DPX-Survivac and checkpoint inhibitor in DLBCL

Phase 2 Study of an Immune Therapy, DPX-Survivac with Low Dose Cyclophosphamide administered with Pembrolizumab in Patients with persistent or Recurrent/refractory Diffuse Large B-Cell Lymphoma (DLBCL)

(SPiReL)

Protocol Number: *0891*

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Regulatory Sponsor: Sunnybrook Research Institute
Funder: IMV Inc.
Investigational Product: Pembrolizumab/ DPX Survivac
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SPONSOR STATEMENT OF COMPLIANCE

This study will comply with the International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Participants, as well as applicable regulatory and institutional requirements.

Personnel listed below are authorized to sign the protocol and any subsequent protocol amendments on behalf of the Sponsor:

Name: *(Print)*	Dr. Neil Berinstein
Title: *(Print)*	Professor of Medicine University of Toronto Sunnybrook Research Institute Sunnybrook Health Sciences Centre Odette Cancer Centre 2075 Bayview Avenue Toronto, Ontario, M4N3M5
Signature:	
Date of Approval: *(yyyy-mmm-dd)*	

PROTOCOL SIGNATURE PAGE

I have read this protocol in its entirety and its appendices. I agree to comply with the requirements of the study protocol and procedures for data recording/reporting and acknowledge my responsibility for the well-being of each research participant, and to ensure that all persons involved in study activities are adequately informed about the protocol, the investigational product, and their trial-related duties. The signature below constitutes the agreement to conduct this study in accordance with the REB approved protocol, GCP and applicable regulatory requirements, including confidentiality, ethical guidelines and regulations regarding the conduct of research in humans.

Qualified Investigator:

Name:
(Print) _____

Title & Institution:
(Print) _____

Signature: _____

Date of signature:
(yyyy-mmm-dd) _____

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LIST OF ABBREVIATIONS

The following abbreviations describe terms, documents and study personnel used in the conduct of this study protocol.

AE	Adverse Events/Adverse Experience
ASCT	Autologous Stem Cell Transplant
CC	Coordinating Centre
CIOMS	Council for international Organizations of Medical Sciences
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CCTS	Centre for Clinical Trial Support
DLBCL	Diffuse Large B Cell Lymphoma
EC	Ethics Committee
EOS	End Of Study
ECOG	Eastern Cooperative Oncology Group
HLA	Human Leucocyte Antigen
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IP	Investigational Product
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
pCRF	Paper Case Report Form
EDC	Electronic Data Capture
GCP	Good Clinical Practice
ICF	Informed Consent Form
ISR	Injection Site Reaction
MedDRA	Medical Dictionary for Regulatory Authorities
MTD	Maximum Tolerated Dose
NSCLC	Non-Small Cell Lung Cancer
PBMC	Peripheral Blood Mononuclear Cells
PHI	Personal Health Information
PI	Principal Investigator
PM	Product Monograph
QI	Qualified Investigator
REB	Research Ethics Board
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SRI	Sunnybrook Research Institute
SUADR	Serious and Unexpected Adverse Drug Reaction
TMF	Trial Master File

PROTOCOL SUMMARY

Protocol Title (Short Title)	Phase 2 Study of an Immune Therapy, DPX-Survivac with Low Dose Cyclophosphamide administered with Pembrolizumab in Patients with persistent or recurrent/refractory Diffuse Large B-Cell Lymphoma (DLBCL)
Protocol Number	0891
Phase	II
Study Design	This is a Phase *2* non-randomized, open label, uncontrolled, efficacy and safety study. Study participants will receive two priming doses of 0.5 mL of DPX-Survivac 21 days apart and up to six 0.1 mL maintenance injections every two months with low dose metronomic oral cyclophosphamide (50 mg BID) for one year or until disease progression, whichever occurs first. Pembrolizumab 200 mg will be administered every 3 weeks for up to one year or until disease progression, whichever occurs first.
Study Duration	42 months
Setting	National multi-centre
Sample Size	25 patients
Main Inclusion Criteria	Measurable persistent or recurrent/refractory Diffuse Large B-cell Lymphoma (DLBCL)
Primary Outcome(s):	To document a minimal objective response rate of 24% to treatment with DPX-Survivac and low dose cyclophosphamide administered together with anti-PD-1 (Pembrolizumab) in patients with recurrent, survivin-expressing B cell lymphomas using modified Cheson criteria.
Secondary Outcome(s):	1) To document evidence of regression using waterfall analyses 2) To document the toxicity profile 3) To document duration of response using modified Cheson criteria and immune-related response criteria (irRc) 4) To document time to next treatment and survival
Exploratory Outcomes(s):	1) To document the changes in circulating T cell immune responses to survivin and relationship to peripheral B cell numbers 2) To document changes in T cell and T cell subset infiltration and gene expression pathways in treatment compared to pre-treatment tumour biopsies 3) To assess potential biomarkers of immune and clinical response from subject clinical, biological and immunologic data, and pre-treatment and on-treatment tumor biopsies.

	4) To evaluate other relevant biologic assays that may be identified during the conduct of the trial that may have immune or clinical relevance on samples already collected.
Investigational Product and Planned Use	Study participants will receive two priming doses of 0.5 mL of DPX-Survivac 21 days apart and up to six maintenance injections every two months in alternating upper thigh regions for one year or until disease progression, whichever occurs first. Pembrolizumab 200 mg will be administered as a 30-minute IV infusion every 3 weeks for up to one year or until disease progression, whichever occurs first.
Statistical Analysis:	The safety population is defined as all subjects who receive at least one immunization. The efficacy population is defined as all subjects who received at least three injections, four infusions of pembrolizumab and one on-treatment CT-scan between study days 70 and 104. The design has more than 90% power to conclude that the treatment is effective if its true response rate were equal to 35% or more. The design also has less than 5% probability to conclude that the treatment is effective if its true response rate were equal to 10% or less. Standard descriptive statistical methods will be used to summarize the data. The response rate will be estimated along with its exact 95% confidence interval.

1 KEY ROLES AND CONTACT INFORMATION

Regulatory Sponsor:	Sunnybrook Research Institute (SRI) 2075 Bayview Avenue Toronto, ON Canada M4N 3M5
Principal Investigator:	Dr. Neil Berinstein
Academic Research Organization:	Centre for Clinical Trial Support, SRI 2075 Bayview Avenue Toronto, ON Canada M4N 3M5

2 INTRODUCTION

This study document is the protocol for research involving human participants. This study is to be conducted according to Canadian and international standards, and in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice E6 (ICH-GCP), World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Participants, as well as applicable regulatory and institutional requirements and research policies.

2.1 Background

Although many diffuse large cell B cell lymphomas (DLBCL) may be cured or have prolonged remissions with initial therapy using R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone), patients with recurrent DLBCL (other than those who are eligible for high dose therapy and autologous stem cell transplantation (ASCT) will eventually die of their disease. Effective salvage therapies for non-transplant-eligible or post-transplant patients with DLBCL is an unmet medical need. There is an opportunity to develop a successful immune therapy combination treatment against B cell lymphomas, particularly one that could work in concert with other treatments and further extend remissions.

Many different therapeutic vaccines have been evaluated in phase 1, 2, and even phase 3 trials. With the exception of the sipuluecel T dendritic cell based vaccine[1] , these trials have not shown significant clinical activity. Much has been learned, however, about the principles of applying immune-based therapies to cancer patients and about developing vaccines that are sufficiently immunogenic to break tolerance to self tumour antigens[2] . Cancer vaccines appear to have their greatest impact earlier in the disease course or in situations with minimal residual disease. In addition, cancer vaccines alone are not likely to be clinically effective in patients with measurable disease and combinations with immune modulators are essential to overcome some of the immunosuppressive pathways that cancers utilize to avoid immune rejection. The principle behind this trial is to combine a T-cell activating therapy (formerly identified as a highly immunogenic vaccine formulation) to the tumour antigen survivin with an active immunomodulator aimed at reversing T cell anergy. A component of this combination therapy with this immune modulator -metronomic cyclophosphamide- has already been shown to mediate anti-tumour activity in the patient population to be studied[3] .

The programmed cell death 1 (PD-1) pathway represents a major immune control switch, which may be engaged by tumour cells to overcome active T-cell immune surveillance. MK-3475/prembrolizumab (anti-PD-1/checkpoint inhibitor) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2[4]. This blockade enhances functional activity of the target lymphocytes to facilitate tumour regression and ultimately immune rejection. Merck is studying MK-3475 for various oncology indications. For additional information on Merck clinical studies please refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475. MK-3475 has already been approved by regulatory agencies for treatment of metastatic melanoma that is recurrent after dacarbazine and Ipilimumab and is being studied in many other indications either as monotherapy or as a combination therapy.

The principle behind this trial is to combine a highly immunogenic drug formulation (DepoVax) to the tumour antigen survivin (DPX-Survivac) with an active T cell activator aimed at reversing T cell anergy. The tumour-associated antigen survivin is expressed in approximately 60% of DLBCL. DPX-Survivac has already been shown to be highly immunogenic in patients with ovarian cancer particularly when combined with metronomic cyclophosphamide to suppress regulatory T cells. In fact a clinical objective response of patients with recurrent ovarian and gynaecological cancers has been documented[5]. For additional information on IMV clinical studies and DPX-Survivac please refer to the IB.

