.0%)</td>
</tr>
</tbody>
</table>
Summary

01 Maintenance DCVAC/OvCa showed a gain of ~6 months in mPFS

02 Maintenance DCVAC/OvCa showed 57% reduction in risk for progression or death

03 Current data for OS are trending in the same direction as PFS

04 DCVAC/OvCa is well tolerated

05 Results warrant further assessment by expanding Arms B and C and a Phase III trial being planned