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TITLE: A Phase 2 study of Pembrolizumab (MK-3475), DPX-Survivac Vaccine and low dose of Cyclophosphamide combination in patients with advanced ovarian, primary peritoneal or fallopian tube cancer.

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Investigational Agents: Pembrolizumab (MK-3475), DPX-Survivac, Cyclophosphamide

SCHEMA

Dose Escalation phase

Platinum resistant epithelial ovarian, fallopian tube, primary peritoneal cancer with evidence of disease progression.

- All histologies allowed
- Available archival tumor sample
- Unlimited previous chemotherapy lines
- Measurable disease
- ECOG 0-1

Dose level 1
Pembrolizumab: 200 mg/3wks/IV
DPX-Survivac: One 0.25 mL priming dose/6wks plus 0.25 mL boosting doses/6 wks.
Cyclophosphamide 50 mg BID will be taken orally, 7 days before first vaccination, then continuing for 7 days off and 7 days on each cycle

Objectives:
Primary: Efficacy Secondary: Safety
ORR (CT every 6 weeks)
Correlative studies (biopsy requested)

Dose level 2
Pembrolizumab: 200 mg/3wks/IV
DPX-Survivac: One 0.25 mL priming dose/6wks plus 0.5 mL boosting doses/6 wks.
Cyclophosphamide 50 mg BID will be taken orally, 7 days before first vaccination, then continuing for 7 days off and 7 days on each cycle

Dose Expansion phase

Epithelial ovarian, fallopian tube, primary peritoneal cancer with evidence of disease progression.

- All histologies allowed
- Available archival tumor sample
- Measurable disease
- ECOG 0-1

Cohort A: 10 Platinum-sensitive high grade serous or endometriod patients, no more than 4 prior lines of chemotherapy

Cohort B: 10 Platinum-resistant high grade serous or endometriod patients, no more than 4 prior lines of chemotherapy

Cohort C: 10 patients with other epithelial subtypes, irrespective of prior therapy and platinum free interval

Objectives:
Primary: Efficacy
Secondary: Safety
ORR (CT every 6 weeks)
Correlative studies (Biopsy requested)

SYNOPSIS

Title of study: A phase 2 study of Pembrolizumab (MK-3475), DPX-Survivac Vaccine and low dose Cyclophosphamide combination in patients with advanced ovarian, primary peritoneal or fallopian tube cancer.

Objectives:

Primary Objectives:

- To evaluate the clinical anti-tumor activity of Pembrolizumab, DPX-Survivac vaccine and oral Cyclophosphamide combination based on overall response rates (ORR) as assessed by RECIST 1.1 criteria in patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer.

Secondary Objectives:

- To assess the safety and recommended phase two dose of the combination of Pembrolizumab, DPX-Survivac and oral cyclophosphamide in ovarian cancer.
- To assess whether the clinical anti-tumor activity of Pembrolizumab, DPX-Survivac vaccine and oral Cyclophosphamide combination based on ORR assessed by RECIST 1.1 criteria is different in patients with platinum-sensitive and platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer.
- To assess the efficacy of Pembrolizumab, DPX-Survivac vaccine and oral Cyclophosphamide combination in terms of overall response rate by immune related criteria guidelines (iRECIST)[1].
- To evaluate Progression Free Survival (PFS) and Overall Survival (OS) in patients with platinum-sensitive (PFI $\geq$6 months) and platinum resistant disease (PFI<6months).

Exploratory Objectives:

- To assess PD-L1 expression levels in epithelial ovarian, fallopian tube and primary peritoneal cancers patients and to determine whether PD-L1 expression correlates with efficacy endpoints (ORR and PFS).
- To explore activity in clear cell, mucinous and low grade serous or endometrioid ovarian subtypes.
- To explore changes in immune cell subsets in the peripheral circulation and tumor microenvironment during treatment with Pembrolizumab, DPX-Survivac vaccine and oral Cyclophosphamide.

Study Design:

This trial is a multi-center phase 2 study assessing the feasibility of Pembolizumab, DPX-Survivac vaccine and oral Cyclophosphamide combination in patients with advanced epithelial ovarian, fallopian tube and primary peritoneal cancer. A dose escalation phase is planned to define the toxicity profile, select a recommended dose for further evaluation in an expanded population (dose expansion phase) and to assess preliminary signal of activity in correlation with translational studies. This escalation cohort will include approximately 9-12 patients with recurrent platinum resistant epithelial ovarian, fallopian tube or primary peritoneal cancer, regardless PD-L1 expression. Following the escalation phase, if the

combination is well tolerated and shows early signals of activity, a follow up dose expansion phase will be proposed. In the dose expansion phase, 30 patients will be enrolled across three independent cohorts as follows:

- Cohort A: Platinum-sensitive patients with high-grade serous or endometrioid tumor subtypes (treated at RP2D)
- Cohort B: Platinum-resistant patients with high-grade serous or endometrioid tumor subtypes (treated at RP2D)
- Cohort C: An exploratory cohort allowing for the enrollment of recurrent advanced epithelial ovarian, fallopian tube and primary peritoneal patients with uncommon tumor histologies, including clear cell, mucinous and low grade serous or low grade endometrioid ovarian subtypes.

Safety profile will be defined monitoring incidence, grading and duration of adverse events according to NCI Common Terminology Criteria for Adverse Event (CTCAE) version 4.03. Treatment efficacy will be evaluated every 6 weeks (42 days ±7 days) with radiographic imaging to assess response to treatment according to RECIST 1.1 and iRECIST criteria. Treatment with Pembrolizumab, DPX-Survivac vaccine and oral Cyclophosphamide will continue until documented disease progression as per RECIST1.1, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements or administrative reasons. Patients will have tumor and blood sample collected at serial time points to investigate changes in genomic and immune landscape of tumors treated with combination of Pembrolizumab, DPX-Survivac vaccine and low dose oral Cyclophosphamide.

Patients will have image-guided fresh tumor core needle biopsy at a maximum of three time points:
1) prior to day 1 cycle 1 of Pembrolizumab, DPX-Survivac immunovaccine and Cyclophosphamide;
2) on day 15 of cycle 1 (± 7 days);
3) at radiological confirmed disease progression.

Opportunistic biopsy or cytology sample from fluid collection (ascites, pleural effusion or cystic lesion) could be used for exploratory analysis.

Biopsy at time point 1) and 2) are mandatory; biopsy at time point 3) is optional.
Peripheral blood mononuclear cells (PBMCs) and serum will be obtained by phlebotomy at baseline and at several time points during investigational treatment (see section 9)

Number of patients: The escalation cohort will include approximately 9-12 patients with recurrent platinum resistant epithelial ovarian, fallopian tube or primary peritoneal cancer, regardless of PD-L1 expression. Additional patients may be included as per PI discretion for a comprehensive safety review or to confirm RP2D.Following the escalation phase, if the combination is well tolerated a follow up dose expansion phase will be proposed. Thirty patients will be included in three independent cohorts (platinum sensitive patients, cohort A; platinum resistant patients, cohort B; and uncommon tumor histologies, including clear cell, mucinous,

low grade serous or low grade endometrioid ovarian subtypes, cohort C) treated at the recommended Phase 2 dose.

Main Criteria for Inclusion/Exclusion

Inclusion Criteria:

- Patients must have histologically or cytologically confirmed advanced epithelial ovarian, primary peritoneal or fallopian tube carcinomas. All histological subtypes are allowed in the Dose Escalation phase. Whilst all subtypes will be allowed in the Dose Expansion Phase, outcome statistics will be calculated based on patients with high-grade serous or endometrioid ovarian cancer. Patients with non-high grade serous or endometrioid ovarian cancer will be considered as part of an exploratory cohort.
- Patients must have radiologically documented disease progression from their prior line of therapy.
- Patients must have measurable disease based on RECIST 1.1. See section 10 for definition of measurable disease. NOTE: tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions. Patient with single lesion could be enrolled if in the opinion of the investigator the biopsy will not interfere with evaluation of response.
- Have received a front line platinum-based regimen (administered via either IV or IP) following primary or interval debulking surgery with documented disease recurrence.
- Eastern Cooperative Group (ECOG) performance status ≤ 1 (see Appendix A).
- Life expectancy greater than 16 weeks.
- Availability of archival tumor tissue samples. Additional samples may be requested if tumor tissue provided is not adequate for quality and/or quantity as assessed by the laboratory.
- Be willing to provide tumor tissue from a newly obtained core or excisional biopsy prior to start treatment and on day 15 of cycle 1. Newly-obtained biopsy is defined as a specimen obtained up 28 days prior to initiation of treatment on Day 1. Additional samples may be requested if tumor tissue provided is not adequate for quality and/or quantity as assessed by the laboratory.
- Have fulfilled the following additional requirements regarding prior treatments depending on the cohort that the subject is to be enrolled in.

Dose Escalation phase:
There is no limit to the number of prior treatment regimens. Patients must be platinum-resistant, defined as having a platinum-free interval (PFI) of <6 months to the last platinum-based regimen.

Dose Expansion phase:

– High grade or endometrioid platinum-sensitive patients: have received no more than 4 previous lines of chemotherapy and must have a platinum-free interval (PFI) of ≥ 6 months to the last platinum-based regimen. Targeted therapies, hormonal therapies and maintenance therapies do not count toward prior lines.
– High grade or endometrioid platinum-resistant patients: have received no more than 4 previous lines of chemotherapy and must have a platinum-free interval (PFI) of <6 months to the last platinum-based regimen. Targeted therapies, hormonal therapies and

maintenance therapies do not count toward prior lines.

– Non-high grade serous or endometrioid patients: there is no limit to the number of prior treatment regimens, or restrictions based on platinum sensitivity.
NOTE: PFI is defined as the time elapsed between the last dose of platinum and the date of documented evidence of disease progression.

Exclusion Criteria:

-Patients who are receiving any other investigational agents.
-Diagnosis of immunodeficiency or therapy with systemic steroid or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
-History of autoimmune disease, such as but not restricted to, rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematous, ankylosing spondylitis, scleroderma, or multiple sclerosis requiring treatment within the last two years. Patients with vitiligo or diabetes are not excluded.
-Patients with history of thyroiditis within 5 years. Subjects with remote history (greater than 5 years) of thyroiditis are not excluded.
-Patients with known history of active TB (Bacillus Tuberculosis).
-Patients with known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
-Hypersensitivity to Pembrolizumab, DPX-Survivac immunovaccine, Cyclophosphamide or any of their excipients.
-Patients that have received a live vaccine within 30 days of planned start of study therapy. NOTE: No adjuvanted vaccine or live attenuated vaccine (such as Flumist) should be given while on this study. Non-adjuvanted vaccines (such as most influenza vaccines) can be given.
-Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2 agent or DPX-Survivac vaccine. Prior anti-CTLA4 agents are allowed. Prior therapy with T-cell co-stimulatory agents (e.g. anti-CD137 antibody, anti-OX40 antibody) are allowed.

Intervention:

Treatment with Pembrolizumab, DPX-Survivac vaccine and oral Cyclophosphamide will continue until documented disease progression as per RECIST 1.1, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements or administrative reasons.

Correlatives:

- To explore changes in immune cell subsets in the peripheral circulation and tumor microenvironment during treatment with Pembrolizumab, DPX-Survivac vaccine and oral Cyclophosphamide.
- To characterize the tumor microenvironment for immune-related features such as immune-related mRNA expression signatures, presence of tumor infiltrating T lymphocytes (TILs), PD-L1/PD-L2 expression, and to characterize genetic

changes/aberrations and mutational burdens within tumor tissues in patients with advanced epithelial ovarian, fallopian tube and primary peritoneal tumors during Pembrolizumab, DPX-Survivac vaccine and oral Cyclophosphamide treatment, and to perform a thorough immunological response evaluation.
Statistics: During the dose escalation phase a 3 + 3 design will be applied and the dose level will be considered safe if 0 or 1 dose limiting toxicities (DLTs) occur in 6 subjects. A subject will be considered evaluable for safety if treated with at least one immunization and one Pembrolizumab dose. This phase will be conducted with two escalating dose levels and one de-escalation dose level. Adverse events will be reported detailing frequency and severity according to NCI CTCA version 4.03. The dose escalation phase will enroll approximately 9-12 patients (additional patients as per PI discretion may be enrolled) and 30 patients will be enrolled in the dose expansion phase to further analyze safety and to define preliminary efficacy of Pembrolizumab, DPX Survivac and Cyclophosphamide combination. The treatment efficacy will be defined based on overall response rate as per RECIST 1.1 criteria. The signal of activity for the expansion phase will be at least 3/10 partial response or stable disease for 12 weeks according RECIST 1.1 for the platinum-sensitive group and 2/10 for the platinum-resistant group.

Dose Escalation Schedule			
Dose Level	**Dose***		
	Pembrolizumab (mg)	***DPX-Survivac***	***Cyclophosphamide (mg)***
Level -1	200	One 0.1 mL priming doses/6 weeks plus 0.1 mL boosting doses/6 weeks apart	Cyclophosphamide 50 mg BID will be taken orally, 7 days before first vaccination, then continuing for 7 days off and 7 days on each cycle ensuring Cyclophosphamide is always given in the week preceding a Boosting dose of DPX-Survivac
Level 1	200	One 0.25 mL priming dose/6 weeks plus 0.25 mL boosting doses/6 weeks apart	Cyclophosphamide 50 mg BID will be taken orally, 7 days before first vaccination, then continuing for 7 days off and 7 days on each cycle ensuring Cyclophosphamide is always given in the week preceding a Boosting dose of DPX-Survivac
Level 2	200	One 0.25 mL priming dose/6 weeks plus 0.5 mL boosting doses/6 weeks apart	Cyclophosphamide 50 mg BID will be taken orally, 7 days before first vaccination, then continuing for 7 days off and 7 days on each cycle ensuring Cyclophosphamide is always given in the week preceding a Boosting dose of DPX-Survivac
**Doses are stated as exact dose in units (*e.g., *mg/m^2, mcg/kg, etc.) rather than as a percentage.*			

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1. OBJECTIVES AND ENDPOINTS

1.1 Study Objectives

1.1.1 Primary Objectives

To evaluate the clinical anti-tumor activity of Pembrolizumab, DPX-Survivac vaccine and oral Cyclophosphamide combination based on overall response rates (ORR) as assessed by RECIST 1.1 criteria in patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer.

1.1.2 Secondary Objectives

- To assess the safety and recommended phase two dose of the combination of Pembrolizumab, DPX-Survivac and oral cyclophosphamide in ovarian cancer. To assess whether the clinical anti-tumor activity of Pembrolizumab, DPX-Survivac vaccine and oral Cyclophosphamide combination based on ORR assessed by RECIST 1.1 criteria is different in patients with platinum-sensitive and platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer.
- To assess the efficacy of Pembrolizumab, DPX-Survivac vaccine and oral Cyclophosphamide combination in terms of overall response rate by immune criteria guidelines (iRECIST)[1].
- To evaluate Progression Free Survival (PFS) and Overall Survival (OS) in patients with platinum-sensitive (PFI $\geq$6 months) and platinum resistant disease (PFI<6months).

1.1.3 Exploratory Objectives

- To assess PD-L1 expression levels in epithelial ovarian, fallopian tube and primary peritoneal cancers patients and to determine whether PD-L1 expression correlates with efficacy endpoints (response rate and progression free survival).
- To explore activity in clear cell, mucinous, low grade serous and low grade endometrioid ovarian subtypes.
- To explore changes in immune cell subsets in the peripheral circulation and tumor microenvironment during treatment with Pembrolizumab, DPX-Survivac vaccine and oral Cyclophosphamide.

1.2 Study Endpoints

1.2.1 Primary Endpoint

- Overall response rate (ORR): ORR will be based on the disease evaluation by investigator assessment per RECIST 1.1

1.2.2 Secondary Endpoints

- Safety - adverse event reporting. The following safety parameters will be analyzed: adverse events and serious adverse events graded per NCI CTCAE version 4.03 criteria, casualty and outcome, clinical significant changes in laboratory values and vital signs since baseline, treatment discontinuation and reason for discontinuation, death and cause of death.
- Overall response rate (ORR) defined by immune related RECIST (iRECIST)[1].
- Progression free survival (PFS): from start of study treatment to time of progression as per

iRECIST or death, whichever comes first.
- Overall survival (OS): from start of study treatment until death for every cause.

1.2.3 Exploratory Endpoints
- Difference in ORR and PFS between patients with PD-L1 positive tumors and patients with PD-L1 negative tumors.
- ORR, PFS and OS at in patients with clear cell, mucinous, low grade serous and low grade endometrioid ovarian subtypes.

2. BACKGROUND AND STUDY RATIONALE

2.1 Disease Background

2.1.1 Epidemiology and histologic categorization of ovarian cancer

Ovarian cancer is the most lethal gynecologic cancer and the fifth-leading cause of cancer death among women in the United States (US). In the US, the estimated number of new cases and deaths from ovarian cancer in 2016 was 22,280 and 14,240 respectively[2]. Contributing to high mortality rates, the absence of tumor-specific signs and symptoms, no effective screening tests for early detection, more than 70% of ovarian cancer patients are typically diagnosed at advanced stages[3]. Based on data from the United States between 2003 and 2009, at the time of initial diagnosis, 61% of patients had distant metastasis, 18% had regional disease and 21% had localized disease. The overall 5-year survival rate of ovarian cancer was 44% counting all stages; the 5-year survival rate in patients with distant metastasis was only 27%[4].