2.2 Pharmaceutical and Therapeutic Background

A. Investigation Product Background of MK-3475 (Pembrolizumab)

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades[6]. Accumulating evidence shows a correlation between tumour-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumours.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumours to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2)[7,8]. The structure of murine PD-1 has been resolved[9]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70, which are involved in the CD3 T-cell signaling cascade[10-12]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins[13,14]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells[15,16]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells[17] as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumours[6,14,18,19]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably 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 serves to

dampen unwarranted T-cell function in peripheral tissues[14]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor[20-22]. PD-1 has been suggested to regulate tumour-specific T-cell expansion in subjects with melanoma[23]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumour immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor. In Canada, pembrolizumab is approved for renal call carcinoma, baldder cancer, non-small cell lung carcinoma, melanoma, classical Hodgkins lymphoma and urothelia carcinoma.

B. Investigational Product Background: DPX-Survivac

IMV, formerly ImmunoVaccine Technologies Inc. has developed a patented prophylactic/ immune therapy platform demonstrated to enhance peptide immunogenicity in animal models with its ability to maintain an immune response to the peptides delivered after repeated immunizations[24]. The DepoVax (DPX) platform is a lipid-based depot formulation able to enhance cellular immune responses. It is oil based; making it particularly well suited for therapeutic cancer treatment applications since it allows for practical delivery of peptide antigens without having to resort to cumbersome emulsification. DepoVax also includes a T-helper peptide, a polynucleotide immunostimulant, synthetic lipid and cholesterol inactive ingredients to enhance and sustain the immune response.

The safety concerns with therapeutic cancer treatments emanate from the risk of antigen-specific autoimmune disease as well as non-specific side effects (local and systemic) from the adjuvant system itself. The proposed DPX-Survivac immune therapy is designed to target survivin, a member of the inhibitor of apoptosis protein family. Survivin over-expression has been detected in many cancer types, yet expression in normal adult tissues is limited. It was identified as the fourth most highly abundant transcript in several common cancers such as melanoma, colon, brain, breast, and ovarian cancers[25,26]. In blood cancers, survivin over-expression has been consistently demonstrated, particularly in lymphomas and multiple myeloma[27]. Animal studies performed by others using mouse tumour cell lines expressing survivin have demonstrated that targeting survivin inhibits tumour growth[28,29], without affecting any normal tissue with survivin expression. Survivin-specific T cells have been detected in cancer patients, but not in healthy individuals suggesting a differential presentation of survivin epitopes by cancer cells[30]. The presence of persistent survivin-specific T cells in cancer patients also suggests that the presence of anti-survivin immunity may not induce autoimmunity.

DLBCL is the lymphoma subtype consistently expressing “high and strong” expression of survivin compared to other types of lymphoma[31]. Independent studies have shown survivin expression in 60% (134/222) of DLBCL patients by IHC with survivin expression negatively correlated with survival[32] and survivin expression (>45% positive tumour cells) in 39% of DLBCL patients (22/56) with the survivin expression correlated with shorter survival[33]. Survivin is utilized by tumours to evade apoptosis and promote malignancy. Survivin is involved in multiple

signaling pathways that are critical for cancer cell survival and has been described as a "cross-road signaling molecule" in cancer cells[34]. It is extensively studied as an inhibitor of apoptosis, yet is also directly involved in cell cycle progression and mitosis, response to cellular stress, including responses to cancer therapeutics, and through interactions with NF-κB, involved in the promotion of tumour cell invasion and metastasis. It is a molecule within cancer cells, that when targeted, is very difficult for cancer cells to down-regulate without extensively sacrificing its unlimited growth and resistance to standard therapies. This makes survivin a particularly interesting antigen to target with immune therapy.

DPX-Survivac is a T cell activating immune therapy 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 1). The presumed primary mechanism of action of DPX-Survivac is to elicit a cytotoxic T lymphocyte response against tumour 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 ISA 51 VG emulsion). This product was tested in a phase 1 clinical trial (EMR-200032-001) that enrolled 53 patients with advanced solid tumours to evaluate the immunogenicity (primary endpoint) and safety of multiple weekly injections of increasing doses of Survivac in Montanide ISA 51 VG[35]. 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.

Table 1: 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%

2.3 Preclinical Data

Refer to the Merck and IMV Investigator's Brochures for Preclinical data.

2.4 Clinical Data to Date

Refer to the Merck and IMV Investigator's Brochures for Clinical data.

2.5 Potential Risks/Benefits and Rationale

2.5.1 Rationale for the Trial and Selected Subject Population

Study subjects will have recurrent diffuse large cell B cell lymphomas (DLBCL) and are not eligible for high dose therapy and autologous stem cell transplantation (ASCT). This defined population will eventually die of their disease because effective salvage therapies are not available.

2.5.2 **Rationale for Dose Selection/Regimen/Modification**

An open-label Phase I trial (Protocol 001) was conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumours. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumour size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumour activity. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumour burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of Pembrolizumab in solid tumours is based on: 1) similar efficacy and safety of Pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of Pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumour burden or indication on distribution behavior of Pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of Pembrolizumab target engagement will not vary meaningfully with tumour type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of Pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in

melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

IMV completed a phase 1 ovarian cancer vaccine clinical trial with DPX-Survivac (ONC-DPX-Survivac-01)[36]. The study involved a lead-in cohort evaluating the safety of the Survivac peptides formulated in DepoVax, followed by a dose finding safety and immunologic evaluation of two dose levels of DPX-Survivac with low dose cyclophosphamide. In this study nineteen subjects were successfully treated with at least one dose of DPX-Survivac. Six subjects in each of cohort A (0.5 mL of DPX-Survivac), cohort B (0.1 mL of DPX-Survivac plus cyclophosphamide), and cohort C (0.5 mL DPX-Survivac plus cyclophosphamide) received all three scheduled doses, three weeks apart. One subject in cohort A withdrew consent after first dose. The majority of treatment related adverse events were grade 1-2 injection site reactions such as induration, erythema, pain, edema, pruritus, and/or warmth. There were three grade 3 ulcerations reported for DPX-Survivac. One of the grade 3 ulcerations in cohort C was reported as a related SAE but as indicated in the IB and protocol, this is an expected AE. Grade 3 site of injection reactions occurred after the third dose and at the third injection site. These reactions are likely immune mediated, based on the evaluation of a biopsy from one subject with a grade 3 reaction. Three weeks after the second dose there is a strong circulating T cell response, we speculate therefore that placing a large antigen load with the third dose initiates a persistent immune attack at the site of injection increasing the likelihood of severe reactions. Reducing the dose volume and/or delaying subsequent dosing was therefore tested in a Phase 1b study (ONC-DPX-Survivac-03).. Immune monitoring of phase 1 study subjects has established a clear dose response and an enhancement of the immune response when the vaccine is combined with cyclophosphamide. Thus the best antigen-specific immune responses occurred in Cohort C. Robust immune responses were generated after 1-2 vaccinations, and these immune responses were maintained by subsequent vaccinations.

IMV completed ONC-DPX-Survivac-03, the Phase 1b clinical trial with DPX-Survivac in ovarian cancer patients in centers in both Canada in 2018. Subjects in all 5 study cohorts received subcutaneous DPX-Survivac with intermittent low dose cyclophosphamide, similar to ONC0DPX-Survivac-01, but the dose was reduced to 0.25mL from 0.5mL the safety and efficacy of up to six subcutaneous doses of DPX-Survivac. In cohorts 1 and 2 two priming doses of 0.25 mL were delivered 3 weeks apart followed by four 0.1 mL maintenance doses administered 8 weeks apart. Cohort 1 received both 0.25mL doses in the same upper thigh region, while in Cohort 2, the 0.25mL doses were administered in opposite limbs. Cohort 3 received three 0.25 mL doses of DPX-Survivac spread 8 weeks apart, while Cohort 4 received five doses of 0.25mL 6 weeks apart. Cohort 5 received two doses of 0.25mL 4 weeks apart plus three doses of 0.5mL 4 weeks apart. A total of 38 subjects were enrolled into the study; six in Cohort 1, 9 in Cohort 2, 7 in Cohorts 3 and 4, and 9 in Cohort 5. 37 subjects were included in the analysis, as one subject withdrew consent. Of the 38 enrolled, 23 completed the study, which was defined as subjects having completed all their cohort-specific visits. Subjects were treated for up to 38 weeks. The study protocol was designed to incorporate dose omission in the presence of significant injection site reactions, making it an integral part of the study design. All 37 subjects receiving at least one dose of study treatment experienced at least 1 injection site reaction, ranging from Grade 1 – 3. No subject experienced a Grade 4 injection site reaction.

Most injection site reactions were low-Grade; induration Grade 1 was 54% and Grade 2 was 35%, Grade 1 erythema was 43% and Grade 2 was 23%, Grade 1 discoloration was 40%. Reports of Grade 3 erythema and induration were highest overall prior to use of CTCAE version 4.03, occurring in Cohort 1 and Cohort 2, and therefore, may have been overestimated in these cohorts. There were 7 subjects with reported injection site ulcerations in this study: one Grade 1, two Grade 2, and four Grade 3. The highest frequency of ulcerations occurred in Cohort 1, which has led to the recommendation that all doses of DPX-Survivac be administered to alternating limbs. The most commonly observed systemic adverse event was fatigue, and no trends in clinically significant findings in hematology or chemistry parameters were observed. No SAEs were determined to be related to the study drug. Immune responses were assessed by 2 methods of analysis performed on PBMC samples collected from the subjects throughout the study; ELISpot and MHC-tetrameter staining for antigen specific $CD8^+$ T cells. DPX-Survivac induced detectable immune responses in 31 out of 37 subjects evaluated. A secondary objective of the study was to determine if there was any clinical and biochemical evidence of disease regression using standard-of-care radiologic investigations and from cancer antigen 125 test (CA-125). Two subjects demonstrated a CA-125 response and four showed CA-125 progression. One subject from Cohort 1, and one subject from Cohort 5 demonstrated a CA-125 response during the course of the study and completed the study. Two of these subjects completed the study with no radiologic evidence of disease progression, one completed the study but with radiologic evidence of disease progression at study end and one discontinued early due to disease progression. One subject enrolled in Cohort 1 demonstrated a partial response to the treatment, with a measurable reduction in tumour size and positive response to CA-125. This subject also showed remarkably high antigen-specific immune responses as measured by ELISpot and tetrameter analysis. Although the subject did experience a progression of disease approximately 2 months after completing the study, it is interesting to note that the subject's progression-free interval between second chemotherapy and recurrence, which included the DPX-Survivac study, exceeded the progression-free interval between first chemotherapy and first recurrence

IMV conducted a Phase 2 study, which enrolled 4 subjects, but was terminated early to support this trial. Up to 24 subjects were expected to receive two doses of 0.25mL DPX-Survivac 3 weeks apart and four 0.1mL doses 8 weeks apart with intermittent low-dose cyclophosphamide. No new safety or immunogenicity findings were gained from those 4 enrolled subjects.

