Ovarian carcinoma is one of the most chemoresistant solid tumors and early stage patients are most responsive to treatment, with a response rate of 60-90% depending on the aggressiveness of the disease. However, despite improvements to the standard of care over the past three decades, almost all patients with advanced stage disease at presentation will relapse, with a median progression-free survival (PFS) of only 16-18 months. Therefore, there are still significant unmet needs in limiting ovarian cancer patients. There is an opportunity to develop a successful therapeutic vaccine against ovarian cancer, particularly one that would work in concert with existing therapies to provide clinical benefits. Hence the current study evaluated the immunostimulatory capacity of a novel cancer vaccine consisting of Survivin peptides in a patient vaccinated delivery and enhancement platform called Depoval™.

Clinical trial Design

The following study is a Phase 1, multi-center, non-randomized, open label, controlled, dose finding and safety cohort (n=18) study for the evaluation of a therapeutic vaccine, DPX-Survivac with low dose cyclophosphamide, in patients with surgically operable or advanced stage ovarian, fallopian tube or peritoneal cancer. An adaptive clinical design was applied in order to maintain a low phase 1, primarily safety focused trial, finding safety and immunological evaluation of two dose levels of DPX-Survivac with low dose metronomic cyclophosphamide given once a week and one week off.

The primary objective of the study was to determine the safety profile of a subcutaneous administration of DPX-Survivac, and determine the optimal dose in conjunction with cyclophosphamide.

The secondary objective was to measure the vaccine-induced anti-cancer immunity. Immunovaccine Services was contracted to comprehensively monitor blood processing at the clinical sites (n=15) and analyze the cell-mediated immune response to the Survivin epitope peptides in peripheral blood at pre- and post-vaccination time points of enrolled subjects (n=18), NCT03141809.

Investigational Drug: DPX-Survivac

DPX-Survivac is a Survivin-targeted multi-epitope therapeutic cancer vaccine. As Survivin is a critical molecule for cancer cell survival and highly associated with many types of tumor cells, it is considered a universal cancer antigen. Ovarian cancer cells are known to over-express Survivin, which is correlated with poor prognosis.

- Antigens: Survivin (24 epitopes) and Survivin (24) nonpeptides covering 85% of the North American population
- T-helper epitopes: B-cell and T-cell responses to Survivin-derived peptides
- Universal T-helper Epitope
- Uposomes
- Interferon-γ Adjuvant
- Montanide ISA51-VG

Table 1: Selective dose response of peptides and nonpeptides covering 85% of the North American population

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Dose Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivin</td>
<td>High (100 µg)</td>
</tr>
<tr>
<td>Survivin</td>
<td>Medium (50 µg)</td>
</tr>
<tr>
<td>Survivin</td>
<td>Low (25 µg)</td>
</tr>
</tbody>
</table>

Ex vivo frequency of Survivin-specific CD8+ T cells significantly increased in Cohort C

Selective expansion of Survivin-specific CD8+ T cells from PBMC following a 10-day in vitro culture (Ag+IL-2+IL-15).

DPX Survivac generates polyfunctional cancer-specific CD8+ T cells with the potential for cytotoxic anti-tumor immunity

Vaccination with DPX-Survivac (high dose) with low dose cyclophosphamide (Cohort C):

I. Generates strong cancer-specific CD8+ T cells detectable in the peripheral blood
II. Produces significant levels of Survivin-specific CD8+ T cells capable of detecting Survivin
III. Induces polyfunctional (triple- and double-cytokine producing), Survivin-specific CD8+ T cells which persist as central memory T cells
IV. Elicits strong CTL anti-tumor immunity, based on the expression of cytokine markers Granulocyte B and CD207a
V. Generates CD4 T helper responses, which is known to aid in enhancing the CD8-dependent anti-tumor immunity
VI. Induces no major changes in the frequency of total CD25+ or activated CD25+Foxp3+ regulatory T cells, but show a decreasing trend in absolute Treg cell numbers (data not shown)
VII. Low dose Cyclophosphamide enhances the immunogenicity of DPX-Survivac in cohort C, given that cohort A also received the same dose of vaccine

Conclusions

- Vaccination with DPX-Survivac (high dose) with low dose cyclophosphamide in Cohort C:
- Generates strong cancer-specific CD8+ T cells detectable in the peripheral blood.
- Produces significant levels of Survivin-specific CD8+ T cells capable of detecting Survivin.
- Induces polyfunctional (triple- and double-cytokine producing), Survivin-specific CD8+ T cells which persist as central memory T cells.
- Elicits strong CTL anti-tumor immunity, based on the expression of cytokine markers Granulocyte B and CD207a.
- Generates CD4 T helper responses, which is known to aid in enhancing the CD8-dependent anti-tumor immunity.
- Induces no major changes in the frequency of total CD25+ or activated CD25+Foxp3+ regulatory T cells, but show a decreasing trend in absolute Treg cell numbers (data not shown).
- Low dose Cyclophosphamide enhances the immunogenicity of DPX-Survivac in cohort C, given that cohort A also received the same dose of vaccine.

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