Epithelial ovarian cancer (EOC) accounts for >90% of all subtypes of ovarian cancer and has been recognized as a group of heterogeneous diseases with distinct histopathologic features, genetic alterations and clinical behaviors[5]. Five main EOC subtypes have been designated by The International Federation of Gynecology and Obstetrics (FIGO): high-grade serous carcinoma (HGSOC, accounts for ± 70% EOC), endometrioid carcinoma (EC, ± 10% EOC), clear cell carcinoma (CCC, ± 10% EOC), mucinous carcinoma (MC, ± 3% EOC), low grade serous carcinoma (LGSC, ± 5% EOC), and those that are unclassificable[6]. Primary peritoneal carcinoma and fallopian tube carcinoma have typically been managed and studied together with EOC as they share similar clinic-pathologic characteristics in HGSOC.

2.1.2 Current standard treatment and area with unmet medical need

The standard primary treatment for advanced EOC include primary cytoreductive/debulking surgery followed by postoperative front line (i.e., adjuvant) systemic treatment with carboplatin and paclitaxel Q3W IV for 6 cycles. However, weekly paclitaxel has also been frequently used to replace Q3W paclitaxel[7,8]. In suitable cases, postoperative chemotherapy usually cisplatin plus paclitaxel, can be delivered via intraperitoneal (IP) route. If the objective of complete debulking surgery is not feasible upfront, neoadjuvant therapy can be given prior cytoreductive surgery (i.e. interval cytoreductive surgery) followed by standard platinum/taxane-based chemotherapy[9],[10].
The goal of cytoreductive surgery is to achieve resection of all visible tumors and the goals of

postoperative first line chemotherapy are to help achieve complete remission in those with residual disease and to prevent disease recurrence for those with complete tumor resection. However, after first line therapy, only a small proportion of patients will achieve long-term disease-free status. In a meta-analysis performed by du Bois et al.[11] on data from three randomized trials following standard primary treatment with surgery and platinum-taxane based chemotherapy (N=3126), only 24% of patients were recurrent free after a median follow up time of 53.9 months and the remaining 76% had disease recurred or progressed. The overall 5-year PFS and OS rate was 22.6% and 39%, respectively. Based on time to recurrence (TTR) since the last dose of platinum treatment, 22% of patients recurred after 0-6 months, 22.5% recurred after 6-12 months, and 31.6% recurred after more than 12 months. The 12-month survival rate was 30.6%, 55.1% and 66.1% in the group with TTR 0-6 months, TTR 6-12 months, and TTR> 12 months, respectively. The 24-month survival rate was 13.8%, 24.4% and 34.9% in these three groups, respectively. Collectively, this data showed an overall poor prognosis for patients with recurrent disease especially in those with a short time to recurrence.

Despite the improvement in the efficacy of available treatments, recurrent ovarian cancer is still not curable with the available choices of therapies and remains an area of unmet medical need. Selection of treatment for recurrent ovarian cancer should take into consideration several factors including: sensitivity to first line platinum-based therapy, as measured by platinum-free interval (PFI), prior toxicities, comorbidity, age and performance status. PFI, which is defined as the period from the last dose of platinum-based chemotherapy to disease recurrence or progression, has been recognized as an important surrogate for prognosis and predicting response to chemotherapy. Based on PFI, recurrent ovarian cancer can be divided into the following subgroups: platinum-sensitive (PFI $\geq$ 6 months), platinum-resistant (PFI < 6 months) and platinum-refractory (PFI $\leq$ 4 weeks or progression on treatment) according to the consensus achieved by the GCIG in 2010[12].

Based on the current National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines, patients with platinum-resistant recurrence can be treated with single agent chemotherapy, such as gemcitabine, pegylated liposomal doxorubicin (PLD), weekly paclitaxel, topotecan and docetaxel, or the combination of bevacizumab PLD, weekly paclitaxel or topotecan[8,9]. These different monochemotherapies have shown similar clinical efficacy with a response rate around 15-20%, median PFS of 3-5 months and median OS of 10-12 months[13],[14]. When bevacizumab was associated to single agent chemotherapy in the randomized Phase III AURELIA trial, PFS was improved by approximately 3 months compared to single agent chemotherapy alone (6.7 vs 3.4 months, HR: 0.48, p<0.001), and ORR improved (27.3% vs 11.8%)[15]. However, the study did not demonstrate OS benefit, and based on the Kaplan-Meier curve, less than 20% of subjects in the bevacizumab chemotherapy arm remained progression-free by 12 months, and even less in the single agent chemotherapy arm. In addition, in a meta-analysis by Hanker et al.[16] characterizing the impact of second to sixth line of therapy on survival of recurrent ovarian cancer, data on 1620 patients from three large randomized phase III trials investigating primary therapy showed that median PFS after the first, second, third, fourth and fifth relapse was 10.2 [95% confidence interval (CI) 9.6-10.7], 6.4 (5.9-7.0), 5.6 (4.8-6.2), 4.4 (3.7-4.9) and 4.1 (3.0-5.1) months, respectively. Median OS after the first, second, third, fourth and fifth relapse was 17.6 (95% CI 16.4-18.6), 11.3 (10.4-12.9), 8.9 (7.8-9.9), 6.2 (5.1-7.7), 5.0 (3.8-10.4) months, respectively. The overall clinical benefit greatly reduced with increased lines of therapy.
As can be seen, relapsed ovarian cancer and particularly platinum-resistant ovarian cancer is an area with high unmet medical need for novel therapies that can deliver durable clinical benefit and improve

prognosis of these patients.

2.1.3 Targeting PD-1 immune checkpoints for ovarian cancer treatment

Different preclinical data have shown that an intact immune surveillance is needed to control the tumor transformation and growth[17]. In different solid tumors the presence of tumor-infiltrating lymphocytes (TILs) particularly CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells correlates with better prognosis[18].
The immune response is activated trough cancer antigen recognition by T cell receptor (TCR) and regulated by a balance between co-stimulatory and inhibitory signals[19,20]. The inhibitory pathways, also called immune checkpoints, are crucial for maintaining self-tolerance and prevent autoimmunity and minimizing collateral tissue damage when the immune system is activated in response to pathogens. Two different immune-checkpoint receptors have been extensively studied in the last years: cytotoxic T-lymphocyte-associated antigen 4 (CTLA4 or CD152) and programmed cell death protein 1 (PD-1 or CD279).
PD-1 (encoded by the gene Pdcd1) is expressed on the cell surface of activated T-cells as well as 'exhausted' T cells and negatively regulates antigen receptor signaling upon engagement of its ligands (programmed cell death ligand 1 and/or 2, PD-L1 and/or PD-L2)[21]. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 in peripheral tissues. Although normal tissues express little (if any) PD-L1, a variety of cancers were demonstrated to express this T-cell inhibitor[22]. PDL-1 is overexpressed in almost 60% of all EOC, and its expression has been associated with worse prognosis and peritoneal dissemination[23,24]. In order to escape immune system control, tumours dysregulate the expression of immune-check point proteins inducing immune resistance[25].

Restoration of endogenous anti-cancer immunity by immune checkpoint blockade has thus become an attractive strategy for cancer therapy. The success in the clinical development of immune checkpoint inhibitors, in particular the PD-L1 inhibitors, has significantly changed the landscape of cancer treatment, including ovarian, fallopian tube and primary peritoneal tumors[26].

2.1.4 Ovarian tumor associated antigens

The initial characterization of ovarian-tumor-associated antigens (TAAs) specifically recognized by the host immune system, eliciting spontaneous antitumor immune response suggested ovarian cancer as an immunogenic tumor. The role of immune surveillance has been documented with the detection of tumor-reactive T-cells directed against TAAs in peripheral blood, ascites and TILs, showing that the immune response is an independent prognostic factor correlated with clinical outcomes in ovarian cancer patients[27,28]. Among the most studied TAAs, Survivin has emerged as a promising target[29]. Survivin is overexpressed in 90% of epithelial ovarian tumors with limited expression in normal tissues and acts preventing cancer cells immune detection and promoting tumor progression, apoptosis inhibition and mitosis responses to cellular stress, including responses to cancer therapeutics[30,31].

2.1.5 Overcoming resistance to anti-PD-1 inhibitors

The inhibition of an immune checkpoint protein, such as PD-1, will be able to induce tumor regression if there has been a previous antitumor immune response that can be reactivated when the pathway is blocked with anti PD-1.
The development of novel strategies to overcome emerging resistances to anti-PD-1 antibodies is a new paradigm in immunotherapy. Preclinical combination of anti-PD-1 antibodies and tumor-specific peptides vaccines have showed promising synergism leads to tumor regression and anti-PD-1 resistance overcoming through vaccine generated CD8+T-cells expansion in tumor microenvironment[32]. DPX-Survivac vaccine is a lipid-based depot formulation that contains peptides derived from the protein sequence of Survivin. DPX-Survivac enhances cellular immune responses, eliciting a cytotoxic T lymphocyte response against tumor cells presenting the Survivin peptides on HLA class I molecules. DPX-Survivac is currently being investigated in a phase Ib study (NCT01416038) limited to ovarian cancer as maintenance therapy. Preliminary data showed robust immune responses maintained by subsequent vaccinations. Interestingly, low dose Cyclophosphamide enhanced the immunogenicity of DPX-Survivac by reducing the number and function of tumor-infiltrated Tregs and antigen specific CD8+/CD4+ T cells response[33,34,35].

This study aims to assess the feasibility of the addition of anti-PD-1 treatment (Pembrolizumab-MK-3475) with DPX-Survivac immunovaccine and low dose of Cyclophosphamide in patients with advanced epithelial EOC, fallopian tube and primary peritoneal tumors.

2.2 Investigational Agents

2.2.1 Keytruda™ (Pembrolizumab; MK-3475)

Pembrolizumab is a potent and highly selective IgG4/kappa isotype humanized monoclonal antibody (mAb) that acts blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (Pembrolizumab; MK-3475) has been approved in the United States for the treatment of patients with unresectable or metastatic melanoma and disease progression following Ipilimumab or BRAF inhibitor, if BRAF V600 was present and for the treatment of patients with metastatic non small cell lung cancer (NSCLC) whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Considering previous randomized data, no significant differences in terms of efficacy and safety between Pembrolizumab doses of 10 mg/kg Q3W and 2 mg/kg Q3W were observed, defining the recommended Pembrolizumab dose as a flat dose of 200mg administered every 3 weeks[36,37,38]. Furthermore, a correlation between response rate, progression free survival and PD-L1 expression has been suggested and warrants further investigations[39].

Table 2.1 – Pembrolizumab activity in various tumor types

Tumor type	Sample size	PD-L1 status	Objective response	Stable disease or PFS/OS
Advanced Squamous cell carcinoma of head and neck (SCCHN)[40]	192	Both + and -	Overall =17.7% HPV+ =21.9% HPV- =15.9%	SD=17% Median OS 8.5 months
Advanced Triple Negative Breast Cancer (TNBC)[41]	32	+	PR=16.1%	SD=9.7%

Advanced Epithelial Ovarian Cancer (EOC)[42]	26	+	Overall =11.5% CR=3.8%	SD=23.1%
Advanced Metastatic Melanoma (MM)[43]	834	Both + and -	Overall Q2W=33.7% Q3W=32.9%	Median PFS Q2W= 5.5mo Q3W=4.1mo 1-year survival Q2W=74.1% Q3W=68.4%

Pembrolizumab clinical activity in advanced ovarian cancer

Study Keynote 028 (KN028) is an on-going Phase Ib open-label, non-randomized multi-cohort study evaluating clinical activity of Pembrolizumab monotherapy 10 mg/kg Q2W in advanced solid tumors. A cohort of 26 subjects with advanced EOC that have failed prior chemotherapies was included[41]. All enrolled subjects had tumors positive for PD-L1 expression, which was defined as ≥ 1% of cells in tumor nests or PD-L1+ bands in stroma as determined by a prototype immunohistochemistry (IHC) assay at a central laboratory. Mean (standard deviation) age was 58.1 years, 84.6% received prior therapies for recurrent/metastatic disease (38.5% received ≥ 5 therapies), and 50% received prior adjuvant therapies. The best ORR (confirmed) was 11.5% (n=3/26,95% CI: 2.4,30.2); one subject achieved complete response (CR) and 2 subjects experienced partial response (PR). Six out of 26 subjects (23.1%) achieved stable disease. As of clinical cutoff of 04 August 2015, the 3 responders and 1 subject with stable disease (SD) were still on Pembrolizumab treatment without progression: one subject was still ongoing for >46 weeks and 3 were still ongoing for >52 weeks. Another subject with SD showed progression at 48 weeks. In a retrospective analysis, subjects were separated into two subgroups based on treatment-free interval (TFI) between the last dose of their last anti-cancer regimen and the first dose of Pembrolizumab. In the subgroup with TFI of < 3 months (n=15), there were 2SDs, including the on-going SD, with no responders; in the subgroup with TFI ≥3 months (n=11), there were 3 responders and 3 SDs including the SD that progressed at 48 weeks.

2.2.2 DPX-Survivac

DPX-Survivac vaccine is a prophylactic/therapeutic vaccine platform that combine a vaccine against Survivin antigen with a lipid-based depot able to enhance and maintain cellular immune response after repeated immunization[44]. DPX also includes an adjuvant and T-helper peptide to enhance and sustain the immune response. DPX-Survivac vaccine containing one decapeptide and four nonapeptides derived from the protein sequence of survivin. The five peptides have different HLA restrictions (HLA-A1, A2, A3, A24, B7), and this combination covers approximately 85% of the North American population (Table 2.2).

Table 2.2: Five survivin peptides in DPX-Survivac

Name	Sequence	Restriction	% of Population
SurA1.T	FTELTLGEF	HLA-A1	11-27%
SurA2.M	LMLGEFLKL	HLA-A2	22-46%
SurA3.K	RISTFKNWPK	HLA-A3	14-24%
SurA24	STFKNWPFL	HLA-A24	12-24%
SurB7	LPPAWQPFL	HLA-B7	13-18%

The presumed primary mechanism of action of DPX-Survivac is to elicit a cytotoxic T lymphocyte response against tumor cells presenting the survivin peptides on HLA class I molecules. These peptides were initially developed by Merck KGaA as Survivac (EMD640744, which used a Montanide ISA51 VG emulsion). This product was tested in a Phase 1 clinical trial (EMR-200032-001) that enrolled 53 patients with advanced solid tumors to evaluate the immunogenicity (primary endpoint) and safety of multiple weekly injections of increasing doses of Survivac in Montanide ISA51 VG. There was evidence of vaccine induced T cell responses. Adverse events possibly or likely related to EMD640744 were mild to moderate (grade 2-3) and mostly represented injection site reactions and there were no reports of autoimmunity[45].

2.2.3 Cyclophosphamide and combination with DPX-Survivac

The poor efficacy of cancer vaccines has been related to the immunosuppressive environment present in cancer patients. Cancer cells can activate regulatory T (Tregs) cells that inhibit the anti-tumor T cells induced by vaccination[46]. Immuno-modulated strategy can help to overcome this immunosuppressive environment. Metronomic administration of Cyclophosphamide inhibits immunosuppressive Tregs and enhance the vaccine efficacy[47,48].
This treatment regimen has low toxicity and the most common adverse events are leukopenia, lymphopenia, thrombocytopenia, anemia, fatigue, nausea and vomiting[49,50,51].

A phase 1/2 trial (ONC-DPX-Survivac-01) trial assessing safety and immune response with combination of DPX-Survivac and metronomic oral Cyclophosphamide (50 mg bid) in three different patient cohort (cohort A with 0.5 mL of DPX-Survivac, B 0.1 mL of DPX-Survivac plus Cyclophosphamide, and cohort C with 0.5 mL of DPX-Survivac plus Cyclophosphamide). Six patient in each cohort received all three scheduled vaccinations three weeks apart. The treatment has demonstrated good tolerability without relevant side effects other than G1-2 injection site reactions and three G3 ulceration. This study showed that an antigen specific immune response was triggered with one or two vaccinations and following boosting were necessary to maintain this response. An increase immune response has been identified in the cohort with cyclophosphamide and there has been a dose-related immune-response, with higher responses in cohort C where higher dose of DPX-Survivac has been used[52]. The immune-response elicited with this combination was characterized by increased level of CD4+ and CD8+ but no significant change in Treg cells or MDSC (myeloid-derived suppressor cells).
Another Phase 1b clinical trial (ONC-DPX Survivac 03) is currently ongoing assessing extending doses of DPX-Survivac vaccine and low dose oral Cyclophosphamide as maintenance treatment for patients with ovarian, fallopian tube or primary peritoneal cancer. Patients has been enrolled in five different cohorts: 1 with two 0.25 mL priming dose three weeks apart administered in the same upper tight region followed by 4 0.1 mL boosting dose 8 weeks apart; cohort 2 same as cohort 1 but boosting dose was

administered in opposite upper tights; cohort 3 three 0.25 mL doses 8 weeks apart; cohort 4 two 0.25 mL priming doses plus three 0.25 mL boosting doses 6 weeks apart; cohort 5 two 0.25 mL priming dose plus 0.5 mL boosting dose 4 weeks apart. In each cohort patients received also low dose Cyclophosphamide. Subjects treated in cohort 1 and 2 a stronger immune response has been observed. In other cohort patients received priming dose with a longer interval time and this has caused a less intense immune response. In this trial the interval between subsequent vaccine injection has been extended in order to reduce the incidence of injection site reactions (ISR) seen in the previous study. In case of significant ISR dose omission was allowed. No significant adverse events other than ISR or ulceration has been recorded[53]. Auto-immunity toxicity could be possible with this treatment, but at the moment any patient treated with DPX-Survivac has shown this type of adverse event.