IMV is conducting a Phase1b/2 study (ONC-DPX-Survivac-06) in subjects with recurrent, fallopian and peritoneal cancers. Two doses of 0.25mL DPX-Survivac 3 weeks apart, and up to six 0.1mL doses every 8 weeks, with intermittent cyclophosphamide and with or without an oral idoleamine 2.3-dioxygenase 1 (epacadostat IDO-1) inhibitor. The Phase 1b study, now complete, was a single-arm non-randomized dose escalation study using the IDO-1 inhibitor as a means to reverse tumour associated immune suppression. A total of 53 subjects were enrolled, all of whom are evaluable for safety The ongoing Phase 2 portion of the study began as a double-arm, randomized, open-label, non-controlled study. Subjects were initially randomized 1:1 to treatment with DPX-Survivac and cyclophosphamide with or without IDO-1 inhibitor. Following a review of the emerging data, the arm receiving the IDO-1 inhibitor was dropped and enrollment continued as a single arm study. 12 subjects were enrolled into the "with" and "without" IDO-1 inhibitor, and 22 were enrolled into the single arm Phase 2. Enrollment is complete, however, treatment is ongoing. The relatedness of adverse events was collected as group of treatments, and it is therefore possible that some of the observed adverse

events are attributable to the IDO-1 inhibitor and not DPX-Survivac. Injection site reactions: induration Grade 1 was 49% and Grade 2 was 9.4%, erythema Grade 1 was 50.9% and Grade 2 was 7.5% and Grade 3 was 2%, and ulceration Grade 2 was 5.7% and Grade 3 was 3.8%. There were no Grade 4 injection site reactions. Of systemic adverse events, nausea (15%), fatigue (7.5%), diarrhea (7.5%) and blood alkaline phosphatase increased (7.5%) were the most common Grade 2 events, and the most common Grade 1 events were fatigue (28.3%) and nausea (43.4%). The most common Grade 3 events reported were fatigue (11.3%), rash (9.4%), anemia (4%), lipase increased (3.8%), followed by hyponatremia, alanine aminotransferase increased, asparate aminotransferase increased, gama glutaminotransferase increased and abdominal pain (1.9%). There was one Grade 4 event reported, a lipase increased. 5 subjects had a best response of PR, 20 subjects had stable disease, and 19 subjects had disease progression. 10 of 44 subjects showed a decrease in target lesion measurements. In the Phase 2 portion of the trial, 1 suspected unexpected serious adverse reaction (SUSAR) was reported in one study subject; grade 3 myositis at the site of DPX-Survivac administration.

IMV is currently conducting a Phase 2 study (P1719-SUR-Z11) in selected advanced and recurrent solid tumours, as an open-label, multi-indications, safety lead-in study to assess the safety and efficacy of the combination of DPX-Survivac, intermittent low-dose cyclophosphamide and pembrolizumab. Two ovarian cancer arms are being recruited for, one with and one without cyclophosphamide. The DPX-Survivac is administered as two 0.25mL doses 3 weeks apart, followed by up to 11 0.1mL doses every 9 weeks. The cyclophosphamide is 50 mg BID for 7 days on and 7 days off, and 200mg of pembrolizumab is administered by IV every 3 weeks for up to 35 cycles. The safety lead-in data for the first 14 subjects were reviewed and accepted for continued enrollment. Subjects with ovarian cancer, hepatocellular carcinoma, non-small cell lung cancer, bladder cancer and microsatellite instability high solid tumours are being recruited.

Since the immune therapy is a Montanide ISA 51 VG-based depot treatment, it will be delivered subcutaneously to the front, upper half of the thigh region, close to the inguinal lymph nodes to promote uptake and processing by the immune system. All injections will alternate between limbs, and not be administered any closer than 10cm to prior injection sites. Previous studies with Montanide-based treatments have shown that multiple, repeated immunizations over extended periods were critical to maintain the desired T cell responses[37]. The goal of the maintenance cycles is to maintain the immune response when it is starting to decline.

A major barrier to the efficacy of cancer immune therapies has been the immunosuppressive environment in cancer patients, including the induction of regulatory T (T reg) cells that inhibit the anti-tumour T cells induced by immune therapies. Recent studies have indicated that the use of low dose administration of chemotherapeutic agents such as cyclophosphamide can have positive effects on immune therapies. At low doses, cyclophosphamide has been demonstrated to act, not as a strict cytotoxic agent, but as a “biological response modifier”, in that it has been shown to have selective effects on the immune system, such as altering the number and efficacy of the T reg population. Prior treatment with low dose cyclophosphamide administered intravenously prior to injections has been shown to reduce Treg cells in cancer patients in a transient fashion, and it may augment the efficacy of immunotherapies[38-40]. However, a key paper published in 2007, describes a clinical trial in stage IV cancer patients where the oral metronomic delivery of cyclophosphamide (50 mg twice a day, one week on, one week off) resulted in a significant and selective depletion of T regs[38]. The side effect profile was

not clearly defined in this key publication. Although this regimen of treatment is widely accepted as having low toxicity, it is difficult to report the grades and frequencies of toxicities since it varies between studies. The variability amongst the studies is due to the different dosing regimens and the multiple tumour types[41-44]. Some subjects may experience one or more of leukopenia, lymphopenia, thrombocytopenia, anemia, fatigue, nausea, and/or vomiting. In the phase 1 clinical trial with DPX-Survivac in ovarian cancer patients(ONC-DPX-Survivac-01), the immune responses seen in Cohort C, where subjects received DPX-Survivac at 0.5 mL with cyclophosphamide, were clearly better than Cohort A, where subjects received 0.5mL DPX-Survivac without the cyclophosphamide. We do not expect low doses of cyclophosphamide to have significant anti-tumour activity on its own and to date there are no publications demonstrating clinical benefits of low dose cyclophosphamide alone in lymphoma. One publication combined low doses of metronomic cyclophosphamide with high doses of celecoxib and this combination resulted in a 37% objective response rate with a PFS of 4.67 months in a similar patient population[3].

In the phase 1b ovarian cancer trial (ONC-DPX-Survivac-03), the administration of cyclophosphamide during the maintenance cycle was modified to reduce the overall exposure to cyclophosphamide and to avoid toxicities that may possibly occur due to chronic dosing. Cyclophosphamide was administered seven days prior to the first injection and then continuing for seven days off and seven days on for 9 weeks during the priming phase. During the maintenance cycles, cyclophosphamide was administered 7 days before the maintenance injection, then continuing for 7 days off and 7 days on with a five week break between injections. This allowed the immune therapy to be processed by the immune system in the continued absence of cancer induced immune suppression. However, given that continuous low dose cyclophosphamide is well tolerated in DLBCL and is associated with clinical objective response we will increase the exposure to cyclophosphamide by alternating one week on with one off throughout the dosing of DPX-survivac. If platelet levels decrease below 75,000/mm3 or if absolute neutrophil counts decrease below 1000/mm2 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.

3 STUDY OBJECTIVES

3.1 Primary Objective

To document a minimal objective response rate of 24% to treatment with DPX-Survivac and low dose cyclophosphamide administered together with anti-PD-1 (pembrolizumab) in patients with recurrent, survivin-expressing B cell lymphomas using modified Cheson criteria[45].

3.2 Secondary Objective(s)

1. To document changes in tumour volume using waterfall analyses.

2. To document the toxicity profile.

3. To document duration of response using modified Cheson criteria and immune-related response criteria[46] (irRc).

4. To document time to next treatment and survival

3.3 Exploratory Objective(s)

1. To document the changes in circulating T cell immune responses to survivin and relationship to peripheral B cell numbers.

2. To document changes in T cell and T cell subset infiltration and gene expression pathways in treatment compared to pre-treatment tumour biopsies.

3. To assess potential biomarkers of immune and clinical response from subject clinical, biological and immunologic data from pre-treatment and on-treatment tumour biopsies.

4. To evaluate other relevant biologic assays that may be identified during the conduct of the trial that may have immune or clinical relevance on samples already collected.

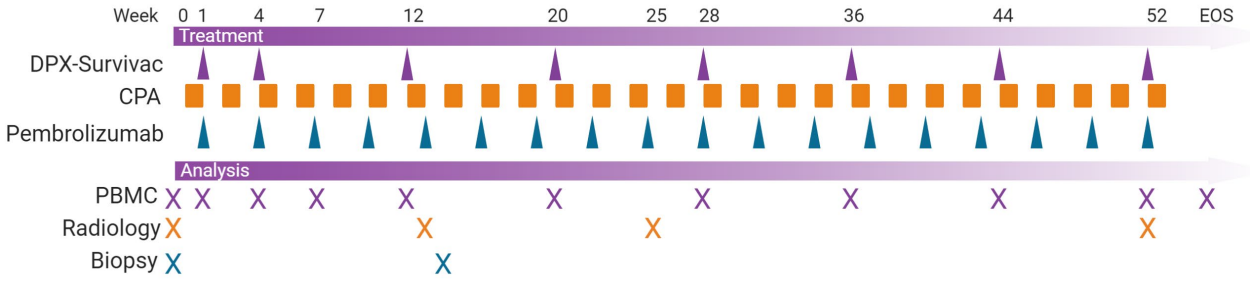
4 STUDY DESIGN

4.1 General Design

Treatment, non-randomized, open label, uncontrolled, efficacy and safety study. Study participants will receive two priming doses of 0.5 mL of DPX-Survivac 21 days apart and up to six 0.1 mL maintenance injections every two months with low dose metronomic oral cyclophosphamide (50 mg BID; 7 days on, 7 days off) for one year or until disease progression, whichever occurs first. Pembrolizumab 200 mg will be administered every 3 weeks for up to one year or until disease progression, whichever occurs first.

4.2 Trial Diagram

An overview of the clinical design and the time points for DPX Survivac injections, cyclophosphamide and pembrolizumab administration, blood collection for immune monitoring, radiology and biopsy is depicted below. This is only a schematic diagram and the screening period is not included (See Appendix B for details).



4.3 Primary Outcomes/Endpoint(s)

Objective clinical and radiologic response rate will be determined using Modified Cheson Criteria (Appendix C)

4.4 Secondary Outcome(s)/Endpoint(s)

Tumour volume recorded at screening will be compared to treatment and end of study (EOS) imaging. Data such as the degree of change or total tumour volume, from baseline through end-of-study, will be plotted on a waterfall plot to demonstrate individual responses using modified Cheson Criteria and irRC. The irRC criteria will also be utilized to evaluate the duration of response. Evidence of toxicity will be assessed at each visit and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 4.03 (Appendix E). When subjects have completed their participation in the study, by either remaining on trial to SD364, or discontinuing study participation early, they will be followed up to document time to next treatment and obtain survival times.

4.5 Exploratory Outcomes/Endpoint(s)

T Cell activation therapy induced generation or enhancement of pre-existing immunity to survivin is considered a prerequisite for the anti-tumour effect of DPX-Survivac. Therapy with DPX-Survivac is expected to increase the frequency and activity of survivin-specific anti-tumour T cells. Survivin-peptide specific T cell immune response will be measured by methods such as ELISpot assay to enumerate T cells that produce molecules associated with anti-tumour immune responses such as IFN-γ and/or Granzyme-B. Other exploratory immunologic assessments may be performed on frozen PBMC samples and subject plasma if a novel method becomes available during the course of the study. Tumour-specific T cells must migrate to the tumour site to mediate anti-tumour activity. Both DPX-Survivac and pembrolizumab should facilitate the migration of antigen-specific T cells into tumour sites. We will quantitate changes in T cell infiltration and the expression profile of this T cells in tumour sites using pre- and on-treatment biopsies. If the subject ends trial participation due to progression and soon after undergoes a post-study tumour biopsy just prior to starting another therapy, we will aim to obtain a sample for comparison of immune and pathologic data to the pre- and on- treatment samples. Analysis will be performed on the collected clinical, biologic and immunologic data obtained from subjects to look for features that distinguish subjects that progress early while on treatment and those that have longer durations of response or are able to remain on treatment for the entire length of the trial without progression.
Other novel exploratory assays such as quantitation of periperhal blood survivin levels may also be explored as new scientific literature arises.

4.5.1 **Biomarker Research**

Peripheral blood will be obtained pre-treatment, before each injection, 2 months after the second injection, and at the end of study visit for immune analyses. Plasma Survivin levels will be obtained as per schedule of events.

Tumour biopsies will be obtained pre-treatment and on-treatment, and where possible when the subject is just off-treatment (usually as standard of care before starting another course of therapy), to assess for changes in lymphocyte infiltrates, lymphocyte subsets, and gene expression profiles with treatment. Novel biomarkers predictive of immune or clinical response will be assessed in pre-treatment tumour biopsies and will include the immune and gene expression profiles. If an injection site biopsy is required for clinical management during the course of this trial, portions of this biopsy may be studied for evidence of antigen specific T cell infiltrates, other biomarkers, or immune activity. The extent and type of analysis on these types of samples will depend on several factors such as, but not limited to; amount and quality of tissue, format (slides vs. block), etc.

4.6 Primary Safety Outcomes/Endpoints

Safety will be assessed through patient reported and investigator observed AE's. This will also include physical examination and clinical laboratory tests. Specific attention will be placed upon injection site reactions and potential immune mediated AE's.

Injection Site Reactions will be graded using the NCI CTCAE v 4.03 (see Appendix E).

5 PARTICIPANT SELECTION AND WITHDRAWAL

5.1 Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be willing and able to provide written informed consent/assent for the trial.
2. Male or female ≥ 18 years of age on day of signing informed consent and of any racial or ethnic group
3. Has:
    - **a.** histologically proven DLBCL with recurrence after first, second or tertiary treatment regimens for DLBCL ***or,***
    - **b.** evidence of transformed lymphoma with past history of indolent lymphoma with current biopsy showing DLBCL) ***or,***
    - **c.** double hit or high grade lymphomas, including Burkitts lymphoma and High Grade B-Cell lymphoma unclassifiable (with features intermediate between Burkitts and diffuse large B cell lymphoma)
4. Has had:
    - **a.** recurrence requiring therapy at least 90 days post aggressive first line combination chemotherapy (e.g. RCHOP, Hyper-CVAD or other aggressive ”curative” combination), autologous stem cell transplantation (ASCT), CART therapy, or aggressive second line combination therapy ***or,***
    - **b.** partial response or measureable disease after first line therapy (who are not candidates for ASCT) or after second or third line therapy without disease progression ***or,***
    - **c.** recurrence any time after non-aggressive combination or single agent therapy with or without Rituximab (i.e. CVP, CHL or, VP16) for first, second or third line disease ***or,***
    - **d.** for subjects with transformed lymphoma, a treatment for indolent lymphoma within the last 2 years
5. Have at least one measurable site of disease based on Cheson Criteria using standard CT imaging.
6. Be willing to provide tissue from a newly obtained (**up to** 3 months + 7 days prior to Study Day 0) biopsy of a tumour lesion. If this is not available, the patient must be

willing to undergo a core biopsy prior to starting treatment. They must also be willing to provide an on-treatment biopsy.

7. Have a performance status of 0-1 on the ECOG Performance Scale.
8. Demonstrate adequate organ function as defined in Table 2, within 48 hours prior to receiving the first dose of study medication (SD0). Patients with abnormal liver enzymes of up to 5 times the upper limit of normal and/or reduced GFR of 50-100% normal range can be considered for enrolment if the alteration is due to lymphoma.
9. Previous localized surgery, radiotherapy, chemotherapy, and immunotherapy more than 21 days prior to SD0. Cyclophosphamide, up to 100 mg/day, may be administered until SD-1 for subjects already receiving as a single agent therapy.
10. A life expectancy > 6 months.
11. Female subject of childbearing potential should have a negative urine or serum pregnancy within 48 hours prior to receiving the first dose of study medication (SD0). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
12. Female 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 childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
13. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through to 120 days from the last dose of study medication.
14. Ability to comply with protocol requirements.

Table 2: Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,000/mcL
Platelets	≥50,000/mcL
Hemoglobin	≥8 g/dL or ≥5.6 mmol/L without EPO dependency
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X

(GFR can also be used in place of creatinine or CrCl)	institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN Unless history of Gilbert's disease **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
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

5.2 Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 21 days of the first dose of treatment (SD0).
2. Patients eligible for possible curative therapies such as ASCT.
3. LDH greater than 5 times the upper limit of normal[47].
4. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 35 days prior to the first dose of trial treatment (SD0), except that used as pre-medication for chemotherapy or contrast-enhanced studies are eligible. Subjects may be on physiologic doses of replacement prednisone or equivalent doses of corticosteroid (<10 mg daily).
5. Has had previous allogeneic stem cell transplant
6. Has known active TB (*Bacillus Tuberculosis*)
7. Hypersensitivity to pembrolizumab or any of its excipients.
8. Has had a prior anti-cancer monoclonal antibody (mAb) within 21 days prior to SD0 or who has not recovered (i.e., ≤ Grade 1) from adverse events due to agents administered more than 21 days earlier.

9. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 21 days prior to SD0. Subjects must have recovered from all acute toxicities from prior treatments; peripheral neuropathy must be ≤ grade 2.
10. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include in situ cervical cancer, basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy.
11. Has 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 35 days prior to trial treatment.
12. Progressive CNS lymphoma requiring treatment within 35 days prior to SD0.
13. Has history of active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). 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.
14. Has known history of, or any evidence of active, non-infectious pneumonitis.
15. Thyroiditis within the past 5 years.
16. Has an active infection requiring systemic therapy. Subjects completing a course of antibiotic for acute infection 7 days prior to SD0 and who do not experience a recurrence of symptoms or fever are eligible.
17. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
18. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
19. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with screening visit to 120 days after last dose of study medication.

20. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
21. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
22. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected). Evidence of Hepatitis B surface antigen without transaminitis is allowed provided patient is treated with anti-viral therapy (Heptavir or Tenofovir).
23. Patients who have received prior survivin based vaccines.
24. Acute or chronic skin disorders that will interfere with subcutaneous injection of the DPX-Survivac or subsequent assessment of potential skin reactions.
25. Serious intercurrent chronic or acute illness, such as cardiac disease (New York Heart Association class III or IV), hepatic disease, or other illness considered by the investigator as an unwarranted high risk for an investigational product.
26. Allergies to any vaccine, that after discussion with the medical monitor are serious enough to warrant exclusion from this study.
27. Received a live vaccine within 30 days of planned start of study therapy. *Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed*

5.3 Participant Recruitment

Patients considered suitable for study selection will be identified by the site investigators at each participating site. Patients may be identified from the local population of patients or from referrals from other physicians aware of the trial.

5.3.1 **Randomization Procedures (if applicable)**

All enrolled subjects will be receiving the same treatment and will be accrued without pause.

5.3.2 **Blinding and Unblinding Procedures (if applicable)**

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

5.4 Participant Withdrawal and Discontinuation of IP

5.4.1 **Reasons for Withdrawal from study or Discontinuation of IP**

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 reasons. Participants whose cancer progresses or who experience other adverse effects that negatively impact patient safety, will be discontinued from IP and study participation. These subjects will be considered to be withdrawn from the study, and to have completed their study participation, excluding follow-up contact or health review (survival) as permitted by consent.

A subject may be withdrawn from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Investigator's decision to withdraw the subject.
- The subject has a confirmed positive serum pregnancy test.
- Noncompliance with trial treatment or procedure requirements.
- The subject is lost to follow-up.
- Administrative reasons.

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

- Disease progression at any time after study entry if the treating physician feels that some other treatment is indicated based upon standard clinical practice parameters.
- Serious adverse experiences as described in Sections 8.2. or 8.3 or life threatening reactions secondary to active immunotherapy.
- Intercurrent illness that prevents further administration of treatment.
- Other reasons not listed.

5.4.2 **Subject Replacement Strategy**

If a subject is removed from the trial prior to the completion of 4 doses of pembrolizumab, 3 injections of DPX-Survivac and an on-treatment CT scan between study days 70-104, that subject may be replaced to determine the efficacy of treatment in a minimum of 16 subjects.

5.4.3 **Clinical 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, such as:

    - Two or more grade 4 SAEs possibly, probably or definitely related to pembrolizumab or DPX-Survivac.

- Any single death, possibly, probably or definitely related to pembrolizumab or DPX-Survivac.

4. Plans to modify or discontinue the development of the study drugs. In the event that Merck or IMV decide to no longer supply study drugs, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

5.4.4 **Data Collection & Follow-up for Withdrawn/Discontinued Subjects**

A subject will be permitted to delay a visit up to two weeks or omit a visit before being taken off study.

If the subject is discontinued from IP and study participation, the reason(s) for discontinuation should be clearly documented. When a subject is discontinued from the study after the first dose of pembrolizumab or DPX-Survivac, an end of study (EOS) visit should be completed prior to initiating another treatment. This visit will allow collection of data necessary to define events leading up to discontinuation. A full follow up visit (as outlined in Section 7.4.25) should be scheduled and completed 30 days after the last DPX-Survivac and pembrolizumab administration, and again at 90 days after the last pembrolizumab infusion, whenever possible.

When a subject withdraws, or is withdrawn from the study, whenever possible and irrespective of the reason for withdrawal, the subject should be examined as soon as possible with an end-of-study (EOS) visit (as outlined in Section 7.4.24). In the event that a subject withdraws from the study, prior to initiating another treatment, the subject will be requested to have approximately 90 mL of blood drawn for immunologic testing. If the subject agrees, they should also complete a follow up visit (as outlined in Section 7.4.24) at 30 days after the last DPX-Survivac and pembrolizumab administration, and again at 90 days after the last pembrolizumab infusion to ensure patient safety. There will be no further study visits scheduled. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. For each subject, every effort should be made to document subject outcome. In addition, a chart review will be performed at 6 months and 12 months after the end of their trial participation to obtain survival data. If a biopsy is performed just after trial discontinuation as part of standard of care and before the commencement of another therapy, efforts will be made to obtain samples of this biopsy, with the consent of the patient, for the purpose of additional immunohistochemistry testing and analysis.

Subjects should also be followed up every 2 months as described in Section 7.4.25.

6 INTERVENTIONS

6.1 Investigational Product

6.1.1 Acquisition Formulation and Packaging

The site investigator shall take responsibility for and shall take all steps 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 affixed with a clinical label in accordance with regulatory requirements. The DPX-Survivac and pembrolizumab and ^{18}F-fluorodeoxyglucose will comply with Health Canada requirements for investigational products. The cyclophosphamide will be received with commercial labels.

The DPX-Survivac labels will comply with FDA and Health Canada requirements for IP's, will be in local languages, and will state that use is limited by federal law to investigational use only.

A. Pembrolizumab

Clinical Supplies will be provided by Merck as summarized in Table 3.

Table 3 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg/ 4mL	Solution for Injection

B. DPX-Survivac composition

The clinical formulation will consist of two vials provided by IMV. Vial 1 contains the lyophilized formulated drug substance, and vial two contains Montanide ISA 51 VG (Seppic) which is used as a diluent and comprised of mannide monooleate and mineral oil. Vials 1 and 2 will be mixed prior to injection (Table 4).

Table 4 DepoVax Formulation

Vials	Component
Vial 1 (lyophilized)	
Liposome	Phosphotidyl choline: DOPC synthetic lipid (GMP grade)
	Cholesterol: Sheep's wool, high purity, non-BSE countrites (GMP grade)
Polynucleotide immunostimulant (didC)	Short synthetic polynucleotide (GMP grade)
Antigen (MHC Class II, T-helper)	Tetanus toxoid peptide A16L: AQYIKANSKFIGITEL (GMP grade)
Antigens (MHC Class I, Tumour specific)	Five synthetic peptides targeting survivin, see *Table 1* (GMP grade)

Vial 2 (oil diluent)	
Hydrophobic carrier (oil diluent)	Montanide ISA51 VG (GMP grade)

Lipids
The lipids are 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 is used without further processing.

Polynucleotide immunostimulant
IMV has demonstrated the enhanced efficacy of DepoVax formulations containing a synthetic polynucleotide-based immunostimulant 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 tumour 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 ISA 51 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 treatment 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 both room temperature and 4^{o}C. The oil is non-animal based and has been used for both DPX-Survivac and DPX-0907 formulations (phase 1 trials). The oil has also been extensively used in other cancer vaccine clinical trials (phase I and II).

C. ^{18}F-fluorodeoxyglucose (FDG)

Commercially available (i.e. Health Canada approved) FDG will be sourced from Canadian market by the clinical sites and used and handled according to the manufacturer's instructions.

D. Cyclophosphamide (Non-Investigational)

Commercially available (i.e. Health Canada approved) cyclophosphamide 50 mg will be provided by the clinical sites and used and stored according to the manufacturer's instructions.

6.1.2 **Treatment Assignment Procedures**

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.

6.1.3 **Dosage, Preparation and Administration**

The treatment to be used in this trial is outlined below in Table 5.

Table 5: Trial Treatment

Drug	Dose	Frequency	Route of Administration	Regimen
Pembrolizumab	200 mg	18 doses 3 weeks apart	IV infusion	Study Days 7, 28, 49, 70, 91, 112,133, 154, 175, 196, 217, 238, 259, 280, 301, 322, 343, 364
DPX-Survivac	0.5 mL	2 doses 21 days apart	Subcutaneous*	Study Days 7 and 28
	0.1 mL	6 doses 8 weeks apart		Study Days 84, 140, 196, 252, 308, 364
Cyclophosphamide	50 mg	BID[t]	orally	Study Days 0-6 then 7 days off and 7 days on. This sequence will be repeated for the duration of the study.

*alternating legs in the upper thigh region. Details provided in the Manual of Operations
[t] if starting platelet value is between 50 and 75 k then starting dose will be 50 mg daily

6.1.3.1 Timing of Dose Administration

Trial treatment should be administered according to schedule of events (Appendix B).

Visits can occur +/- 3 days of the protocol-specified day and over the course of 2 days, except for visit 1 (SD0) and visit 2 (SD7) which must be 7 days apart.

Pembrolizumab 200 mg will be administered as a 30 minute (-5 min/+10 min) IV infusion every 3 weeks.

On injection days, subjects will be monitored with blood pressure, pulse, and temperature assessments at pre-injection, and at approximately 15 +/- 5 minutes after injection.

Low dose cyclophosphamide (50 mg twice a day) will be taken orally. Cyclophosphamide will be dispensed according to institutional guidelines. Cyclophosphamide will be taken, starting on SD0, for 7 days prior to the first injection and then continuing for 7 days off. This schedule will be continued throughout the length of the study. Cyclophosphamide compliance should be completed by site staff, and is calculated when the drug is returned after each cycle, or as per institutional guidelines. Subjects may be withdrawn from the trial if they miss more than 50% of the tablets during either the priming or maintenance cycles of treatment. The dose of cyclophosphamide may be reduced as described for hematologic toxicity.

6.1.4 **Dose Selection/Modification**

The rationale for selection of doses to be used in this trial is provided in Section 2.5.2.

Details on preparation and administration of pembrolizumab (MK-3475) and DPX-Survivac are provided in the Pharmacy Manual.

6.1.4.1 DPX-Survivac

If a subject experiences any grade 2 or greater injection site reaction(s) or any grade injection site ulceration within 4 weeks prior to an injection time point, that has not resolved to a grade 1 or better, the injection will be omitted. *The omitted injection can be given up to one week after the initial omission, provided the injection site reaction has resolved to a grade 1 or better.* If an injection was missed/ omitted, continue on the injection schedule, as per the Schedule of Events (Appendix B). This same evaluation will be repeated at each injection time point. All other study procedures scheduled for that clinic visit will still be conducted including the ongoing administration of the oral cyclophosphamide and the pembrolizumab infusion. Investigators are strongly encouraged to contact the study Sponsor on the day of injection to discuss cases of concern.