2.3 Rationale

2.3.1 Rationale for drugs combination

Even though over 70%-80% of patients with advanced ovarian cancer (stage III and IV) will be in remission following the primary treatment, majority of them will relapse within 3 years. Currently, there is no curative treatment available for recurrent ovarian cancer, that still represents an area of high unmet medical need. Patients with recurrent ovarian cancer respond to platinum-based or non-platinum based therapies with varied response rate; however, responses are mostly short-lived, especially in the setting with a PFI within 12 months. Even though some patients will receive multiple lines of treatment, they will eventually develop refractory disease and die due to increasing resistance. Treatment-related toxicities can be overwhelming especially for those who receive combination chemotherapy[15]. In addition to extending survival and delaying symptomatic disease progression, the goal of treatment in this setting also includes improving quality of life. Novel agents that can deliver curative or long-lasting anti-cancer effect with good tolerability are highly needed in this setting.
Increase number of CD8+ TILs have been associated with better prognosis in ovarian cancer[19]. However, the presence of intra tumour regulatory T cells (CD4+/CD25/FoxP3) that suppressed anti-tumour response, correlated with significantly shorter overall survival in ovarian cancer[54]. Additionaly, different tumour antigens are expressed by ovarian cancer cells representing possible target to develop vaccine strategies. PD-1 and its receptor PD-L1 play an important role in the interaction between tumour-specific T cells and tumour cells. Antibodies against PD-1 and PD-L1 can block this interaction and activate an anti-tumour response. In 20 ovarian cancer patients treated with the anti PD-1 agent Nivolumab the disease control rate was 45%[55]. Another phase I study with the anti PD-L1 antibody Avelumab showed a 54.7% of disease control rate in 75 patients with relapsed or refractory ovarian cancer[56].

The anti PD-1 antibody Pembrolizumab has shown preliminary activity in a small cohort of advanced ovarian cancer patients in Study KN028[41]. Most subjects were heavily pretreated and chemo-refractory. Even though the observed response rate was relatively low (11.8%), 3 subjects with PRs and 1 subject with SD were observed and still on Pembrolizumab treatment for >48 weeks without progressive disease as of 04 August 2015, the clinical cutoff for this dataset.
However, most of the patients had progressed and their diseases were resistant to Pembrolizumab treatment. The development of novel strategies to overcome the emerging resistances to anti-PD-1 antibodies is a new paradigm in immunotherapy. Preclinical combination of anti-PD-1 antibodies and tumour-specific peptides vaccines have showed promising synergism leads to tumour regression and

anti-PD-1 resistance overcoming through vaccine generated CD8+T-cells expansion in tumour microenvironment[57].

DPX-Survivac vaccine is a lipid-based depot formulation that contains peptides derived from the protein sequence of Survivin. DPX-Survivac enhances cellular immune responses, eliciting a cytotoxic T lymphocyte response against tumour cells presenting the Survivin peptides on HLA class I molecules. Preliminary data showed robust immune responses were maintained by subsequent vaccinations. Interestingly, low dose Cyclophosphamide enhanced the immunogenicity of DPX-Survivac by reducing the number and function of tumour-infiltrated T_{regs} and antigen specific CD8+/CD4+ T cells response[51]. Immune vaccine did not show significant benefit in the treatment of cancer, mainly related to the immune suppressive environment typically found in different type of cancer.

Combining check point inhibitors and vaccine could result in an increase stimulation of effector T cells activity combined with inhibitions of T regs, causing a potential immune response able to induce significant tumour responses and prolong progression free survival in ovarian cancer patients.

2.3.2 Rational for immune-related RECIST (iRECIST)

Immunotherapeutic agents such as Pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with these agents may extend beyond the typical time course of response seen with cytotoxic agents, and a clinical response may occur after an initial increase in tumor burden or even the appearance of new lesions (“flare effect” or pseudoprogression). Standard RECIST 1.1 may not provide an accurate response assessment of immunotherapeutic agents such as Pembrolizumab. Based on analysis of patients with melanoma enrolled in Keynote-001, 7% of evaluable patients experienced delayed or early tumor pseudoprogression. Of note, patients who had progressive disease by RECIST 1.1 but not by immune related Response Criteria had longer OS than patients with progressive disease by both criteria. Additionally, RECIST 1.1 criteria may underestimate the benefit of Pembrolizumab in approximately 15% of patients[58]. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical response with immunotherapy and enable treatment beyond initial radiographic progression.

Immune-RECIST (iRECIST) is RECIST 1.1 adapted to account for the unique tumor response seen with immuno-therapeutics as described by Seymour et al[1].

At the time of first disease progression according to RECIST 1.1 by radiologic imaging assessment, it is at the Investigator’s discretion to continue with trial treatment based on the clinical status of the patient (see Table 10.1) while awaiting radiologic local site confirmation of progression as assessed by repeat imaging ≥4 weeks later.

2.4 Correlative Studies Background

2.4.1 Tumor-based Biomarker Research

2.4.1.1 DNA/RNA Sequencing

To determine genomic correlatives associated with combination immunotherapy treatment, we will assess genomic alterations in tumor tissue. This will be done to determine predictive factors for response by sequencing of archival tumor tissue (or 1st tumor biopsy), and potentially compare genomic changes post treatment (via analysis of 2nd tumor biopsy). This analysis will be conducted by integrated targeted or whole exome/genome sequencing, as deemed appropriate.

2.4.1.2 Tumor immune marker expression

A comprehensive analysis of the tumor microenvironment will be performed and comparison between on-treatment and pre-treatment will help elucidate changes induced by treatment with Pembrolizumab, DPX-Survivac and Cyclophosphamide treatment. Tumor samples will be obtained at baseline and during treatment (as well as optionally on progression). Core biopsies or, when possible, excisional biopsies will be performed. For this analysis tumor samples will be prepared for IHC (formalin fixed, paraffin embedded). Fresh tissues will also be digested enzymatically into a single-cell suspension for immune phenotyping by multiparameter flow cytometry/CyTOF analysis. Exploratory analysis by IHC may include characterization of immune cell populations and assessment of tumor microenvironment. Additional characterization of tumor infiltrating lymphocytes using *in vitro* immunological assays may also be performed.

At the Applied Molecular Profiling Laboratory (AMPL)/Drug Development Biomarker Laboratory (DDBL), led by Dr. Ming Tsao, we have optimized IHC methods and use standard operating procedures (SOP) to use an automated slide staining platform (Benchmark XT module from Ventana Medical Systems, Inc.) for PD-L1 using the antibodies E1L3N (Cell Signaling) and SP142 (Ventana). The diagnostic assay for Pembrolizumab is the DAKO 22C3, which requires a DAKO autostainer and EnVision FLEX + HRP-Polymer kit to perform [59]. In this study, samples will be sent to QualTek for PD-L1 testing using DAKO 22C3. We will also be performing PD-L1 staining in AMPL/DDBL using our in-house optimized assay. The comparison of the two sets of results will be considered exploratory. AMPL/DDBL has also optimized staining for additional immune-markers including IDO, CD4, CD8, CD3 and FOXP3, using the Ventana BenckMark stainer. In addition, the expression of Survivin, one of the most studied TAAs, which is overexpressed in 90% of epithelial ovarian tumors with limited expression in normal tissues, will be assessed. An antibody to Survivin (Novus, NB500-201) has also been optimized at AMPL. The automation offers high volume output combined with consistent and high-quality staining results. Additional markers will be optimized as needed on tumor sections.

2.4.2 Blood-based Biomarker Research

In addition to expression on the tumor tissue, PD-L1 can be shed from tumor and released into the blood[59,60]. Enzyme-linked immunoassay can measure PD-L1 in serum and correlate this expression with response to Pembrolizumab therapy, as well as levels of PD-L1 in immunohistochemistry (IHC) in the tumor. Blood would be less invasive compartment compared to tumor from which to measure

PD-L1 protein biomarker. This approach could identify novel protein biomarkers that could aid in patient selection for Pembrolizumab therapy. Survivin-peptide specific T cell immune response will be measured by different methods such as multi-parametric flow cytometry for antigen-activated T cells. Other exploratory immunologic assessments may be performed on frozen PBMC samples and patient plasma/serum, if a novel method becomes available during the course of the study.

2.4.2.1 Peripheral Blood Flow Cytometric Analysis

An exploratory analysis of peripheral blood will be performed to phenotypically characterize cellular subsets such as effector lymphocyte, dendritic cell, regulatory T cell, and myeloid derived suppressor cell populations. Analysis will be performed using multiparameter flow cytometry. Additional comprehensive analysis may be performed using CyTOF. Analysis (as sample material allows) will include characterization of cell populations: CD3, CD4, CD8 (T cells), CD19 (B cells), CD14 (monocytes), CD56 (NK cells), CD11c/HLA-DR (DCs); differentiation/memory status: CD45RO, CD28, CD27, CCR7; characterization of CD4+ T helper cell subsets: CD161, CCR6, CXCR3, CCR4; CD4+ regulatory T cells: HELIOS, Foxp3, CD127 (IL7-Ralpha), CD25; Effector T cells: ICOS, TIA-1, perforin, granzyme B; and putative markers of T cell exhaustion such as: LAG-3, Tim-3, PD-1, CTLA-4, KLRG1, CD160, 2B4, BTLA. Serum will also be collected with each cycle and stored for correlation with clinical activity and development of toxicity. Multiplex platforms such as the Luminex platform will be used to measure chemokines/cytokines involved in: Th1/Tc1 responses (e.g. IFN-γ, TNF, IL-2), Th2/Tc1 responses (e.g. IL-4, IL-5, IL-10), pro-inflammatory innate responses (e.g. IFN-α, IL-1β, IL-6), homeostatic lymphocyte expansion (e.g. IL-7, IL-15) and chemotaxis of immune cells (e.g. IP-10, MCP-1, MIP-1α, MIP-1β, RANTES). Measure induction of Survivin specific T cell responses (using peptide pool re-stimulation assays, ELISPot for IFN-γ producing T cells, and multiparameter flow cytometry; MHC/peptide multimer will be analyzed when possible). Flow cytometric analyses may include additional studies as part of exploratory studies.

2.4.2.2 Whole blood and peptide-pool re-stimulation assay, with IFNg detection by ELISA and flow cytometry

Fresh whole blood (WB) samples will be diluted in culture media and cultured with peptide pool mixtures (negative control, TT positive control, Flu/EBV/CMV positive control and 5-survivin peptide pool) with or without Alum/TLR4 adjuvant mixture for 7 days, according to established protocols (Brookes et al. 2014 PMID: 24401565[62]; Smith et al. 2015 PMID: 26367374[63]). The supernatant will be collected and secreted IFNg detected by ELISA or cytometric bead array (CBA). Responding patients will be further assess for vaccine peptide-specific responses in WB or cryopreserved PBMCs by re-stimulating cultures with individual peptides in the presence brefeldin A to block cytokine secretion, followed by surface staining for CD8+ T cells and intracellular detection of IFNg for measurement by flowcytometry.

2.4.2.3 Circulating Tumor DNA

Genetic determinants of treatment-resistance can be found within plasma-derived circulating tumour DNA (ctDNA). The emergence of drug-resistant clones is detectable by ctDNA analysis well before cancer progression is appreciated using conventional medical imaging [60,61]. Next generation

sequencing of ctDNA has revealed tumour evolution and clonal selection for acquired resistance to anticancer therapies in patients with advanced cancers; however, such studies have not yet been performed in the context of ICIs such as Pembrolizumab and DPX-Survivac. At each collection time point on this protocol, ~30 mL of peripheral blood will be analyzed for ctDNA characterization.

3. PATIENT SELECTION

3.1 Eligibility Criteria

- Histologically or cytologically confirmed advanced epithelial ovarian, primary peritoneal or fallopian tube carcinomas. All epithelial subtypes of ovarian cancer will be allowed

- Patients must have radiologically documented disease progression from their prior line of therapy.

- Patients must have measureable disease based on RECIST 1.1. See section 10 for definition of measurable disease. NOTE: tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions. Patient with single lesion could be enrolled if in the opinion of the investigator the biopsy will not interfere with evaluation of response.

- All histological subtypes are allowed in the Dose Escalation phase. In the Dose Expansion phase, all subtypes are allowed, however statistics will be calculated based on patients with high-grade serous ovarian cancer. Patients with non-high grade serous ovarian cancer will be considered as part of an exploratory cohort.

- Have received a front line platinum-based regimen (administered via either IV or IP) following primary or interval debulking surgery with documented disease recurrence.

- Have fulfilled the following additional requirements regarding prior treatments depending on the cohort that the subject has to be enrolled in.

  Dose Escalation phase: There is no limit to the number of prior treatment regimens. Patients must be platinum-resistant defined as having a platinum-free interval (PFI) of <6 months to the last platinum-based regimen.

  Dose Expansion phase:
  - High grade serous and endometrioid platinum-sensitive patients: have received no more than 4 previous lines of chemotherapy, including adjuvant treatment and must have a platinum-free interval (PFI) of ≥ 6 months to the last platinum-based regimen. Targeted therapies, hormonal therapies and maintenance therapies do not count toward prior lines.
  - High grade serous and endometrioid platinum-resistant patients: have received no more than 4 previous lines of chemotherapy, including adjuvant treatment and must have a platinum-free interval (PFI) of <6 months to the last platinum-based regimen. Targeted

therapies, hormonal therapies and maintenance therapies do not count toward prior lines.
- Non-high grade serous or endometrioid patients: there is no limit to the number of prior treatment regimens, or restrictions based on platinum sensitivity.

NOTE: PFI is defined as the time elapsed between the last dose of platinum and the date of documented evidence of disease progression.

- At time of registration, if the patient has had previous treatment it must have been at least 28 days since major surgery or radiation therapy or from any other previous anti-cancer therapy including monoclonal antibody (mAb), chemotherapy, targeted small molecule therapy.

- Age ≥18 years on day of signing informed consent. As no dosing or adverse event data are currently available on the use of Pembrolizumab in combination with DPX-Survivac and Cyclophosphamide in patients <18 years of age, children are excluded from this study.

- Eastern Cooperative Group (ECOG) performance status ≤ 1 (see Appendix A).

- Life expectancy greater than 16 weeks.

- Availability of archival tumor tissue samples. Refer to Section 8.1 in protocol for explanation. Additional samples may be requested if tumor tissue provided is not adequate for quality and/or quantity as assessed by the laboratory.

- Be willing to provide tumor tissue from a newly obtained core or excisional biopsy. Newly-obtained is defined as a specimen obtained up 28 days prior to initiation of treatment on day 1. Refer to Section 9 for explanation. Additional samples may be requested if tumor tissue provided is not adequate for quality and/or quantity as assessed by the laboratory. Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may still be eligible for this study.

- Within 10 days of the proposed start of treatment, patients must have normal organ and marrow function as defined in Table 3.1 below:

Table 3.1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
White blood cell	$\geq 2.5 \times 10^9$/L
Absolute neutrophil count (ANC)	$\geq 1.5 \times 10^9$/L
Platelets	$\geq 100 \times 10^9$/L
Hemoglobin	≥90 g/L without transfusion or EPO dependency within 7 days of assessment
Renal	

Serum creatinine OR Measured or calculated[a] creatinine clearance	≤1.5 X upper limit of normal (ULN) OR CrCl≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN OR
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN OR ≤ 5 X ULN for subjects with liver metastases
Albumin	>2.5 mg/dL
Alkaline phosphatase	Subjects with bone metastases and no hepatic parenchymal metastases on screening radiographic examinations may enroll if alkaline phosphatase is < 5.0 X ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT), and Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
[a] Creatinine clearance should be calculated per Cockcroft-Gault formula	

- Ability to understand and willing to sign a written informed consent document. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trail without participating in Future Biomedical Research.

- Ongoing prior toxicities related to previous treatments (surgery, radiotherapy, chemotherapy or other systemic treatment) must be recovered to ≤ grade 1 at the time of registration (with the exception of grade 2 neuropathy, alopecia and lymphocytopenia).

- Women of child-producing potential must agree to use effective contraceptive methods prior to study entry, during study participation, and for at least 120 days after the last administration of study medication. A serum pregnancy test within 72 hours prior to the initiation of therapy will be required for women of childbearing potential.

  Highly effective contraception methods include:
  • Total abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
  • Male or Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case ooophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
  • Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.

• Combination of any two of the following (a+b or a+c, or b+c):
a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
Note: Female patients of childbearing age are defined as follows:
• Patients with regular menses
• Patients, after menarche with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding
• Women who have had tubal ligation

Female patients may be considered to NOT be of childbearing potential for the following reasons:

- The patient has undergone total abdominal hysterectomy with bilateral salpingo-oophorectomy or bilateral oophorectomy
- The patient is medically confirmed to be menopausal (no menstrual period) for 24 consecutive months

3.2 Exclusion Criteria

- Patients who are receiving concurrent chemotherapy, radiotherapy, immunotherapy or any other investigational agents.

- Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

- History of active TB (Bacillus Tuberculosis).

- Patients with known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

- Hypersensitivity to Pembrolizumab, DPX-Survivac immunovaccine and Cyclophosphamide or any of its excipients.

- Patients who have received a live vaccine within 30 days of planned start of study therapy. NOTE: No adjuvanted vaccine or live attenuated vaccine (such as Flumist) should be given while on this study. Non-adjuvanted vaccines (such as most influenza vaccines) can be given. For subjects receiving the flu vaccine, it is strongly recommended the shot be given but at least one week before immunological assessments.

- Prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or surviving based vaccines. Prior anti-CTLA4 agents are allowed. Prior therapy with T-cell co-stimulatory agents (e.g. anti-CD137 antibody, anti-OX40 antibody) are allowed.

- Concurrent malignancy that is progressing or requires active treatment within the last 5 years. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy, in situ cervical cancer or superficial bladder cancer.

- History of autoimmune disease, such as but not restricted to, rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematous, ankylosing spondylitis, scleroderma, or multiple sclerosis requiring treatment within the last two years. Patients with vitiligo or diabetes are not excluded. Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

- Patients with recent history of thyroiditis within 5 years. Subjects with remote history (greater than 5 years) of thyroiditis are not excluded

- Patients with known history of non-infectious symptomatic pneumonitis or any evidence of active symptomatic pneumonitis

- Uncontrolled inter-current illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

- Pregnant women are excluded from this study because effects of Pembrozilumab and DPX-Survivac on a fetus are unknown. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with Pembrolizumab and DPX-Survivac, breastfeeding should be discontinued.

- Patients with known HIV-positive status. Patients with known Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected)

- Malignant bowel obstruction or gastrointestinal condition that might limit absorption of oral agents

- Patients with extensive pelvic mass at high risk of fistulization.

- Any other acute or chronic condition, such as cardiac disease, hepatic disease or other illness that would, in the Investigator's judgment, contraindicate the patient's participation in the clinical study.

- Acute or chronic skin disorders that will interfere with subcutaneous injection of the vaccine or subsequent assessment of potential skin reactions.

- Edema or lymphedema in the lower limbs > grade 1, regardless of attribution

- Patients with known psychiatric or substance abuse disorders that would interfere with adherence to study requirements.

3.3 Inclusion of Women and Minorities

Women of all races and ethnic groups are eligible for this trial. This study is designed to include minorities as appropriate. However, the trial is not designed to measure differences in intervention effects. The population of Southern Ontario is ethnically diverse and the proportion of different ethnic groups in the community is provided in the table below. Universal access to health care will ensure that there is no discrimination on the basis of race or gender (Guide to Canadian Human Rights Act: www.chrc-ccdp.ca/public/guidechra.pdf). Individual hospital registries and databases do not routinely collect racial data, under the direction of the Canadian Human Rights Code.

The population demographics and distribution of minorities in Canada is included in the following table:

Table: Visible minority population by Consortium Provinces (2001 Census)

	British Columbia		**Alberta**		**Ontario**		**Nova Scotia**		**Total**	
Total population of province	3,868,870		2,941,150		11,285,550		897,570		**18,993,140**	
Visible Minorities	**Population**	**%**	**Population**	**%**	**Population**	**%**	**Population**	**%**	**Population**	**%**
Black	25,465	1%	31,390	1%	411,095	4%	19,670	2%	487,620	**3%**
Asian	768,435	20%	268,660	9%	1,513,825	13%	12,630	1%	2,563,550	**13%**
Latin American (Hispanic)	23,880	1%	18,745	1%	106,835	1%	520	0%	149,980	**1%**
Visible minority, not included elsewhere	4,195	0%	4,220	0%	78,915	1%	1,170	0%	88,500	**0%**
Multiple visible minority	14,465	0%	6,910	0%	42,375	0%	535	0%	64,285	**0%**
Total Visible minority population	836,440	22%	329,925	11%	2,153,045	19%	34,525	4%	3,353,936	**18%**

Source: Statistics Canada, Census of Population.

Data from our consortium has been compiled regarding the representation of minorities on previous clinical trials, and the distribution is as follows:

Population Percentage of Minority and Gender of entering PMHC Trials			
	2010	2011	2012
Visible Minorities			
Black	0.9	2.3	1.2
Asian	10.1	10.9	11.6
Hispanic	10.1	2.3	3.5
Total	**21.1**	**15.5**	**16.3**
Women	**59.6**	**56.6**	**44.2**

4. REGISTRATION PROCEDURES

4.1 General Guidelines

The Central Office Coordinator at the Drug Development Program Central Office will enter eligible patients centrally. All sites should call the Central Office Coordinator (listed on cover page) to verify dose level availabilities. The required forms (Registration Checklist) will be provided upon site activation.

Following registration, patients should begin protocol treatment within 3 days. Issues that would cause treatment delays should be discussed with the Principal Investigator (cc the Central Office Study Coordinator). If a patient does not receive protocol therapy following registration, the patient's registration on the study may be cancelled. The Central Office Coordinator should be notified of cancellations as soon as possible.

4.2 Registration Process

Before registering a patient, each institution must have submitted all necessary regulatory documentation to the Drug Development Program Central Office. The registration checklist will only be sent once this has been received.

No patient can receive protocol treatment until registration with the Central Office has taken place. All eligibility criteria must be met at the time of registration. There will be no exceptions. Any questions should be addressed with the Central Office prior to registration.

To register a patient, the following documents are to be completed by the research nurse or data manager and sent/faxed to the Central Office Study Coordinator:

- Signed and dated patient consent form
- Registration Checklist CRF signed by the Investigator

To complete the registration process, Central Office will review the checklist and once eligibility has been confirmed:

- Assign patient study number
- Assign the dose level (for escalation phase only)
- Assign the cohort (for expansion phase only)

- Register the patient on the study
- Fax or e-mail the confirmation worksheet with the patient study number and dose level or study cohort to the participating site.

To ensure immediate attention is given to the faxed checklist, each site is advised to also call the Study Coordinator listed on the protocol front sheet. Patient registration will be accepted between the hours of 9am to 5pm Monday to Friday, excluding Canadian statutory holidays when the Central Office will be closed.

5. TREATMENT PLAN

This is a multi-center phase 2 trial assessing Pembrolizumab, DPX-Survivac and low dose of oral Cyclophosphamide combination in subjects with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer. Approximately 40 patients will be enrolled in this trial to examine the safety and preliminary efficacy of different doses of DPX-Survivac vaccine and low dose Cyclophosphamide in combination with a flat dose of Pembrolizumab 200 mg administered every 3 weeks. An escalation cohort is planned to define the toxicity profile, selected RP2D for further evaluation in an expanded population and to assess preliminary signal of activity in correlation with translational studies. This escalation cohort will include approximately 9-12 patients with recurrent platinum resistant epithelial ovarian, fallopian tube or primary peritoneal cancer, regardless PD-L1 expression. Additional patients may be included as per PI discretion for a comprehensive safety review or to confirm the RP2D

Following the escalation phase, a dose expansion phase will be initiated. Twenty patients will be included in two independent cohorts (platinum sensitive patients, cohort A, and platinum resistant patients, cohort B) of high-grade serous or endometrioid tumor subtypes, treated at RP2D. An exploratory cohort of 10 patients will allow enrollment of recurrent advanced epithelial ovarian, fallopian tube and primary peritoneal patients with uncommon tumor histologies, including clear cell, mucinous and low grade serous or endometrioid ovarian subtypes (cohort C) treated at RP2D.

Subjects will be evaluated every 6 weeks (42 days ±7 days) with radiographic imaging to assess response to treatment. RECIST 1.1 criteria will be used to define response to treatment. Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Treatment with Pembrolizumab, DPX-Survivac vaccine and oral Cyclophosphamide will continue until documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements or administrative reasons.

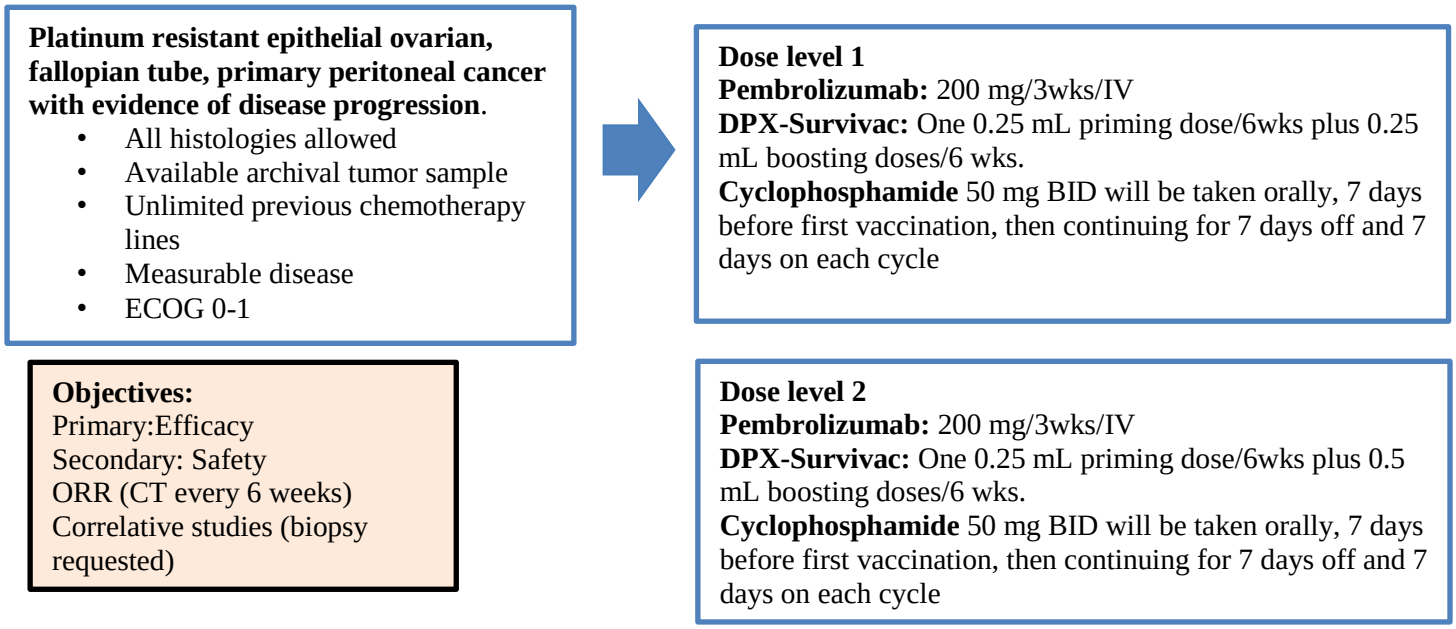
Mandatory archival tumor samples are required. Patients will have image-guided fresh tumor core biopsy at a maximum of 3 time points: 1) prior to commence Pembrolizumab, DPX-Survivac immune vaccine and Cyclophosphamide treatment, 2) on-treatment at day 15 of cycle 1 (+/- 7 days) during Pembrolizumab, DPX vaccine and oral Cyclophospahmide, and if possible, 3) when radiological disease progression is confirmed. Biopsy at time point 1) and 2) are mandatory; biopsy at time point 3) is optional. Opportunistic biopsy or cytology sample from fluid collection (ascites, pleural effusion

or cystic lesion) could be used for exploratory analysis. Peripheral blood mononuclear cells (PBMCs) and serum will be obtained at baseline and at several time points during investigational treatment. After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment). Subjects who discontinue treatment for reasons other than disease progression will have post-treatment follow-up of disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone contact for overall survival until death, withdrawal of consent or the end of the study, whichever comes first, for a maximum of 2 years.

This study will be conducted in conformance with Good Clinical Practices. Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Section 9.

F**IGURE** 5.1**: trial schema**

<u>Dose Escalation phase</u>



Dose Expansion phase

Epithelial ovarian, fallopian tube, primary peritoneal cancer with evidence of disease progression.

- All histologies allowed
- Available archival tumor sample
- Measurable disease
- ECOG 0-1

Objectives:
Primary: Efficacy
Secondary: Safety
ORR (CT every 6 weeks)
Correlative studies (Biopsy requested)

Cohort A: 10 Platinum-sensitive high grade serous or endometriod patients, no more than 4 prior lines of chemotherapy

Cohort B: 10 Platinum-resistant high grade serous or endometriod patients, no more than 4 prior lines of chemotherapy

Cohort C: 10 patients with other epithelial subtypes, irrespective of prior therapy and platinum free interval

5.1 Dosing and administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.1.1 Dose Escalation phase

Patients will participate in dose escalation starting with dose level 1 as indicated in the table. Patients will be escalated in a 3+3 design based on tolerance and toxicity. If dose limiting toxicity is seen in >1 patient in the first cohort, a de-escalation cohort will be evaluated. There are one de-escalation cohort and two escalation cohorts. A subsequent safety assessment will be performed after the boosting dose of DPX-Survivac vaccine, but observed adverse events will not be considered DLTs.

	DPX-SURVIVAC	**CYCLOPHOSPHAMIDE**	**PEMBROLIZUMAB (MK3475)**
DL (-1)	One Priming 0.1mL/6W/SC Boosting 0.1mL/6W/SC	50mg/bid (week before C1D1) and then continuing for 7 days off and 7 days on each cycle ensuring Cyclophosphamide is always given in the week preceding a boosting dose of DPX-Survivac	200mg/3W/IV
DL1	One Priming 0.25 mL/6W/SC Boosting 0.25mL/6W/SC	50mg/bid (week before C1D1) and then continuing for 7 days off and 7 days on each cycle ensuring Cyclophosphamide is always given in the week preceding a Boosting dose of DPX-Survivac	200mg/3W/IV
DL2	One Priming 0.25mL/6W/SC Boosting 0.5mL/6W/SC	50mg/bid (week before C1D1) and then continuing for 7 days off and 7 days on each cycle ensuring Cyclophosphamide is always given in the week preceding a Boosting dose of DPX-Survivac	200mg/3W/IV

5.1.2 Dose Expansion phase

In the Dose Expansion phase, the recommended Phase 2 dose (determined in the Dose Escalation phase) will be tested in expanded cohorts enrolling patients with ovarian, primary peritoneal and fallopian tube carcinoma. Three cohorts are planned: a cohort of 10 women with platinum sensitive recurrent disease (high grade serous or endometrioid) who have received no more than 4 prior lines of chemotherapy, a second cohort of 10 women with platinum resistant disease (high grade serous or endometrioid) who have received no more than 4 prior lines of chemotherapy and a cohort of 10 patients with epithelial,

non-high grade serous or endometrioid histology (clear cell, low grade serous, low grade endometrioid, transitional or mucinous), irrespective of prior therapy and platinum free interval

5.1.3 Treatment administration

- Pembrolizumab: should be administered on day 1 of each cycle after all procedures/assessments have been completed as detailed in Section 9. Trial treatment may be administered up to 3 days before or after the scheduled day 1 of each cycle due to administrative reasons. Pembrolizumab will be administered as a 30-minute IV infusion every 3 weeks at the flat dose of 200 mg. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min). The Pharmacy Manual contains specific instructions for the preparation of the Pembrolizumab infusion fluid and administration of infusion solution.

- DPX- Survivac: should be administered on day 1 of every other cycle. All preparations of the reconstituted vaccine will be performed at room temperature on the day of immunization. In all cohorts the injection will be performed subcutaneously in the upper thigh regions with limbs alternation in the following administrations. An alcohol swab will be used to clean the site prior to injection. If subjects experience pain during first injection, then cooling of the injection site with ice packs 15 minutes prior to subsequent immunization is permitted.

  Instructions below needs to be followed to avoid exaggerated injection site reactions:

  1. Inject the vaccine on the front and/or outer upper half of the thigh region closer to the inguinal lymph nodes so the vaccine can be processed by the immune system.
  2. Inject the vaccine deep subcutaneously and NOT intracutaneously. The full length of the needle must be inserted at the correct angle based on the size of the subject's upper thigh region.
  3. Whether or not an injection site reaction is present, vaccine should not be administered in the identical site of a previous vaccination(s). Immunizations should not be administered any closer than 10 cm to prior injection sites that still have erythema, induration, or other visible injection site reaction.
  4. It is recommended that the same trained study staff inject all subjects at their sites.

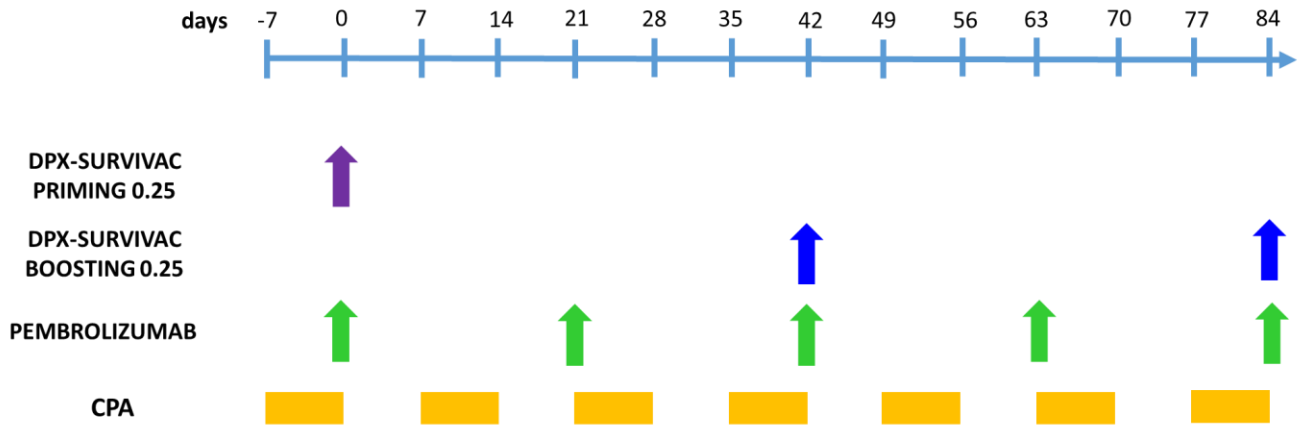
  All subjects will be treated in an outpatient unit equipped with emergency equipment. Subjects will be monitored with blood pressure, pulse, and temperature assessments at pre-injection, at approximately (i.e. within 5 minutes) 15 minutes, and approximately (i.e. within 5 minutes) 30 minutes after injection. At the discretion of the study nurse, the subjects may remain for an additional 1-2 hours for observation. Diphendydramine 50 mg, hydrocortisone 100 mg, and epinephrine 1:1000 (1 mL) must be available at the bedside and the clinic must have a code cart available for emergency use.