If two consecutive grade 3 injection site reactions occur in the same subject, it is up to the investigator's discretion whether to continue with DPX-Survivac (after the reaction has resolved to a grade 1 or better) or to stop all further injections for that subject due to safety concerns. The investigator should contact the study Sponsor if a grade3 injection site reaction or any grade injection site ulceration occurs.

In the event that an individual's immune response has dropped or is not being maintained at the level of their initial response (as measured by the severity of their injection site reaction(s), or observation of an injection site induration – a hallmark of DPX-Survivac immune therapy) they should be given a "re-priming" dose of 0.5 mL DPX-Survivac instead of the planned 0.1 mL maintenance injection. If the immune response has not returned to the expected level, and/or injection site induration is not observed within 4 weeks of the re-priming dose, subjects will receive another re-priming dose in place of their next scheduled maintenance injection. All other study related procedures at this visit will remain as per protocol. Re-priming doses should only be substituted for 2 consecutive maintenance injections. If the subject is not showing signs of immune response, the site should contact the Sponsor for guidance and approval of additional re-priming doses.

Table 6: Dose Modification Guidelines for Drug-Related Adverse Events for DPX-Survivac

	Severity (Grade)	Treatment Modification
Injection Site Reaction	Grade 2 or greater	Hold DPX-Survivac until resolved to Grade 1 or better. Reassess at each visit. Administer DPX-Survivac if within 1 week of omitted injection.
Injection Site Ulceration	Any grade within 4 weeks of next injection	

6.1.4.2 Pembrolizumab and Combination Therapy

Adverse events (both non-serious and serious) associated with pembrolizumab exposure, including coadministration with additional compounds, may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment/combination therapy, and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most AEs were reversible and could be managed with interruptions of pembrolizumab/combination treatment, administration of corticosteroids and/or other supportive care. For suspected AEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation.

See Table 7 for the dose modification guidelines for pembrolizumab/combination therapy related adverse events. Events not listed below are to be discussed with the Sponsor, and may require additional medical guidance from Merck. Infusions should follow that outlined in the Schedule of Events (Appendix B). A missed or omitted dose of pembrolizumab may be given a maximum of +3 days after originally scheduled, and if the omission was due to an Adverse Event, the AE should be resolved to Grade 1 or better before administration.

Tapering up or down of pembrolizumab is prohibited. Pembrolizumab should always be given at the full and intended dose (200 mg).

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events and/or unforeseen circumstances not related to study intervention. However, intervention is to be restarted within 3 weeks of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant study record.

Attribution of Toxicity:

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to the combination, to DPX-Survivac or Cyclophosphamide alone, or to pembrolizumab alone, for adverse events listed in Table 7, both interventions must be held according to the criteria in Table 7 Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Pembrolizumab Monotherapy and IO Combination.

Holding Study Interventions:

When study interventions are administered in combination, if the AE is considered immune-related, both interventions should be held according to recommended dose modifications.

Restarting Study Interventions:

Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in Table 7.

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions.

If the toxicities do resolve and conditions are aligned with what is defined in Table 7, the combination of DPX-Survivac, cyclophosphamide and pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to DPX-Survivac or cyclophosphamide alone, re-initiation of pembrolizumab as a monotherapy may be considered at the principal investigator's discretion .]

Table 7: Dose Modification Guidelines for Immune-Related Adverse Events for Pembrolizumab Monotherapy and IO combination (March 2021)

*note that this guidance uses CTCAE V5.0 as per the manufacturer guidance, however, for consistency in the trial, we will continue to use CTCAE v4.03 (see Appendix C).

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last study intervention treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If study intervention has been withheld, study intervention may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to	• Monitor participants for signs and symptoms of

	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue	2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 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
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or	• Monitor with liver function tests (consider weekly or more frequently until liver

			equivalent) followed by taper	enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic 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 [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading	Grade 2	Withhold	• Administer corticosteroids	• Monitor changes of renal

according to increased creatinine or acute kidney injury	Grade 3 or 4	Permanently discontinue	(prednisone 1 to 2 mg/kg or equivalent) followed by taper	function
Neurological Toxicities	Grade 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		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include, but are not limited to:encephalitisand other clinically important irAEs.

† ULN = Upper Limit of Normal

*If corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks or a treatment-related toxicity does not resolve to Grade 0-1 within 12 weeks after last dose of Pembrolizumab, then Pembrolizumab should be permanently discontinued

6.1.4.3 Cyclophosphamide

Possible side effects from low dose 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 75,000/mm^3 or if absolute neutrophil count decreases below 1000/mm^2 in any cycle, then the dose of cyclophosphamide can be reduced to 50 mg once daily in that subject once neutrophils increase and severity is reduced to grade 2 or better. Growth factors may be used if grade 3 or 4 neutropenia occurs even after dose reduction of cyclophosphamide. For ongoing grade 3 or 4 neutropenia not responsive to dose reduction and growth factor support, cyclophosphamide may be discontinued after discussion with the Sponsor. **The role of pembrolizumab and holding pembrolizumab needs to be considered for refractory neutropenia not responsive to the above measures.**

Grade 3 or 4 thrombocytopenia and or anemia may be managed with transfusions as required and dose reduction of cyclophosphamide (50 mg daily) after anemia or thrombocytopenia has recovered to grade 2 or better.

If Cyclophosphamide was reduced to 50 mg for an adverse event which has since resolved to grade 1 or better, it can be increased to the expected dose (100 mg daily) if, in the opinion of the investigator, it would benefit the subject to do so.

6.1.4.4 Dosing Interruption

Dosing interruptions 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 2 weeks of the scheduled interruption, or up to 4 weeks at the discretion of the study Sponsor. The reason for interruption should be documented in the patient's study record.

6.1.5 **Receiving, Storage, Dispensing and Return**

6.1.5.1 Receipt of Investigational Product

Upon receipt of the investigational product and/or study supplies, an inventory must be performed and a receipt log filled out and signed by the research team member accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable product in a given shipment will be documented in the study files. The site must notify the study Sponsor of any damaged or unusable product that was supplied to the site. Additional instructions are supplied by the manufacturer with each shipment and can also be found in the Manual of Operations.

6.1.5.2 Storage and Stability

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. This includes 24 hour temperature monitoring, and logs maintained by pharmacy staff.

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.

- Pembrolizumab will be stored under refrigerated conditions (2° to 8°C). Protect from light. Do not freeze. Do not shake.

- A bulk supply of DPX-Survivac Vial 1 will be provided in a box to be stored at 2 to 8 °C in the pharmacy. Vial 2 (oil diluent) and the ancillary components will be stored at ambient temperature.

- Cyclophosphamide will be stored according to the storage conditions in the package insert.

6.1.5.3 Dispensing of Investigational Product

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck and IMV or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

6.1.5.4 Return and/or Destruction of Investigational Product

Upon completion or termination of the study, all unused and/or partially used investigational product provided by Merck or designee 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.

IMV must be contacted prior to destruction of any unused and/or partially used clinical trial material provided by them.

6.2 Concomitant Medications (Acceptable & Prohibited)

Medications specifically prohibited in the exclusion criteria are not allowed during the subject's participation in the trial. If there is a clinical indication for one of these or other medications, therapies or vaccinations specifically prohibited during the trial, discontinuation from trial therapy may be required. The investigator should discuss any questions regarding this with the study Sponsor. The final decision on any supportive therapy rests with the investigator and/or the

subject's primary physician.

6.2.1.1 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 and/or therapies will be recorded on the case report form (CRF) 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 should also be included on the CRF.

Erythropoietins or granulocyte stimulating factors are acceptable if felt necessary by the treating physician.

All concomitant medications received from the date of consent to the last dose of trial treatment should be recorded. Specifically these include systemic steroid therapy or any other form of immunosuppressive therapy within 35 days prior to the first dose of trial treatment (SD0), except those used as pre-medication for contrast-enhanced studies are eligible. Subjects may be on physiologic doses of replacement prednisone or equivalent doses of corticosteroid (<10 mg daily). Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded as per the guidance of follow-up visits for SAEs and Events of Clinical Importance (ECIs).

6.2.1.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) 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, low dose metronomic cyclophosphamide
- 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.
- No adjuvant vaccine or live attenuated vaccine (such as Flumist) should be given while on this study. Non-adjuvant vaccines (such as most influenza vaccines) can be given. For subjects receiving the flu vaccine, study Sponsor strongly recommends the shot be given at least one week before immunological assessments (such as investigational blood draw) and DPX-Survivac administration.

- 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 Sponsor.

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, with the exception of systemic corticosteroids as described in section 6.1.6.1, or as part of rescue medication. 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. These include systemic steroid therapy or any other form of immunosuppressive therapy within 35 days prior to the first dose of trial treatment (SD0), except that used as pre-medication for contrast-enhanced studies are eligible. Subjects may be on physiologic doses of replacement prednisone or equivalent doses of corticosteroid (<10 mg daily).

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

6.3 Rescue Medications & Supportive Care

6.3.1.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance as outlined below. Refer to Section 6.1.4 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. These, and the respective results, should be recorded in the Source and Case Report Forms.

Pneumonitis:

- For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

Diarrhea/Colitis:

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

- All subjects who experience 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. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA):

- For **T1DM** or **Grade 3-4** Hyperglycemia
  - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
  - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

Hypophysitis:

- For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Replacement of appropriate hormones may be required as the steroid dose is tapered.

Hyperthyroidism or Hypothyroidism:

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

- **Grade 2** hyperthyroidism events (and **Grade 3-4** hypothyroidism):
  - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
  - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
- **Grade 3-4** hyperthyroidism
  - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

Hepatic:

- For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
  - Treat with IV or oral corticosteroids
- For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

Renal Failure or Nephritis:

- For **Grade 2** events, treat with corticosteroids.
- For **Grade 3-4** events, treat with systemic corticosteroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

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 8, below, shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 8: Infusion Reaction Treatment Guidelines

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

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
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 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.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
<u>Grades 3 or 4</u> Grade 3: 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) Grade 4: 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.		

At the discretion of the study team, the subjects may remain for an additional 30 minutes to 1 hour for observation. Diphendydramine 50 mg, solumedrol 100 mg, and epinephrine 1:1000 (1 mL) and a code cart must be readily available for emergency use. 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, an intravenous catheter will be placed and the diphendydramine 50 mg and solumedrol 100 mg will be administered. The physician 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.

Possible immediate side effects from 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 autoimmunity (manifests as arthritis, serositis, nephritis,

thyroiditis, colitis, neutropenia, etc.) is theoretically possible. Delayed events such as rash or hives maybe treated with diphenhydramine (25-50 mg); topical steroids should not be given without consultation with the study's principle investigator.

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.

Possible side effects from Montanide ISA 51 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.

6.4 Diet/Activity/Other Considerations

6.4.1.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, dehydration or vomiting.

6.4.1.2 Contraception

Pembrolizumab or DPX-Survivac may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab or DPX-Survivac has transient adverse effects on the composition of sperm. 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 greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be; 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 until 120 days after the last dose of study medication.

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 progestational 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 the study, subjects must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in Section 8.4.1:Reporting of Pregnancy and Lactation to the Sponsor. 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.

6.4.1.3 Use in Nursing Women

It is unknown whether pembrolizumab or DPX-Survivac 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 Administration of Intervention

Subjects will attend on their assigned day. They will have blood samples and physical examinations, including injection site assessment, as outlined in Schedule of Events (Appendix B). Compliance with Cyclophosphamide will be reviewed routinely. A record of concomitant medications/therapies and AE's will be sought at each review. Radiological imaging and repeat biopsies will be performed as detailed in the Schedule of Events (Appendix B). Participants will receive DPX-Survivac and pembrolizumab in accordance with the product SPC. There are no dietary restrictions or fasting requirements prior to treatment initiation or routine laboratory sample collection.

6.5.1 **Procedures for Intervention Training and Monitoring**

All QI's at each study site will attend a study initiation meeting to ensure protocol, study requirements and data capturing processes are clearly understood. This will be completed prior to any study activity. Study sites are responsible to ensure that existing and new staff are adequately trained, that training is documented and that they are delegated to the tasks for which they have been trained.

6.6 Assessment of Subject Compliance

Subject compliance with study protocol will be assessed on a regular basis. This will be confirmed by study staff. Subjects with less than 50% compliance with cyclophosphamide will be considered for withdrawal. Compliance to DPX-Survivac and pembrolizumab will be determined by attendance for treatment.

7 STUDY SCHEDULE AND PROCEDURES

The Schedule of Events (Appendix B) summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator. See Section 7.5 for additional information on types of visits that may be considered an "Unscheduled Study Visit".

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1 Administrative Procedures

7.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

7.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.1.4 Prior and Concomitant Medications Review

7.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 21 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

7.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 8.

7.1.5 **Disease Details and Treatments**

7.1.5.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

7.1.5.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments (maximum 3), radiation and surgeries.

7.1.6 **Assignment of Screening Number**

Subjects will be assigned a screening identification number after consenting to participate, as it will be used while documenting eligibility for the study. This identification will consist of the site number followed by a hyphen and then chronologically defined digits. Additional details can be found in the study Manual of Operations.

7.1.7 **Clinical Procedures/Assessments**

7.1.7.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs at each study visit and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study according to NCI CTCAE v4.03 (see Appendix E). Injection site reactions are considered adverse events and should be documented and evaluated using NCI CTCAE v 4.03 (see Appendix E). Injection Site Reactions are also to be graded by their individual events such as; pain, induration, erythema, edema and ulceration. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to Section 8 for detailed information regarding the assessment and recording of AEs.

7.1.7.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant or abnormal findings should be recorded as medical history. A full physical exam should be performed during screening, and as per the Schedule of Events (Appendix B), prior to trial treatment administration at those visits. Investigators should

pay special attention to clinical signs related to previous serious illnesses.

7.1.7.3 Directed Physical Exam

For all other treatment days that do not require a full physical exam per the Schedule of Events (Appendix B), the investigator or qualified designee will perform a directed physical exam as clinically indicated, prior to trial treatment administration. Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.1.7.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each IP dose of trial treatment and at treatment discontinuation as specified in the Schedule of Events (Appendix B). Vital signs should include temperature, pulse, respiratory rate, pulse oximetry, weight and blood pressure. Height will be measured at screening only.

7.1.7.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (Appendix F) at Screening, disease staging (SD112 and SD196) and again at EOS (see Schedule of Events Appendix B).

7.1.7.6 Tumour Imaging and Assessment of Disease

Tumour imaging will be done during the screening period, at SD70 or SD91 (based on evidence of injection site reaction of grade 2 or higher or any grade ulceration at SD49), at SD175 and EOS or SD364, whichever comes first, to document progression using Modified Cheson Criteria (Appendix C). Tumour Imaging will be done prior to EOS visit or 30 days after any other suspected disease progression to rule out pseudo-progression and evaluate using IrRC (Appendix D) whenever possible. Tumour imaging will be performed based on the Modified Cheson Criteria (Appendix C). A maximum of six (6) target lesions, selected at Screening, will be followed through the course of the study. While only one tumour is required to meet the Modified Cheson Criteria for the purpose of eligibility, ***all*** tumours selected at screening for study follow through, should meet the Modified Cheson Criteria (Appendix C). Sites are encouraged to specify these instructions to radiologists. Additional guidance can be found in the Manual of Operations.

7.1.7.7 Tumour Tissue Collection and Correlative Studies Blood Sampling

Tumour biopsy samples will be collected for evidence of survivin expression and for other biomarker analyses. Samples will be collected during the screening period, and again while on-treatment at approximately 3 months. If possible, samples will be collected from the participant soon after trial completion, as part of standard of care, and prior to the start of a new course of therapy. Samples, ideally 5 cores, will be processed and handled by the site pathology lab for study related procedures. The Lab Manual contains the specific instructions for sample collection and processing. The screening biopsy may be eliminated if a biopsy has been obtained within three months (+ 7 days) of SD0 and FFPE slides and /or a tissue block are

available. Patients with less than 5 cores can still be included.

Investigational Blood Draw (PBMC), for both routine monitoring and investigational assessment (HLA, Survivin levels, and PBMC T cell responses to survivin) will be obtained as per Schedule of Events (Appendix B).

The samples may be stored for up to 5 years after the study is completed for future analysis as new immune monitoring assays are being developed. Any sample not completely used in analysis will be destroyed after the 5 years has elapsed

7.1.7.8 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below, and further specified in Table 9.

Laboratory tests for screening should be performed within 35 days prior to SD0. Laboratory samples will be taken again prior to enrollment (<48 hours of SD0) to confirm eligibility criteria for adequate organ function. After first infusion of pembrolizumab, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee for clinical significance prior to each dose of trial treatment. Blood draw for research tests (PBMCs and plasma isolation) may also be drawn at the same time as the pre-dose laboratory procedures, up to 72 hours prior to dosing as long as staff are available to process the PBMCs and plasma within 4 hours of collection.

7.1.7.9 ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) Injection and PET Imaging

PET imaging will be performed following the institutional standard protocol and guidelines. 5 MBq/kg of ^{18}FDG with a maximum dose of 12 mCi will be administered. Imaging will begin 60 minutes post injection. The participant will be observed carefully throughout the scanning session. AE's attributable to ^{18}F-fluorodeoxyglucose have not been reported in previous studies that have used ^{18}F-fluorodeoxyglucose (FDG) for PET imaging[49]. The risks associated with ^{18}F-fluorodeoxyglucose include discomfort, bruising, bleeding or clotting at the site of insertion of the intravenous catheter. These side effects occur occasionally. All AEs experienced by the participants will be recorded and reported.

Table 9 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total triiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free thyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or bicarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
Red cell distribution width	Uric Acid		HIV Ab*
Mean corpuscular hemoglobin	Calcium		Hepatitis BsAg*
Mean corpuscular volume	Chloride		Hepatitis C Ab*
%Reticulocytes	Glucose		Blood for correlative studies
	Phosphorus		• Whole blood for HLA typing
	Potassium		
	Sodium		• Whole blood for PBMC isolation
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		• Plasma for Survivin levels
	Total protein		
	Blood Urea Nitrogen		
	Creatinine		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

‡ If considered standard of care in your region.

* Not required but recommended if status unknown or unclear

7.1.8 **Immune Evaluations**

7.1.8.1 Blood Collection for Plasma Survivin levels

Sample collection, storage and shipment instructions for plasma samples will be provided in the Laboratory Manual.

The time points for blood sampling are described in Schedule of Events (Appendix A & B).

7.1.8.2 Blood Collection for PBMCs

Sample collection, storage and shipment instructions for blood samples will be provided in the Laboratory Manual. Peripheral Blood Mononuclear Cells (PBMC) will be collected for immune monitoring at the time points specified in the Schedule of Events (Appendix B). Blood samples will be processed by the local laboratory and frozen PBMC vials stored according to the Laboratory Manual. These will be used to assess antigen specific T cell responses.