- Cyclophosphamide: low dose Cyclophosphamide (50 mg twice a day) will be administered orally. Cyclophosphamide will be taken for 7 days prior to day 1 of first cycle and then continuing for 7 days off and 7 days on each cycle ensuring Cyclophosphamide is always given in the week preceding a boosting dose of DPX-Survivac.

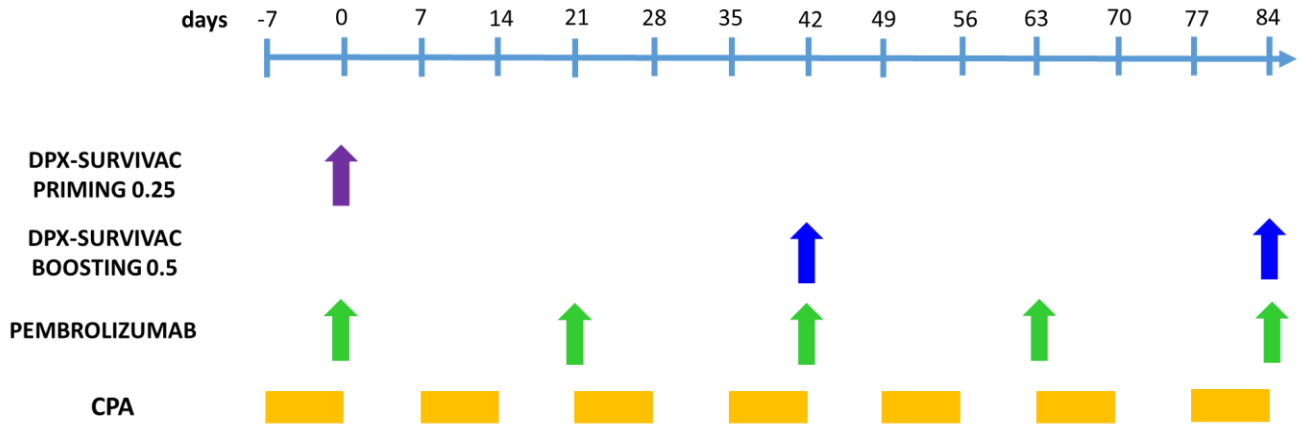
At each clinic visit subjects will be provided with enough cyclophosphamide to be taken at home until the next clinic visit. The patient will be requested to maintain a medication diary of each dose of Cyclophosphamide. The medication diary will be returned to clinic staff at the end of each course and reviewed by the study staff. The subject diary template can be found in Appendix C

FIGURE 5.2 Drugs administration

Dose level 1



Dose level 2



5.2 Definition of Dose-Limiting Toxicity (DLT)

Toxicity will be graded according to the NCI Cancer Therapy Evaluation Program, CTCAE version 4.03.

During the Dose escalation phase a DLT is defined as:

1. All grade 4 non hematologic toxicity
2. Grade 3 non hematologic toxicity lasting >3 days despite optimal supportive care
3. Grade 3 non hematologic laboratory value that persisted for >1 week or required medical intervention or hospitalization
4. Grade ≥3 febrile neutropenia
5. Grade 2 or greater ulcerations if persist > 1 week: a more severe skin ulceration that requires surgical intervention as defined by the "General disorders and administration site conditions – Injection site reaction" in NCI CTCAE version 4.03 (less severe ulceration should be defined by "Skin and subcutaneous tissue disorders- Skin ulceration" in NCI CTCAE version 4.03)
6. Grade 2 or greater allergic reaction and grade 2 generalized urticaria
7. Grade 2 or greater autoimmune reactions except for vitiligo or a fever >101.5ºF (>39ºC) for less than 2 days.

DLTs will be monitored from the day of first administration of Pembrolizumab and DPX-Survivac until 21 days after this first administration. A subsequent safety assessment will be performed for the 21 days after the boosting dose of DPX-Survivac vaccine, but observed adverse events will not be considered DLTs.

Management and dose modifications associated with the above adverse events are outlined in Section 5.4.

Dose escalation will proceed within each cohort according to the following scheme.

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if

	only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

The dose regimen during the escalation cohort phase will be considered safe if 0 or 1 DLTs occur in 6 subjects. A subject will be considered evaluable for safety if treated with at least one immunization and one Pembrolizumab dose.

5.3 General Concomitant Medication and Supportive Care Guidelines

5.3.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medications will be recorded on the electronic case report form (eCRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF. All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for Serious Adverse Events (SAEs) and Events of Clinical Interest (ECIs).

5.3.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the screening and treatment phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than Pembrolizumab, DPX Survivac or Cyclophosphamide
- Radiation therapy (radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion).
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Principal Investigator.
- No adjuvanted vaccine or live attenuated vaccine (such as Flumist) should be given while on this study.
- Non-adjuvanted vaccines (such as most influenza vaccines) can be given. For subjects receiving the flu vaccine, Immunovaccine strongly recommends the shot be given but at least one week before immunological assessments. Possible immediate side effects from vaccine injections,

including DPX-Survivac, may include allergic reactions such as fever, hives, or rash. For fever >101.5 ^{o}F (>39 ^{o}C), acetaminophen (650 mg) may be given orally. The induction of auto-immunity (manifests as arthritis, serositis, nephritis, thyroiditis, colitis, neutropenia, etc.) is theoretically possible. Acute allergic reactions may be treated with diphenhydramine, and/or epinephrine as needed. Delayed events such as rash or hives maybe treated with diphenhydramine (25-50 mg); topical steroids should not be given without consultation with the medical monitor.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications which are prohibited in this trial. Refer to the product monograph for Cyclophosphamide for drug-drug interactions with cyclophosphamide

There are no prohibited therapies during the Post-Treatment Follow-up.

5.3.3 Supportive Care Guidelines

5.3.3.1 Pembrolizumab

Pembrolizumab may induce immunologic adverse events that are required to be treated adequately with steroids as described below and as reported in the "Monograph of product"[61]. Use of oral or intravenous corticosteroids is required in case of immune-related adverse events. It is also necessary to rule out other possible causes such as metabolic disease or bacterial or viral infections before administering a high dose of steroids. Detailed toxicity management guidelines are outlined in Table 5.2.

Management of Infusion Reactions
Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.
Table 5.1 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of Pembrolizumab.

Table 5.1 Management of Pembrolizumab infusion reaction

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	
Grades 3 or 4 <u>Grade 3:</u> Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) <u>Grade 4:</u> Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.3.3.2 DPX-Vaccine

<u>Allergic reaction</u>

Possible immediate side effects from vaccine injections may include allergic reactions such as fever, hives or rash. For fever > 101.5^{o}F (> 38.6 ^{o}C), acetaminophen 650 mg may be given orally. Acute allergic reaction may be treated with diphenhydramine, hydrocortisone and/or epinephrine as needed.
If hypotension (systolic blood pressure (SBP) <90 mmHg for subjects with a baseline SBP >110 mmHg or >20 mmHg decrease for those with a baseline SBP <110 mmHg), urticaria, orofacial or laryngeal edema, or bronchospasm occur, diphendydramine 50 mg and solumedrol 100 mg will be administered. The study investigator in charge will be notified and the epinephrine will be administered for reactions that do not begin to resolve within 10 minutes or continue to become more severe. In this event, subject will be transported immediately to the emergency room if stabilized, or the code team will be contacted if subject continues to have progression of symptoms or worsening hypotension.

Injection site reaction or infection

Delayed injection site reactions such as rash or hives may be treated with diphenhydramine (25-50 mg); topical steroids should not be given without consultation with the medical monitor.

To care for possible infected injection site reactions proper wound care is appropriate. It is recommended that infected areas should be kept clean and exposed. Topical antibiotics such as fucidin or polysporin may be applied. Cultures should be sent for infections and treated promptly with oral antibiotics. Topical corticosteroid (hydrocortisone ointment) may be used to help reduce inflammation following consultation with the medical monitor.
Possible side effects from Montanide ISA51 VG are granuloma, abscess, and fever. Acetaminophen 650 mg every 4 hours may be given for fever after appropriate blood cultures are taken. Referral to a surgeon is encouraged for abscess.

5.3.3.3 Cyclophosphamide

Possible side effects from low doses cyclophosphamide are grade 1 nausea and/or vomiting, grade 1 and 2 anemia, neutropenia, leukopenia, and lymphopenia as well as low-grade fatigue. If platelet levels decrease below 75.0 x 10^9/L or if absolute neutrophil count decreases below 1.0 x 10^9/L in any cycle then the dose of cyclophosphamide can be reduced to 50 mg once daily in that subject for the duration of their treatment. Following consultation with the medical monitor, a subject's cyclophosphamide could be additionally or alternatively modified by extending the interval between cycles of administration

5.4 Dose modification or treatment discontinuation

5.4.1 Pembrolizumab

No dose reduction is allowed. Pembrolizumab has to be held temporarily or permanently according to grade and duration of adverse event as described in the table below.

Table 5.2 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions: **1.** Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks. **2.** For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks. **3.** For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.				
Immune-related AEs	**Toxicity grade or conditions (CTCAE**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**

	v4.0)			
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		

Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:
For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

With investigator and Sponsor/Principal Investigator agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue in the trial only if asymptomatic.

In case of G3-G4 adverse event requiring Pembrolizumab permanent discontinuation, it will be at Principal Investigator discretion if continue with DPX-Survivac treatment.

Pembrolizumab can be delayed up to 7 days for any reason. Administration of DPX-Survivac vaccine and subsequent Pembrolizumab will continue as per the original schedule. If Pembrolizumab is delayed > 7 days, that dose will be omitted and DPX-Survival vaccine, Cyclophosphamide and subsequent doses of Pembrolizumab will continue as per original schedule, if feasible. If at the subsequent cycle Pembrolizumab cannot be resumed, DPX-Survivac and Cyclophosphamide can continue at Investigator's discretion. Refer to Table 5.2 for guidelines regarding hold/discontinuation of Pembrolizumab in case of drug-related adverse events.

5.4.2 DPX-Survivac

Injection site reaction (ISR) are expected to happen after DPX-Survivac vaccination. Patients need to be monitored carefully for this adverse event. At minimum, the following types of photographs of the injection sites must be taken at each clinic visit whether or not the subject has an injection site reaction (1) close ups of each injection site with a ruler, (2) wide shot of each injected upper thigh region, and (3) aerial shot of both legs. The injection sites should be clearly marked by number and date on the photographs.

Table 5.4 Injection Site Reaction and Dose Modification of DPX-Survivac, Pembrolizumab and Cyclophosphamide

Injection Site Reaction (ISR)	**DPX-Survivac**	**Pembrolizumab**	**Cyclophosphamide**
Grade 2 ISR within 4 weeks prior to the next vaccination	Omit next vaccination until ISR improves to Gr. 1, then resume vaccination at the same dose level. Evaluation of injection sites will be repeated at each vaccination time point and all the study procedure will continue even when the vaccination has been held.	Continue as per dosing schedule.	Continue as per dosing schedule.

Grade 3 and 4 ISR within 4 weeks prior to the next vaccination	Omit next vaccination until ISR improves to Gr. 1, then dose at one dose level reduction (refer to section 5.1.1 for guidelines about dose escalation/de-escalation). If patient is already at the lowest dose level, it will be at the Investigator's discretion to continue with vaccination. Evaluation of injection sites will be repeated at each vaccination time point and all the study procedure will continue even when the vaccination has been held.	Withhold until ISR improves to Gr. 2, then resumed at the same dose level and schedule. If ISR improves to Gr. 2 within 7 days from the scheduled dosing time point, pembrolizumab will be administered and subsequent doses will continue as per scheduled. If not, omit pembrolizumab from that cycle and commence dosing in the next cycle at Investigator's discretion..	Withhold until ISR improves to Gr. 2, then resumed at the same dose level and schedule.
For two consecutive Grade 3-4 ISR despite dose reduction	Withhold or permanently discontinued[1]	Continue as per dosing schedule at Investigator's discretion	Continue as per dosing schedule at Investigator's discretion.

1. It is in Investigator's discretion whether to continue with vaccination (after the reaction has resolved to a grade 1 or better) or to stop all further vaccination in that subject due to safety concerns.

Note:

1.1.1.1.1.1.1 When applicable, resumption of Cyclophosphamide and Pembrolizumab dosing will not be delayed until a scheduled vaccination.

5.4.3 Cyclophosphamide

Lead in Cyclophosphamide is generally for 7 days prior to DPX-Survivac. In the case of an AE or delays/modification in schedule, please consult Principal Investigator.

Adverse Event	**Grade**	**Action taken**
Thrombocytopenia	G2	Reduce CPA to 50 mg once daily for duration of study
	G3-4	At the first occurrence, interrupt CPA. When recovered to ≤ G2, reduce dose to 50mg once daily. At second occurrence, permanently discontinue CPA and discuss with Sponsor if Pembrolizumab and DPX-Survivac can continue once recovered to G1 or less.
Neutropenia	G3-4	At the first occurrence, interrupt CPA. When recovered to ≤ G2, reduce dose to 50mg once daily. At second occurrence, permanently discontinue CPA and discuss with Sponsor if Pembrolizumab and DPX-Survivac can continue once recovered to G1 or less.
Anemia	Any grade	No dose modification required unless deemed necessary.
Fatigue	≥G3	At the first occurrence, interrupt CPA. When recovered

		to ≤ G2, reduce dose to 50mg once daily. At second occurrence, it is Investigator's discretion whether to hold or permanently discontinue CPA. Discuss with Sponsor if Pembrolizumab and DPX-Survivac can continue once recovered to G1 or less.
Diarrhea/Colitis	G2	Interrupt CPA. When resolved to ≤G1 restart at same level
Pneumonitis	G2	Interrupt CPA. When recovered to ≤ G1 and corticosteroids are ≤ 10 mg prednisone or equivalent daily, if ≤ 4 weeks of hold resume at same dose, if more than 4 weeks reduced to 50 mg daily once
Hypophysitis	G2	Interrupt CPA. When recovered to ≤ G1 and corticosteroids are ≤ 10 mg prednisone or equivalent daily, if ≤ 4 weeks of hold resume at same dose, if more than 4 weeks reduced to 50 mg once daily
Hepatic Toxicity	G2	Interrupt CPA only if steroids treatment is required. When recovered to ≤ G1 and corticosteroids are ≤ 10 mg prednisone or equivalent daily, if ≤ 4 weeks of hold resume at same dose, if more than 4 weeks reduced to 50 mg once daily
Potential drug-induced liver injury	G2 ALT or AST (≥ 3 x ULN) G2 bilirubin (≥ 2 x ULN)	Hy's Law: if ALT or AST is elevated more than 3 x ULN and total bilirubin is elevated more than 2 x ULN, irrespective of alkaline phosphatase, and there is no other immediately apparent possible causes of ALT or AST elevation or hyperbilirubinemia, including but not limited to viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drugs known to be hepatotoxic, then discontinue treatment.
Creatinine increase	G2	Interrupt CPA and treat with steroids. When recovered to ≤ G1 and corticosteroids are ≤ 10 mg prednisone or equivalent daily, restart CPA at the same dose levels and schedule. Omit any vaccinations while cyclophosphamide and pembrolizumab dosing is on hold. If treatment is not resumed within 6 weeks subject will be removed from study.
Other non-hematological toxicities	≥ G3	At the first occurrence, interrupt CPA until recover to baseline or G1. Consider reduction to 50 mg daily if deemed necessary by the Investigator. At second occurrence, it is at the Investigator's discretion whether to hold or permanently discontinue CPA. Discuss with Sponsor if Pembrolizumab and DPX-Survivac can continue once recovered to G1 or less
In case of clinically significant adverse reaction deemed to be related to Cyclophosphamide and		

persistent despite dose reduction, interrupt Cyclophosphamide. Pembrolizumab and/or DPX-Survivac vaccine may continue after discussion with Sponsor/Principal Investigator.

Dosing interruptions of all agents are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

5.5 Criteria for treatment discontinuation

Treatment must be discontinued if one of the following events occur:

- Disease progression per RECIST 1.1 criteria as defined by section 10. It is at the Investigator's discretion to continue with trial treatment based on the clinical status of the patient, as per Table 10.1
- Clinical progression
- Women who become pregnant or are breastfeeding
- Sexually active subjects who refuse to use medically accepted forms of barrier contraception (e.g. male condom, female condom) during the study and for 120 days following discontinuation of study treatment
- Termination of the protocol by a regulatory agency or Sponsor, or study medication can no longer be provided
- Significant non-compliance with the protocol schedule in the opinion of the investigator
- Patients requiring a delay in treatment beyond the 6 weeks. At Investigator discretion patient can continue one or all the drugs if patient has benefit
- Intercurrent illness that prevents further administration of treatment
- Life threatening reactions secondary to active immunotherapy
- Unacceptable adverse event as defined by section 5.4.1 and 5.4.2
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Necessity for treatment with another anti-cancer treatment prohibited by this protocol

5.6 Second Course Phase (Retreatment Period)

Subjects who benefit from therapy (clinical/radiologic response, or SD > 6 months) but have stopped Pembrolizumab, DPX-Survivac, Cyclophosphamide treatment may be eligible for additional therapy if they progress after stopping study treatment.

This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets all the following conditions:

1a) Stopped initial treatment with Pembrolizumab, DPX-Survivac and Cyclophosphamide after attaining an investigator determined confirmed CR according to RECIST 1.1, and

- Was treated for at least 8 administrations of Pembrolizumab +/- DPX-Survivac before discontinuing therapy
- Received at least two treatments with Pembrolizumab beyond the date when the initial CR was declared

OR

1b) Had SD, PR or CR and stopped Pembrolizumab treatment before 35 administrations for reasons other than disease progression or intolerability

AND

2) Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with Pembrolizumab, DPX-Survivac and Cyclophosphamide
3) Did not receive any anti-cancer treatment since the last dose of Pembrolizumab, DPX-Survivac and Cyclophosphamide
4) Has a performance status of 0 or 1 on the ECOG Performance Scale
5) Demonstrates adequate organ function as detailed in Section 3.1
6) Subjects of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
7) Subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
8) Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is in the best interest of the subject to participate, in the opinion of the treating investigator. Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received Pembrolizumab/DPX-Survivac/Cyclophosphamide. Subjects who are re-treated must re-sign consent form.

5.7 Duration of Follow Up

5.7.1 Safety Follow-up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0- 1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 4 weeks of the end of treatment or

before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with Pembrolizumab/DPX-Survivac (as described in Section 5.6) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

Investigator may choose to complete a confirmatory scan at ≥ 4 weeks to document iCPD, per iRECIST, for subjects who came off treatment due to disease progression as per RECIST 1.1.

5.7.2 Follow-Up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks (84 ± 7 days) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with Pembrolizumab/DPX-Survivac as detailed in Section 5.6.

Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated. Subjects who are eligible to receive retreatment with Pembrolizumab/DPX-Survivac according to the criteria in Section 5.6 will move from the Follow-Up Phase to the Second Course Phase when they experience disease progression.

5.7.3 Survival Follow Up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks (± 14 days) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first for a maximum time of 2 years.

5.8 Criteria for Removal from Study

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the Investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

A subject must be discontinued from the trial for any of the following reasons:

- Investigator's decision to withdraw the subject
- The subject is lost to follow-up
- Administrative reasons
- Termination of the protocol by regulatory authorities, or Sponsor-Investigator

5.9 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with Pembrolizumab and had at least two treatments with

Pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up additional treatment with Pembrolizumab, DPX-Survivac and oral Cyclophosphamide via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of study drugs, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 5.6.

5.10 Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:
1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study drug. In the event of Merck/ ImmunoVaccine decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6. ADVERSE EVENTS

6.1 Definition

6.1.1 Adverse Event (AE)

An adverse event is any untoward medical occurrence in a subject receiving an investigational product during the course of a study and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the medicinal product.

Disease signs, symptoms, and/or laboratory abnormalities already existing prior to the use of the product are not considered AEs after administration of the study product unless they reoccur after the subject has recovered from the pre-existing condition or they represent an exacerbation in intensity or frequency.

A laboratory test abnormality considered clinically relevant (e.g. causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations) or judged relevant by the Investigator that is CTCAE gradable should be reported as an adverse event.

6.1.2 Definition of Serious Adverse Event (SAE)

Any event occurring at any dose that results in any of the following outcomes:

- Death

- A life-threatening AE (the patient was, in the view of the Investigator, at immediate risk of death from the event as it occurred. It does not mean that the event, had it occurred in a more severe form, might have caused death).
- Hospitalization or prolongation of existing hospitalization (complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria the event is serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered to be an AE).
- A persistent or significant disability/incapacity (a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, accidental trauma (i.e., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption).
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (examples include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization or the development of drug dependency or drug abuse).

Any malignancy possibly related to cancer treatment (including AML/MDS) is considered a secondary malignancy should be reported as an SAE. A new, second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy).

Events not considered to be serious adverse events are:

- hospitalizations for the routine treatment or monitoring for trial procedures, not associated with any deterioration in condition,
- treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen,
- admission to a hospital or other institution for general care, not associated with any deterioration in condition,
- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission,
- any events or hospitalizations that are unequivocally due to progression of disease will not be reported as an SAE

Any SAE occurring after the patient has provided informed consent and until 90 days after the patient has stopped study treatment must be reported, regardless of relatedness. This includes the phase in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during screening phase, change in treatment to a fixed dose of concomitant medication). Serious adverse events occurring more than 4 weeks after study discontinuation need only be reported if a relationship to investigational drug is suspected.

6.2 Expected Adverse Events

6.2.1 Pembrolizumab

Common (≥ 1% to <10%)	
Blood and lymphatic system disorders	Anemia
Infections and infestations	Pneumonia
Respiratory, thoracic and mediastinal disorders	Pneumonitis, dyspnoea
Gastrointestinal disorders	Diarrhoea
General disorders and administration site condition	Pyrexia
Uncommon (≥ 0.1% to <1%)	
Blood and lymphatic system disorders	Thrombocytopenia
Endocrine disorders	Hypophysitis (hypopituitarism), adrenal insufficiency, hyperthyroidism, hypothyrodism
Metabolism and nutrition disorders	Decreased appetite, Type 1 diabetes mellitus (diabetic ketoacidosis), hyponatraemia, hypokalaemia, hypercalcaemia
Nervous system disorders	Dizziness, headache
Cardiac disorders	Pericardial effusion
Vascular disorders	Hypertension
Gastrointestinal disorders	Pancreatitis, colitis, vomiting, abdominal pain (abdominal pain upper), constipation, nausea
General disorders and administration site condition	Asthenia, fatigue, oedema peripheral
Hepatobiliary disorders	Hepatitis, autoimmune hepatitis
Skin and subcutaneous tissue disorders	Rash
Musculoskeletal and connective tissue disorders	Arthralgia, back pain, musculoskeletal pain, myositis, pain in extremity
Renal and urinary disorders	Tubulointerstitial nephritis,renal failure
Investigations	Alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, blood creatinine increased
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease
Rare (≥ 0. 1% to <0.1%)	
Blood and lymphatic system disorders	Immune thrombocytopenic purpura, haemolytic anaemia, eosinophilia, neutropenia
Cardiac disorders	Myocarditis, pericarditis
Endocrine disorders	Addison's disease, adrenocortical insufficiency acute, secondary adrenocortical insufficiency, thyroiditis
Eye disorders	Iritis, uveitis, Vogt-Koyanagi-Harada syndrome
General disorders and administration site condition	Chills, oedema (face oedema, generalized oedema, localized oedema), influenza like illness
Hepatobiliary disorders	Drug-induced liver injury, hepatitis acute, immune-mediated hepatitis, jaundice
Immune system disorders	Anaphylactic reaction, anaphylactoid reaction, cytokine release syndrome, drug hypersensitivity, hypersensitivity, myelitis, sarcoidosis, haemophagocytic lymphohistiocytosis
Infections and infestations	Chorioretinitis, encephalitis, meningitis aseptic
Injury, poisoning and procedural complications	Contusion, infusion related reaction
Investigations	Blood alkaline phosphatase increased
Metabolism and nutrition disorders	Fluid overload, fulminant type 1 diabetes mellitus, hypocalcaemia
Musculoskeletal and connective tissue disorders	Arthritis, joint effusion, musculoskeletal chest pain, myalgia, myopathy, polyarthritis, rhabdomyolysis, synovitis, tendonitis, tenosynovitis
Nervous system disorders	Epilepsy, Guillain-Barré syndrome, lethargy, limbic encephalitis,

	myasthenic gravis, myasthenic syndrome, neuropathy peripheral
Gastrointestinal disorders	Autoimmune colitis, autoimmune pancreatitis, colitis microscopic, enterocolitis, immune-mediated enterocolitis, oral lichen planus, pancreatitis acute, abdominal pain lower, small intestinal perforation
Renal and urinary disorders	Autoimmune nephritis, nephritis
Respiratory, thoracic and mediastinal disorders	Cough, organizing pneumonia
Skin and subcutaneous tissue disorders	Acute febrile neutrophilic dermatosis, dermatitis, drug eruption, erythema multiforme, lichen planus, lichenoid keratosis, pemphigoid, pruritus, psoriasis, rash generalized, rash macular, rash macular-papular, toxic epidermal necrolysis, Stevens-Johnson syndrome, toxic skin eruption, urticaria
Vascular disorders	Hypertension

Immune-mediated adverse reactions	**Incidence (%)**
Common (≥ 1% to <10%)	
Hypothyroidism	8.5
Hyperthyroidism	3.4
Pneumonitis	3.4
Colitis	1.7
Arthritis	1.6
Skin reaction	1.6
Uncommon (≥ 0.1% to <1%)	
Adrenal insufficiency	0.8
Hepatitis	0.7
Hypophysitis	0.6
Nephritis	0.3
Type 1diabetes mellitus	0.2

In addition to the above, there is a new potential risk of graft versus host disease (GVHD) after Pembrolizumab in patients with a history of allogeneic hematopoietic stem cell transplant (HSCT).

Adverse events (both non-serious and serious) associated with Pembrolizumab, DPX-Survivac immunovaccine and Cyclophosphamide exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment.

6.2.2 DPX-Survivac

Common (> 10%)	
Injection site reaction	induration, pain, erythema, swelling, pruritus, warmth, ulceration, dryness, discoloration,
Gastrointestinal disorders	Nausea
General disorders	Fatigue
Skin	Rash
Occasional(1-10%)	
Injection site reaction	rash, vesicles, hematoma, lipodystrophy, necrosis, infection, extravasation/exudate, hypersensitivity, nodule, scab
General disorders	pain in extremities, chills, chest discomfort, pyrexia, headache, influenza-like illness, mobility decreased, Back Pain, Groin Pain, Visual Impairment,weight decrease

Psychiatric disorders	Anxiety, Depression, Insomnia
Endocrine disorders	Adrenal insufficiency
Gastrointestinal disorders	Constipation, Diarrhea, Vomiting, Abdominal distension, Abdominal discomfort, Abdominal pain, Ascites, GERD, Hematochezia
Metabolism & Nutrition	Dehydration, Decreased appetite, Hypomagnesaemia, Hyponatremia
Investigation	alanine aminotransferase increased, aspartate aminotransferase increased,Lipase increase, Amylase increase, Blood alkaline phosphatase increase, Blood creatinine increased, Gamma Glutamyl transferase increase, Hematocrit decreased, Hemoglobin decreased, Platelet count decreased, Red blood count decrease
Infections & Infestations	Herpes Zoster, UTI
Blood and lymphatic disorders	Lymphadenopathy, anemia, leucopenia, neutropenia, lymphocytopenia, thrombocytopenia
Oral	Glossodynia, pain in jaw, oral herpes, Dysgeusia
Nervous System disorders	neuropathy peripheral, Dizziness
Muscoloskeletal and connective tissue disorders	Myalgia, arthralgia, edema limbs, gait disturbance, muscle spasm, Ligament sprain
Respiratory system	Productive cough, pneumonia, Exertional Dyspnea
Skin	Pruritus, erythema nodosum, dry skin, eczema, urticaria, genital herpes, Hyperhidrosis, Hair texture abnormal
Vascular disorders	hypertension
Rare (< 1%)	
Injection site reaction	Abscess

6.2.3 Cyclophoshamide

Common (> 10%)	
Bone marrow	anemia, leucopenia, neutropenia, thrombocytopenia
Gastrointestinal	anorexia, diarrhea, mucositis, stomatitis, vomit
Dermatology	alopecia
sexual/reproductive function	interferes with oogenesis and spermatogenesis, gonadal suppression (amenorrhea)
Renal/genitourinary	hemorrhagic cystitis (up to 40% with high dose or long term)
Occasional(1-10%)	
Allergy	runny eyes, rhinorrhea, sinus congestion and sneezing
Dermatology	facial flushing, rash, hives, itching
Renal/genitourinary	Cystitis, renal tubular necrosis
Pain	headache
Syndromes	SIADH
Rare (< 1%)	
Cardiovascular	CHF, cardiac necrosis, hemorrhagic myocarditis, pericardial tamponade
Coagulation	hypoprothrombinemia, risk of bleeding
Constitutional symptoms	asthenia, sweating, dizziness
Hepatic	Hepatotoxicity, jaundice
Gastrointestinal	hemorrhagic colitis
Dermatology	skin and nails hyperpigmentation, toxic epidermal necrolysis
Secondary malignancy	urinary bladder, myeloproliferative or lymphoproliferative malignancies
Metabolic	hyperkalemia, usually related to tumor lysis, hyperuricemia (with high dose and long term)
Renal/genitourinaty	hemorrhagic ureteritis
Pulmonary	interstitial pulmonary fibrosis (high dose or long term), pneumonitis (high dose or long term)
Fluid overload	

6.3 Adverse Event Reporting

AE and SAE will be collected from the time of the signature of informed consent, throughout the treatment period and during the follow-up.

All AEs must be recorded on case report forms (CRFs). Documentation must be supported by an entry in the subject's file. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product as judged by the Investigator, action taken and outcome.
All abnormal laboratory values that correspond to CTCAE 4.03 gradable events should be captured on source documentation and assessed for clinical significance by the Investigator at the site. Only abnormal laboratory values considered clinically significant will be reported as AE and these laboratory results will be followed up until the related AE resolves, returns to < grade 1 or baseline value in the follow-up period. Clinically significant laboratory abnormalities will be dictated in the clinic notes. Additionally, laboratory abnormalities resulting in an intervention are considered to be clinically significant.

AEs should be followed for 30 days respectively after the last dose of study drug/biologic or until they are resolved (return to normal or baseline values), stabilized, improve to < Grade 2, or the patient is lost to follow-up and cannot be contacted. Additional investigations (*e.g.*, laboratory tests, diagnostic procedures, or consultation with other healthcare professionals) may be required to completely investigate the nature and/or causality of an AE. If the patient dies during the study or within 4 weeks following the last dose of study medication, any postmortem findings (including histopathology) should be provided to the Sponsor. CRF data should be updated with any new information as appropriate

6.3.1 Characteristic of Adverse Events and Serious Adverse Events

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE4.03. A copy of the CTCAE 4.03 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Attribution of the AE o SAE:

- Definite – The AE/SAE *is clearly related* to the study treatment.
- Probable – The AE/SAE *is likely related* to the study treatment.
- Possible – The AE/SAE *may be related* to the study treatment.
- Unlikely – The AE/SAE *is doubtfully related* to the study treatment.
- Unrelated – The AE/SAE *is clearly NOT related* to the study treatment.

Unexpected AE
An unexpected AE is defined as any AE where the nature or severity of which is not consistent with the known risk information described in current IB, package insert, or available reference safety information.

6.3.2 Variables to be collected

The following variables will be collected for each AE:

- AE description
- The date when the AE started and stopped
- CTCAE grade and changes in grade during the course of the AE
- Whether the AE is serious
- Causality rating against the IP or procedure (yes or no)
- Action taken with regard to IP
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- Reason AE is serious
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication(s)
- Description of AE

6.3.3 Serious Adverse Event Reporting

6.3.3.1 Sponsor Notification

Any serious adverse event or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study, that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck/ ImmunoVaccine product, must be reported to the Princess Margaret Cancer Centre Drug Development Program (DDP) within 24 hours of the Investigator at the site learning of the event by a completed SAE form. The adverse event must be completely described in the case report form.

The Princess Margaret Cancer Centre DDP Clinical Trials Group will provide expedited reports of on-study SAEs to Health Canada, Merck Global Safety and ImmunoVaccine Technologies Inc. for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected (as determined by reference to the Investigator Brochure), AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment cannot be ruled out). Merck Global Safety and ImmunoVaccine Technologies Inc. are to be notified within 2 working days of the Central Office's learning of the SAE.

6.3.3.2 SAE Follow-up

Follow-up SAE reports is subject to the same timelines as the initial report, and is sent to the same parties to whom the original Serious Adverse Event Form was sent. A new serious adverse event form is completed for the follow-up, stating that this is a follow-up to the previously reported serious adverse event and giving the date of the original report. Each re-occurrence, complication or progression of the original event should be reported as a follow-up to that event. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or discontinued study participation.

The Sponsor-Investigator and Institution will assist Merck and Immunovaccine in investigating any SAE and will provide any follow-up information reasonably requested by Merk or Immunovaccine.

6.3.3.3 REB Notification of SAEs

Investigators must notify their Research Ethics Boards (according to their local REB policies) and file the report in their study files. Documentation as outlined below must be maintained for reportable SAEs. Documentation that serious adverse events (SAEs) have been reported to REB must be forwarded to the DDP and kept on file at the Centre. Documentation can be any of the following:
- letter from the REB acknowledging receipt
- stamp from the REB, signed and dated by REB chair, acknowledging receipt
- letter demonstrating the SAE was sent to the REB

6.3.3.4 Health Canada SAE Reporting

All serious, unexpected adverse drug reactions must also be reported by the Princess Margaret Cancer Centre DDP Clinical Trials Group to Health Canada within 15 days if the reaction is neither fatal nor life threatening, and within 7 days if the reaction is fatal or life threatening.

As Princess Margaret Cancer Centre is the sponsor of this study in Canada, the Principal Investigator of this study will be responsible for reporting all serious unexpected adverse events to Health Canada.

6.4 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours of learning of the event to the Central Office, and within 2 working days by Central Office to Merck Global Safety and to ImmunoVaccine Technologies Inc. Unless otherwise instructed, any such reports should be directed to:

MERCK CANADA INC.
Fax: 1-800-369-3090

Immunovaccine (Attn: Safety reporting)
Fax: 902-492-0888

For the time period beginning at treatment allocation/randomization through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the investigational product(s), must be reported within 24 hours of learning of the event to the Central Office, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of special interest must be identified as such in the eCRF. These include any immune related AEs or any other observed autoimmune phenomenon. Events of special interest must be recorded with other AEs in the eCRF whether or not they are deemed related to the investigational product(s).

Events of clinical interest for this trial are:

1. G3 or G4 immune related AEs
2. G3 or G4 injection site ulcerations
3. Overdose of Pembrolizumab
4. Potential drug-induced liver injury, also called Hy's Law: an elevated AST or ALT value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

6.5 Reproductive Concerns

6.5.1 Contraception

DPX-Survivac, Pembrolizumab or Cyclophosphamide may have adverse effects on a fetus in utero. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for 24 consecutive months will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy. The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progesteronic agent (including oral, subcutaneous, intrauterine, or intramuscular agents). Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in this study they must adhere to the contraception requirement for the duration of the study and during the follow-up period. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

6.5.2 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with Pembrolizumab, DPX-Survivac

and Cyclophosphamide, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck and ImmunoVaccine without delay and within 24 hours to the Sponsor and within 2 working days to Merck and ImmunoVaccine if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor.

6.5.3 Use in Nursing Women

It is unknown whether DPX-Survivac or Pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

6.5.4 Reporting of Pregnancy and Lactation to the Sponsor and to Merck/ ImmunoVaccine

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), that occurs during the trial or within 120 days of completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported. Such events must be reported within 24 hours to the Central Office, which will then be communicated within 2 working days by the Central office to:

MERCK CANADA INC.
Fax: 1-800-369-3090

Immunovaccine (Attn: Safety reporting)
Fax: 902-492-0888

6.6 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck/ ImmunoVaccine

For purposes of this trial, an overdose of Pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of Pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met. If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or

intentional overdose without adverse effect." All reports of overdose with and without an adverse event must be reported within 24 hours to the Central Office, which will then be communicated within 2 working days by the Central office to:

MERCK CANADA INC.
Fax: 1-800-369-3090

Immunovaccine (Attn: Safety reporting)
Fax: 902-492-0888

6.7 Investigator Notifications

The Sponsor-Investigator will receive Investigator Notifications (INs) issued by Merck and ImmunoVaccine for suspect, unexpected SAEs which have occurred in Merck-sponsored or ImmunoVaccine-sponsored studies with the study drug. The Sponsor-Investigator is responsible for forwarding these INs to all sub-investigators participating in the study, as well as to the Research Ethics Boards, according to local practice.

6.8 Data Safety and Monitoring Board

A Data Safety and Monitoring Board (DSMB), an independent group of experts, will be reviewing the data from this research throughout the study to see if there are unexpected or more serious side effects than described in the consent. For this trial, the Drug Development Program DSMB will be used for these tasks.

7. PHARMACEUTICAL INFORMATION

7.1 Investigational Agent(s)

The investigator shall take responsibility to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by Merck and ImmunoVaccine Technologies Inc.

7.1.1 **Pembrolizumab**

Product Name & Potency	**Dosage Form**
Pembrolizumab 50 mg/vial	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

Reconstitution of KEYTRUDA for Injection (Lyophilized Powder)

- Add 2.3 mL of Sterile Water for Injection, USP by injecting the water along the walls of the vial and not directly on the lyophilized powder (resulting concentration 25 mg/mL).
- Slowly swirl the vial. Allow up to 5 minutes for the bubbles to clear. Do not shake the vial.

Preparation for Intravenous Infusion

- Visually inspect the solution for particulate matter and discoloration prior to administration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.
- Dilute KEYTRUDA injection (solution) or reconstituted lyophilized powder prior to intravenous administration.
- Withdraw the required volume from the vial(s) of KEYTRUDA and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.
- Discard any unused portion left in the vial

Storage of Reconstituted and Diluted Solutions

The product does not contain a preservative.

Store the reconstituted and diluted solution from the KEYTRUDA 50 mg vial either:

- At room temperature for no more than 6 hours from the time of reconstitution. This includes room temperature storage of reconstituted vials, storage of the infusion solution in the IV bag, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of reconstitution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Store the diluted solution from the KEYTRUDA 100 mg/4 mL vial either:

- At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the infusion solution in the IV bag, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Do not freeze.

7.1.2 **DPX-Survivac Vaccine**

The clinical formulation of DPX-Survivac will consist of two vials provided by Immunovaccine. Vial 1 contains the freeze-dried adjuvant system and antigens. Vial 2 will contain the oil component alone (Montanide ISA51 VG). Vials 1 and 2 or will be mixed prior to injection.

Vials	**Component**
Vial 1 (lyophilized)	
Lipids	Phosphotidylcholine: DOPC synthetic lipid (GMP grade)
	Cholesterol: Sheep's wool, high purity, non-BSE countries (GMP grade)
Polynucleotide Adjuvant	Short synthetic polynucleotide (GMP grade)

Antigen (MHC Class II, T-helper)	Tetanus toxoid peptide A16L: AQYIKANSKFIGITEL (GMP grade)
Antigens (MHC Class I, Tumor specific)	Five synthetic peptides targeting survivin, (GMP grade)
Vial 2	
Hydrophobic carrier (oil diluent)	Montanide ISA51 VG (GMP grade)
Cyclophosphamide 50 mg	Pill form

Lipids-DPX-Survivac
The lipids will be composed of a mixture of the synthetic phosphatidylcholine molecule DOPC in a 10:1 (w:w) ratio with cholesterol. This mixture is supplied as a blend from the supplier, Lipoid GmbH (Ludwigshafen, Germany) and will be used without further processing.

Polynucleotide Adjuvant
Immunovaccine has demonstrated the enhanced efficacy of DPX formulations containing a synthetic polynucleotide-based adjuvant in nonclinical cancer models. The synthetic short polynucleotide (less than 30 bases) contained in DPX-Survivac is the same as that used in DPX- 0907. This adjuvant is favored over others for several reasons: (1) it is effective in tumor challenge models, (2) it can be produced by chemical synthesis and is characterizable by several analytical techniques, and (3) it has been used in clinical trials.

T-helper Peptide
A peptide from the tetanus toxoid, A16L (TT829-843), is included in all formulations of DepoVax-based products. The T-helper epitope A16L has been used extensively in the clinic.

Survivin Antigens for DPX-Survivac.
The five survivin peptides within DPX-Survivac were licensed from Merck KGaA and originally developed as Survivac. The Survivac product was formulated by emulsifying an aqueous mixture of the peptides with Montanide ISA51 VG. The peptides range between 9 and 10 amino acid residues.

Oil Diluent
The oil component, sterile Montanide ISA51 VG, will be provided for the vaccine pre-packaged in 3 mL vials by the supplier, Seppic (Paris, France). It is composed of mannide monoleate in a mineral solution and is a clear viscous, slightly yellow liquid that is stable at room temperature and 4 o C. The oil is non-animal based and was also used for the DPX-0907 formulation in the phase 1 trial. The oil has also been extensively used in other cancer vaccine clinical trials (Phase 1 and 2) [REF].

7.1.3 **Cyclophosphamide**

Commercially available (i.e. FDA/Health Canada approved) Cyclophosphamide 50 mg tablets will be provided by the clinical sites and used and stored according to the manufacturer instructions.

7.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements. The

Pembrolizumab and DPX-Survivac labels will comply with the Food and Drug Adminstration (FDA) requirements for an investigational product in the US or with Health Canada requirements for investigational product in Canada (as applicable).
The Cyclophosphamide will be received with commercial labels.

7.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

7.4 Storage and handling requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site. Clinical supplies may not be used for any purpose other than that stated in the protocol.

7.5 Returns and Reconciliation

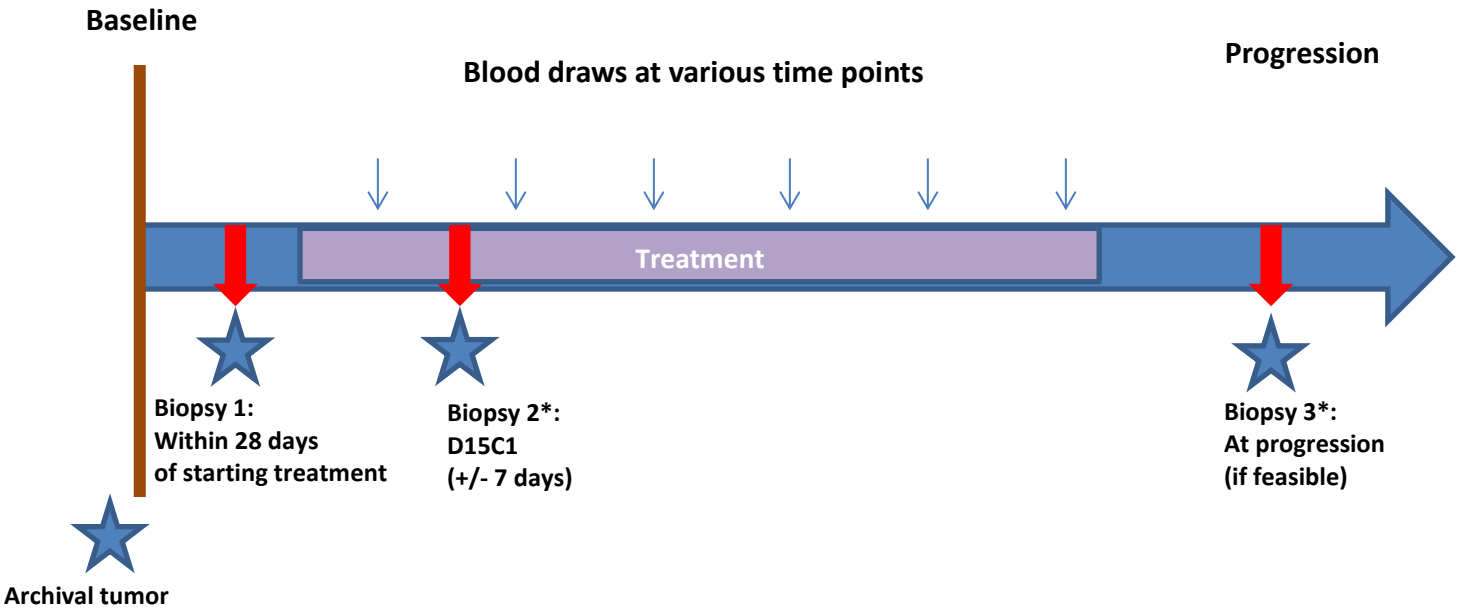
The investigator is responsible for keeping accurate records of the clinical supplies received from Merck, Immunovaccine or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

8. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

8.1 Correlative Studies

A summary of the samples being collected as part of this study are shown in Figure 8.1. Further elaboration regarding each sample can be found in Table 8.1.
Any tissue collected from clinical necessary procedures for patient care whilst patient is on trial protocol may be used for correlative studies - examples include therapeutic paracentesis, surgical procedures for clinical management, therapeutic aspiration of abscesses or fluid collections.

Figure 8.1 – Correlatives sampling schema



* Collection of opportunistic biopsies and sample from ascites, pleural effusion or cystic lesion drainage is allowed

Assay	Archival	Biopsy pre-treatment		Biopsy post-treatment		Biopsy on progression		Whole Blood
	FFPE (15 slides)	FFPE	Fresh Frozen	FFPE	Fresh Frozen	FFPE	Fresh Frozen	All time points
DNA/RNA Sequencing	FFPE unstained slides		1 core		1 core		1 core	1 x 10-mL tube baseline
IHC	Slides	Slides		Slides		Slides		
Characterization of peripheral blood by flow cytometry								3 x 10-mL tubes per time point
Characterization of tumor infiltrating lymphocytes by flow cytometry			2-3 cores (fresh saline)		2-3 cores (fresh saline)		2-3 cores (fresh saline)	
ctDNA								3x10 mL tubes per time point

Table 8.1 Correlative Studies

Markers	Days of sample collection	Sample	Processing	Shipment
Tumor-based				
Priority 1. DNA/RNA Sequencing	Pre-treatment: Screening (baseline day -28 to day -1) On-treatment: during cycle 1, day 15 (week 2) Progression biopsy (if taken)	1st core of tumor tissue	Fresh Frozen Co-isolate DNA/RNA for genomic analysis	Princess Margaret Genomics Centre Princess Margaret Genomic Centre-OICR Translational Genomics Lab
Priority 2. Immunoprofiling Immunohistochemistry	Pre-treatment: Screening (baseline day -28 to day -1) On-treatment: during cycle 1, day 15 (week 2) Progression biopsy (if taken)	2nd core of tumor tissue	Formalin-fixed, paraffin embedded	Applied Molecular Profiling Laboratory (AMPL)/Drug Development Biomarker Laboratory (DDBL), Princess

				Margaret Cancer Centre QualTek Molecular Laboratories, Newton, Pennsylvania
Priority 3. Immunoprofiling by flow cytometry and in vitro immunological assays	Pre-treatment: Screening (baseline day -28 to day -1) On-treatment: during cycle 1, day 15 (week 2) Progression biopsy (if taken)	3rd, 4th and 5th cores of tumor tissue (if taken)	Fresh, in saline	Immune Profiling Team, Princess Margaret Cancer Centre
Blood-Based				
Normal DNA Sequence Control Blood Sample (1 sample)	Pre-treatment: Screening (baseline day -28 to day -1)	One 10-mL whole blood once only (lavender tube – EDTA)	DNA extraction as a normal genome sequence control	Princess Margaret Genomics Centre
Immune Assessment: PBMC (multiple samples)	Pre-treatment: Screening (baseline day -14 to day -7) On-treatment: C1D1 (pre-dose), C2D1 (pre-dose) and C5D1 (pre-dose). Beyond Cycle 5, samples should be collected pre-dose at every 3 cycles (i.e. Cycles 8, 11, 14, etc.) and at end of treatment. For those patients who discontinue drug but remain on study, a sample will be obtained approximately every 12 weeks until off study, End of treatment	Three 10-ml green top (sodium heparin) tubes at each time point.	Samples will be ficolled to harvest PBMC within 18 hours. Approximately 5mL of fresh whole blood to be set aside for peptide pool re-stimulation assay	Immune Profiling Team, Princess Margaret Cancer Centre
Immune Assessment:	Pre-treatment: Screening (baseline day -14 to day -7) and day	One 4-ml SST tube	Sample will be centrifuged between 1-2 hours	Immune Profiling Team, Princess

Serum (multiple samples)	of treatment prior to dosing. On-treatment: prior to dosing with each cycle. For those patients who discontinue drug but remain on study, a sample will be obtained approximately every 12 weeks (+/-7 days) until off study.End of treatment.		of collection, to separate serum.	Margaret Cancer Centre
Circulating Tumor DNA (multiple samples)	Pre-treatment: Screening (baseline day -14 to day -7). On-treatment: prior to cycle 3 dosing and then prior to cycle 6 dosing and then every 3 cycles thereafter. End of Treatment.	At each time-point, 30 mL of peripheral blood will be collected in lavender (EDTA) tubes	Plasma will be separated from the cell pellet within 2 hours. Cell-free DNA will be purified from clarified plasma using the Circulating Nucleic Acid Kit (Qiagen)	Princess Margaret Genomics Centre

9. STUDY CALENDAR

Baseline (pre-study) evaluations are to be conducted within 28 days prior to start of protocol therapy, unless specified differently in the study calendar. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. The following schedule of assessments applies to all subjects. More frequent assessments should be obtained if clinically indicated. If pre-study assessments were done within 2 days prior to treatment initiation, they do not need to be repeated for cycle 1 day 1. For subsequent cycles 2+, day 1 assessments can be completed up to 3 days prior to day 1. A cycle is 21 days long for the purposes of this protocol.

After completion of cycle 2, some visits might be conducted remotely and / or some assessments might be deferred as per physician discretion. Some of the safety lab assessments may also be done at external or community laboratories as applicable. In such cases, sites should provide Normal reference ranges of such lab and lab licenses to Central Office Coordinator.

Trial Period:	Screening Phase			Treatment Cycles								End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Visit 1	Visit 2	CPA Run-in	1	2	3	4	To be repeated beyond 8 cycles				Discontinuation	Safety Follow-up	Follow Up Visits	Survival Follow-Up[a]
								5	6	7	8				
Scheduling Window (Days)[b]:	-28 to -7	-14 to -7	-7 to -1		- 3	- 3	- 3	- 3	- 3	- 3	- 3	At time of Discontinuation	30 days post discon (± 7days)	Every 12 weeks (± 7days)	Every 12 weeks (± 7days)
Administrative Procedures															
Informed Consent	X														
Inclusion/Exclusion Criteria	X														
Demographics and Medical History	X														
Prior and Concomitant Medication Review	X	X		X	X	X	X	X	X	X	X	X			
Post-study anticancer therapy status															X
Survival Status															X
Investigational Product															
Pembrolizumab				X	X	X	X	X	X	X	X				
DPX-Survivac				X[q]		X[q]		X[q]		X[q]					
Cyclophosphamide [o]			X	X	X	X	X	X	X	X	X				
Clinical Procedures/Assessments															
Review Adverse Events			X	X[s]	X	X	X	X	X	X	X	X	X		
Full Physical Examination	X											X			
Directed Physical Examination				X[s]	X	X	X	X	X	X	X		X		

Trial Period:	Screening Phase			Treatment Cycles								End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Visit 1	Visit 2	CPA Run-in	1	2	3	4	To be repeated beyond 8 cycles				Discontinuation	Safety Follow-up	Follow Up Visits	Survival Follow-Up[a]
								5	6	7	8				
Scheduling Window (Days)[b]:	-28 to -7	-14 to -7	-7 to -1		- 3	- 3	- 3	- 3	- 3	- 3	- 3	At time of Discontinuation	30 days post discon (± 7days)	Every 12 weeks (± 7days)	Every 12 weeks (± 7days)
Vital Signs (including Height and Weight)[c]	X			X[s]	X	X	X	X	X	X	X	X	X		
ECOG Performance Status		X		X	X	X	X	X	X	X	X	X	X		
Review/collect Cyclophosphamide diary					X	X	X	X	X	X	X				
Evaluation and photograph of injection site [t]				X	X	X	X	X	X	X	X	X	X[o]		
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory															
Pregnancy Test – Urine or Serum b-HCG[d]		X													
PT/INR and aPTT[e]		X													
CBC with Differential[f]		X		X[s]	X	X	X	X	X	X	X	X	X		
Comprehensive Serum Chemistry Panel [f, p]		X		X[s]	X	X	X	X	X	X	X	X	X		
Urinalysis [f, g]		X		X	X	X	X	X	X	X	X		X		
Thyroid Function Tests (T3, FT4 and TSH) [f, g]		X		X	X	X	X	X	X	X	X		X		
ECGs[g]		X		X	X	X	X	X	X	X	X				
Efficacy Measurements															
Radiological Assessment	X				X[h]		X [h]		X [h]		X [h]	X [i]		X [j]	
Archival Tissue Collection															
Archival Tumor Collection (confirm that archival tissue is available)[k]	X														
Correlative Studies															
Fresh Tumor Biopsy[l]	X			X									X		
Normal DNA Sequence Blood[m]	X														
Circulating Tumor DNA Blood Buffy coat [m]		X				X			X			X			
Immune Assessment for PBMC Blood [m]		X		X	X			X			X [n]	X		X	
Immune Assessment for Serum Cytokines[m]		X		X	X	X	X	X	X	X	X	X		X	

a. After documented local site assessed disease progression, or the start of new anticancer treatment; contacts are every 12 weeks (3 months) by telephone for a maximum of 2 years.

b. In general, assessments/procedures are to be performed on Day 1 and prior to the dose of treatment for each cycle unless otherwise specified.

c. Height will be measured at visit 1 only.

d. For women of reproductive potential, serum pregnancy test should be performed within 72 hours prior to first dose of cyclophosphamide.

e. PT/INR, aPTT may be repeated pre-tumor biopsy if clinically indicated.

f. After Cycle 1, laboratory samples can be collected up to 3 days prior to Day 1 of subsequent cycles.

g. To be repeated every cycle until the end of treatment.

h. Radiologic imaging for response assessment be performed every 6 weeks (42 ±7 days) after the date of first dose of trial Pembrolizumab and DPX-Survivac. Local site investigator readings will be used for subject management. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. It will be at Investigator choice to perform radiological assessment in advance if clinically indicated.

i. In subjects who discontinue study therapy without local site confirmed disease progression, a radiologic evaluation should be performed at the time of treatment discontinuation (i.e., date of discontinue ± 4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory.

j. In subjects who discontinue study therapy without documented local site disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 12 weeks (84 ± 7 days) in the first year and every 24 weeks (168 ± 7days) after year 1 until (1) the start of new anti-cancer treatment, (2) disease progression as assessed by the local site assessment, (3) death, or (4) the end of the trial, whichever occurs first.

k. An archival tissue sample (10-15 unstained slides) must be available prior to study registration. For patients who do not have any archival tumor tissue available or fewer than 10 slides available, enrollment may be allowed based on discussion with Principal Investigator.

l. Fresh tumor biopsies should be done at these time points: 1) Pre-treatment at day -28 to day -1, 2) On-treatment at day 15 of cycle 1 (± 7 days), and if possible, 3) when radiological disease progression on therapy is confirmed (optional). For handling and processing details for tumor biopsies, please refer to Table 8.1.

It is also allowed to collect opportunistic and sample from ascites, pleural effusion or cystic lesion drainage.

m. For details regarding handling and processing of blood-based biomarkers, please refer to Table 8.1.

n. For PBMC samples after cycle 5, please draw every 3 cycles (i.e. cycle 8, 11, 14, etc).

o. Cyclophosphamide will be given for 7 days prior to the first priming dose of DPX-Survivac, then 7 days off, 7 days on. Cyclophosphamide should always be given in the week prior to a boosting dose of DPX-Survivac. In the event, there is a delay in DPX-Survivac Cyclophosphamide may be given for more than 7 days.

p. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

q. Please refer to Section 5.1 for frequency of priming and boosting doses for DPX-Survivac

s. During first cycle patients will be evaluated weekly (day 7 and day 15 +/- 3 days) with repeated blood test, physical examination and adverse events assessment. During the following cycles will be at the Investigator discretion if asses the patient between cycles.

t. At minimum, the following types of photographs of the injection sites must be taken at each day 1 clinic visit whether or not the subject has an injection site reaction (1) close ups of each injection site with a ruler, (2) wide shot of each injected upper thigh region, and (3) aerial shot of both legs. The injection sites should be clearly marked by number and date on the photograph. Evaluation and photography of injection site is required only when patient was observed to have injection site reaction at EOT, otherwise this is optional.

10. MEASUREMENT OF EFFECT

In order to define efficacy of Pembrolizumab, DPX-Survivac and Cyclophosphamide combination, patients should be re-evaluated every 6 weeks.

10.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (uni-dimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

10.1.1 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitic involvement of skin or lung, inflammatory breast disease, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not

be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

10.1.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical Lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

CT & MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. CT should be performed with slice thickness of 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Cytology, Histology: These techniques can be used to differentiate between PR and CR in rare cases. The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

10.1.3 Response Criteria

10.1.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the baseline measurements.

10.1.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

10.1.3.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

10.1.4 iRECIST

When radiologic imaging assessment by the investigator shows disease progression by RECIST 1.1, the trial subject has the option of continuing treatment while awaiting radiologic local site confirmation of progression as assessed by repeat imaging ≥4 weeks later.

The decision to continue trial treatment after the first evidence of disease progression is at the Investigator's discretion based on the clinical status of the subject as described in Table 10.1 below

(Imaging and Treatment After First Radiologic Evidence of Disease Progression).
Clinically stable subjects may continue to receive trial treatment and tumor assessment should be repeated ≥ 4 weeks later in order to confirm local site disease progression by RECIST 1.1.

Clinical stability is defined by the following criteria:

- Absence of signs and symptoms of clinically significant progression of disease, including worsening of laboratory values
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., CNS metastasis with potential for cord compression) requiring urgent alternative medical intervention

NOTE: Subjects exhibiting toxicity from trial therapy as outlined in Section 5.4 may NOT continue to receive trial therapy.

Table 10.1 Imaging and treatment after first radiologic evidence of disease progression

	Clinically stable		Clinically unstable	
	Imaging	Treatment	Imaging	Treatment
1st radiologic evidence of disease progression (RECIST 1.1 by local site assessment)	Repeat imaging at >4 weeks at site to confirm disease progression	May continue trial treatment at the investigator's discretion while awaiting confirmatory scan by site	Repeat imaging at >4 weeks at site to confirm disease progression per physician discretion only	Permanently discontinue study treatment
Repeat scan confirms disease progression (RECIST 1.1 by local site assessment)	No additional imaging required	Permanently discontinue study treatment	No additional imaging required	N/A
Repeat scan shows no evidence of disease progression (RECIST 1.1 by local site assessment)	Continue regularly scheduled imaging assessments	Continue trial treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments	May restart trial if condition has improved and/or clinically stable per investigator's discretion

In determining whether or not the tumor burden has increased or decreased per iRECIST, the local site investigator should consider all target and non-target lesions as well as any incremental new lesion(s). New lesions are to be assessed and categorized as measurable or non-measurable based on RECIST 1.1. Up to five additional new targets can be recorded, but should not be included in the sum of measures of the original baseline targets. New lesions are to be reviewed along with the previously identified lesions at the subsequent scan in order to determine if the patient has confirmed progressive disease.

Scenarios where progressive disease is confirmed at repeat imaging if ANY of the following occur by

iRECIST:

- New target lesions previously identified has further increase by at least 5mm since last evaluation
- Further increase in the size of new non-target lesions since last evaluation (does not need to meet RECIST 1.1 criteria for unequivocal progression)
- Additional new lesion(s) (target or non-target) since last evaluation

If repeated imaging confirms progressive disease due to any of the scenarios listed above, subjects will be discontinued from trial therapy.

10.2 Endpoint Definitions

10.2.1 Overall Response Rate (ORR)

ORR will be based on the disease evaluation by investigator assessment per RECIST 1.1 and immune-related RECIST (iRECIST) and will include complete response and partial response.

10.2.2 Progression-Free Survival (PFS)

Progression free survival (PFS) is defined as the duration of time from start of treatment to time of progression as per iRECIST or death, whichever occurs first.

10.2.3 Overall Survival (OS)

Overall Survival (OS) is defined as the duration of time from start of treatment to death from any cause.

11. DATA REPORTING / REGULATORY REQUIREMENTS

11.1 Data Collection and Reporting

All data obtained in the clinical trial described in this protocol will be reported on eCRFs in the Medidata Electronic Document Capture system (Medidata). Data reported on eCRFs should be consistent with the source documents and verifiable. All data for the primary and secondary endpoints will be source verified prior to publication. The Investigator will review the data and electronically sign the eCRFs to acknowledge agreement with the data entered. Data entered into Medidata will be used for developing tables and listings for the final study report.

Prior to the start of the study, the Investigator will complete a Site Participant's Log showing the signatures and handwritten initials of all individuals who are authorized to make or change entries on source documents and eCRFs.

11.2 Source Documents

Source documents refer to the original documents, data, and records where the first recording of a data point occurred.

Examples of source documentation include, but are not limited to: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial.
Please ensure that source document entries are attributable, legible, contemporaneous, original, and accurate. Note that sign-off of source documents should be attributable to a single record and "bracketing" multiple entries on source document pages for a single signature is not allowed. Corrections to source document entries should only be completed by drawing a single line through the previous entry and then recording the corrected data, initialing the change, and dating the change. Only the individual that initially recorded the data should make any corrections.

11.3 Retention of Patient Records and Study Files

The ICH (International Conference on Harmonisation) guidance document "Good Clinical Practice (GCP): Consolidated Guidelines" (ICH Guidance Document E6) (1997) states that the investigator and sponsor shall retain study records relating to the study until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. In the event of a trial discontinuation, sponsor records should also be kept for a minimum of 2 years. Per Health Canada, all original records should be maintained for 25 years after the above requirements are satisfied and the final report has been issued. Records contained in the Clinical Trial Application should be maintained on file for at least 25 years. We will comply with these regulations. The Sponsor will notify sites when documents are to be destroyed.

11.4 Site and Study Closure

Upon completion of the study, the following activities, when applicable, will be completed by the Central Office in conjunction with the Investigator, as appropriate:

- Collection of study materials (i.e., specimen collection kits, drug shippers, etc.)
- Data clarifications and/or resolutions
- Accounting, reconciliation, and final disposition of used and unused study medication
- Review of site study records for completeness

If the Sponsor or Investigator or appropriate regulatory officials identify conditions arising during the study that indicate that the study should be halted or that the study center should be terminated, this action may be taken after appropriate consultation among the Sponsor and Investigator. Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the patients enrolled in the study
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product
- Failure of the Investigator to enroll patients into the study at an acceptable rate

- Failure of the Investigator to comply with pertinent regulations of appropriate regulatory authorities
- Submission of knowingly false information to the Sponsor, or appropriate regulatory authority
- Insufficient adherence to protocol requirements
- Refusal of the Investigator to supply source documentation of work performed in this clinical trial

Study termination and follow-up will be performed in compliance with the conditions described in the ICH GCP E6 Guidelines, section 4.12, ICH E6 4.13, ICH E6 5.20, and ICH E6 5.21.

11.5 Informed Consent

All subjects are required to sign an IRB (Institutional Review Board)/REB (Research Ethics Board) approved informed consent form (ICF) before starting any procedure related to the trial. Each investigator has the responsibility to complete inform the patient about all the procedure and treatments required by the protocol and the relative risks. The subject needs to be informed also about the possibility to withdraw the consent every time during the study.
After adequate information the Investigator has to obtain a signed ICF and a copy has to be given to each subject before enrollment.

11.6 IRB/REB

This study must be approved by the IRB/REB. The IRB/REB must also approve any significant changes to the protocol as well as a change of investigator. Records of all study review and approval documents must be kept on file by the investigator and are subject to FDA/Health Canada inspection during or after completion of the study.

The IRB/REB has to be notified of any serious adverse events that meet local IRB/REB reporting criteria, of the completion or termination of the study and a final report will be provided. Any change in the protocol or in the trial procedure needs to be approved by IRB/REB.

12. STATISTICAL CONSIDERATIONS

12.1 Study Design/Endpoints

12.1.1 Efficacy Endpoint Analysis

Efficacy of Pembrolizumab, DPX-Survivac and oral Cyclophosphamide combination will be assess based on overall response rate as per RECIST 1.1 and iRECIST. The signal of activity for the expansion cohort will be at least 3/10 partial response or stable disease for 12 weeks according RECIST 1.1 for the platinum-sensitive group (Cohort A) and 2/10 for the platinum-resistant group (Cohort B).
Only patients with high grade serous or endometrioid cancers will be considered for the efficacy endpoint analysis

12.1.2 Safety Endpoint Analysis

The dose regimen during the escalation cohort will be considered safe if 0 or 1 DLTs occur in 6 subjects. A subject will be considered evaluable for safety if treated with at least one immunization and one Pembrolizumab dose. Frequency and severity of adverse events will be tabulated using counts and proportions detailing frequently occurring, serious and severe events of interest according to CTCAE 4.03.

12.1.3 Biomarker Endpoint Analysis

Changes of biomarkers in genomic and immune landscapes in patients before and after treatment will be compared between responders and non-responders by using T-test or Wilcoxon's test. For all the other objectives, summary statistics, such as the mean, median, counts and proportion, will be used to summarize the patients. Overall response rate (ORR), Progression Free Survival (PFS) and overall survival (OS) will be reported. Survival estimates will be computed using the Kaplan-Meier method. Potential association between variables will be measured using Pearson correlation coefficients, chi-square tests, one- or two-sample t-tests or logistic regression analyses as appropriate. Non-parametric tests such as Spearman correlation coefficients, Fisher's exact tests and Wilcoxon rank sum tests may be substituted if necessary. Ninety-five percent confidence intervals will be constructed and selected results will be illustrated using figures and plots.

If sufficient numbers of patients have a clinical response, the treatment-related marker effect on clinical response will be evaluated. Logistic regression analysis will be used to test whether the mean marker value difference (pre-treatment biopsy value - post-treatment biopsy value) and the mean marker value at the pre-treatment biopsy are statistically significant predictors of clinical response. Plots and tables of the data will be presented to visually inspect the findings. These tests will be considered purely exploratory in nature and exact p-values given. Thus, no p-value adjustment will occur; however, significant results will be interpreted understanding the exploratory nature of these tests and the increased probability of observing statistically significant results under the null hypothesis due to multiple testing.

12.2 Sample Size/Accrual Rate

A total of 39-42 patients will be recruited on this study, which will be broken down as follows:

- 9-12 platinum resistant patients of all histological sub-types will be recruited to the Dose Escalation phase. Additional patients may be included as per PI discretion for a comprehensive safety review or in order to confirm the established RP2D
- 10 patients with high grade serous or endometrioid ovarian cancer who are considered platinum-sensitive in the Dose Expansion phase
- 10 patients with high grade serous or endometrioid ovarian cancer who are considered platinum-resistant in the Dose Expansion phase
- 10 patients with non-high grade serous or endometrioid ovarian cancer in the Dose Expansion phase

Accrual will end when the required number of patients with high grade serous or endometrioid ovarian cancer has been reached.

APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: DATA MANAGEMENT GUIDELINES

Data Management Guidelines

Case Report Form Submission Schedule

The Eligibility Checklist will be a paper CRF that will be provided by the Drug Development Central Office and all other data required for the study will be collected in eCRFs in Medidata. The form submission schedule is outlined below.

Case Report Form	Submission Schedule
Eligibility Checklist	At the time of registration
Baseline Form	Within 3 weeks of on study date
On Treatment Form	Within 3 weeks of the end of each cycle of treatment
Off Treatment Form	Within 3 weeks of the patient coming off-study
Short Follow-up Form	Within *3* weeks of the patient coming to clinic. Required every 12 weeks until death.
Final Report Form	Within 3 weeks of the patient's death being known to the investigator unless this constitutes a reportable adverse event when it should be reported according to expedited guidelines

Case Report Form Completion

The paper Eligibility Checklist CRF must be completed using black or blue ink. Any errors must be crossed out so that the original entry is still visible, the correction clearly indicated and then initialed and dated by the individual making the correction. eCRFs will be completed according to the schedule noted above.
All patient names or other identifying information will be removed prior to being sent to the Central Office and the documents labeled with patient initials, study number and the protocol number if applicable.

Monitoring

This is an investigator initiated study and study monitoring will be performed by the Drug Development Program Central Office or its designate.
Data in the Medidata Rave eCRFs will be monitored on a regular basis and quality assurance measures will be performed. Electronic data queries as well as paper query letters may be issued to the site.

Regulatory Requirements

- Please submit all required documents to the DDP Central Office.
- Canadian Principal Investigators must submit a completed Qualified Investigator Undertaking.
- All investigators must have an up-to-date CV (signed within 2 years) on file with the DDP Central Office.
- Laboratory certification/accreditation and normal ranges are required

- Confirmation of all investigators having undergone training in the Protection of Human Research Subjects is required. It is preferred that other staff involved in the trial also undergoes such training.
- Investigators and site staff are required to complete Medidata eCRF training modules depending on delegated tasks
- Consent forms must be reviewed by the Central Office before submission to the local ethics regulatory board (REB/IRB) and must include a statement that 1) information will be sent to and 2) medical records will be reviewed by the DDP Central Office.
- A Membership list of the local ethics board is required.
- A copy of the initial approval letter from the ethics board must be submitted to the DDP Central Office.
- A completed Site Participant List/Training Log is required and must be submitted to DDP
- Continuing approval will be obtained at least yearly until follow-up on patients is completed and no further data is being obtained for research purposes.

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