7.1.8.3 Blood Collection for HLA typing

HLA typing will be performed at SD0 via blood test by either a central or a local lab. When sending a request for HLA-typing, the study staff will ask for two a low-resolution (2 digit) HLA typing or high resolution (4 digit) HLA-sub-typing. Note that subjects can be positive for one or more HLA super type. If a patient has previously undergone HLA typing and subtyping at a certified laboratory and the documented results are available, then HLA typing and subtyping will not have to be repeated for study purposes.

7.1.9 **Other Procedures**

7.1.9.1 Injection Site Reaction Biopsy

If the investigator feels a biopsy of an injection site reaction is warranted, the Sponsor should be contacted in advance to discuss the case. This biopsy would be used for additional immune profiling, which would be useful in addition to any clinical indications. . If a tissue biopsy is collected, it is recommended to include the following tests:

- Sections of formalin fixed paraffin embedded (FFPE) tissue for standard H&E stain
- Any other standard immunohistochemistry (IHC) method

Samples may be sent for additional analysis if the participant consents. Before the collection of tissue sample, the subject has to explicitly agree to the donation of the tissue sample on the informed consent. The samples may be stored for up to 5 years after the study is completed for future analysis as new immune monitoring assays are being developed. Any sample not completely used in analysis will be destroyed after the 5 years has elapsed.

7.1.10 **Visit Requirements**

Visit requirements are outlined in Appendix B: Schedule of Events and detailed in Section 7.4. Specific procedure-related details are provided above in Section 7 – Study Schedule and Procedures.

7.2 Screening

Subjects will be screened for eligibility between 35 and 1 day prior to the first day of treatment (SD0). Subjects must be off previous treatment for 21 days prior to SD0. Fresh biopsy samples will be sent to a central lab for evaluation of survivin expression. This biopsy may be performed with an image-guided core biopsy. Archived tumour samples may also be assessed for evidence of survivin expression but will not replace the pre-treatment biopsy unless obtained less than 3 months (+7 days) prior to SD0 and unless at least 10 FFPE slides or a tumour block are available.

The CT scan results will need to show at least one site of measurable disease as per Cheson Criteria (2007). The site will be responsible for the initial selection of "target" nodes to be followed during the study.

Survivin expression will be sent on tumour biopsy from the screening tumour sample. Results of this will be collected but do not need to be obtained prior to enrollment into study. Lymphoma survivin expression is not an inclusion/exclusion critera. Patients with survivin expression less than 10% will be analyzed for safety but will be analyzed separately for efficacy and will not be included in the efficacy evaluation for evaluable paitents.

Assessments in Appendix A will be performed to assess the subject's eligibility for the study. Assessments may occur over the course of multiple days within the screening period. Adverse Event recording begins at the time of consent. Any medical events occurring prior to screening will be captured as medical history.

7.3 Enrollment

Potential candidates for the trial will be identified at local sites. Subjects meeting the eligibility criteria can be enrolled into the study. Study enrollment can only commence once the local site training has been completed. The study will close to recruitment once 25 subjects have met the definition of "evaluable", as defined by having received 4 doses of pembrolizumab and 3 injections of DPX-Survivac and one on-treatment CT scan between SD70 and SD104.

Lab results obtained during screening and used to determine adequate organ function as required to meet eligibility criteria # 6 (Table 2), can be used for subject enrollment, provided they are *completed no more than 48 hours prior to SD0*. If enrollment is the same day as SD0, laboratory results and SD0 physical exam, vitals and results from other procedures can be used for both purposes and do not need to be duplicated. However***, if*** the date of enrollment will be different than SD0, physical exam, vitals, and all screening bloodwork will need to be repeated. It is highly reccommended that Enrollment and SD0 be the same day.

At the time of Enrollment/Baseline, the following additional details will be obtained:

7.3.1 **Adverse Events/Concomitant Medications**

Any adverse events and concomitant medications since the commencement of screening will be collected at enrollment regardless of timeframe.

7.3.2 **Disease Staging**

Disease staging: ECOG, LDH, physical exam, disease stage and modifiers, or other procedures as needed. *These same assessments are to be used for disease re-staging throughout the study (SD112 and SD196) and EOS*.

7.3.3 **Confirmation of Eligibility**

Investigator's confirmation of eligibility should be documented as the date of enrollment, where the subject met all eligibility criteria. This does not need to be the same day as SD0, but is recommended.

7.4 Study Visits

Once the subject's eligibility has been confirmed, the subject will begin the study treatment at Visit 1/SD0 and continue in the treatment period for 1 year, up to Visit 23/SD364, followed by an End of Study Visit, 30 days after trial completion. Visit 1 (SD0) and Visit 2 (SD7) must occur 7 days apart. All other study visits can occur +/- 3 days of the scheduled time. Blood tests can be performed 72 hours prior to visits if necessary (excluding SD0 and SD7).

At the start of every visit during the treatment period, the following assessments will be conducted:

- Blood for hematology and clinical chemistry (see Table 9)
- Adverse events (AE)
- Concomitant medications
- Vital signs: temperature, pulse, pulse oximetry, respiratory rate, weight and blood pressure
- Pregnancy verification *(if subject is of childbearing potential as per eligibility criteria)*
- Cyclophosphamide Accountability *(including compliance and dispensing as per institutional policy)*

7.4.1 Visit 1 (SD0)

The following assessments will be conducted at the start of the visit prior to cyclophosphamide dispensing:

- Procedures listed in Section 7.4
- PBMC blood draw (~ 90 mL)
- Human leukocyte antigen (HLA) haplotype testing blood sample and subtyping (Not an eligibility requirement)
- Aerial photograph of thighs*

At the end of the visit, after all blood draws are completed and blood counts are confirmed as normal, the subject will be provided with cyclophosphamide and instructed to take it SD0 to SD6 and to repeat taking the cyclophosphamide every second week. *If the first dose is taken before 2 pm, the subject should be instructed to take the evening dose of cyclophosphamide as instructed on the label. However, if the first dose of cyclophosphamide is taken after 2 pm on SD0, then the subject should not take the second dose that day. This will result in one extra tablet being returned at the next visit.*

*The aerial photograph of the Left and Right thigh will be used as baseline to identify any marks on the skin that might confound the results of a suspected Injection Site Reaction.

7.4.2 Visit 2 (SD7)

The following assessments will be conducted at the start of the visit prior to injection:

- Procedures listed in Section 7.4
- PBMC blood draw (~ 90 mL)
- Directed physical examination

After these assessments, the subject will be administered a 0.5 mL priming dose of DPX-Survivac as detailed in Section 6.1.3. Vital signs will be collected approximately 15 +/- 5 minutes after injection.

At least 30 minutes following the injection of DPX-Survivac, the infusion of 200 mg pembrolizumab will begin. The infusion will take place over a 30 minute (-5/+10) time period.

7.4.3 Visit 3 (SD28)

The following assessments will be conducted at the start of the visit prior to injection:

- Procedures listed in Section 7.4
- PBMC blood draw (~ 90 mL)
- Directed physical examination
- Injection site evaluation* (for injection #1 SD7)

After these assessments, the subject will be administered a 0.5 mL injection as detailed in section 6.1.3. Vital signs will be collected approximately 15 +/- 5 minutes after injection.

At least thirty minutes following the injection, the infusion of 200 mg pembrolizumab will begin. The infusion will take place over a 30 minute (-5, +10 mins) time period.

* Injection site evaluations for injection site reactions (ISRs) will be performed and graded using the NCI CTCAE version 4.03 criteria (see Appendix E). **ISRs must also be broken down and evaluated according to the individual "events": pain, induration, erythema, edema and ulceration.** Injection site number, location, grade and description must be recorded in the Source and Electronic Case Report Form (eCRF). When applicable, measure and record the size of each ISR and each individual event as necessary. Close-up photographs of the ISR should be taken at each subsequent visit. Additional instruction on the expectations of ISR photographs can be found in the study Manual of Operations.

7.4.4 Visit 4 (SD49)

The following assessments will be conducted at the start of the visit prior to infusion:

- Procedures listed in Section 7.4
- PBMC blood draw (~ 90 mL)

- Directed physical examination
- Injection site evaluation* (for injection #1 SD7 and injection #2 SD28)

After these assessments, the infusion of 200 mg pembrolizumab will begin. The infusion will take place over 30 minutes (-5, +10mins).

For those subjects who present at this visit with any grade 2 or greater ISR or any grade injection site ulceration, a routine CT scan will be scheduled for SD70 and a tumour biopsy will be scheduled between SD77 - SD83 (see Section 7.4.5).** ***A grade 2 ISR, or any grade ulceration that was observed before this visit, but has resolved to grade 1 or better, does not qualify for an early CT or biopsy.

7.4.5 Visit 5 (SD70)

The following assessments will be conducted at the start of the visit prior to infusion:

- Procedures listed in Section 7.4
- PBMC blood draw (~ 90 mL)
- Complete or Directed Physical examination*
- Injection site evaluation (for injection #1 SD7 and injection #2 SD28)
- CT Scan**
- Bone Marrow Aspirate & Trephine** *(only if results were positive at Screening)*

After these assessments, the infusion of 200 mg pembrolizumab will begin. The infusion will take place over 30 minutes (-5, +10mins).

*If a subject has a tumour biopsy scheduled for SD77 - SD83, Visit 5 should include a Complete physical examination.

** Required only for subjects that presented at the visit with a grade 2 or greater ISR, or any grade injection site ulceration. *Reminder to book tumour biopsy between SD77 - SD83.*

7.4.6 Visit 6 (SD84)

The following assessments will be conducted at the start of the visit prior to injection:

- Procedures listed in Section 7.4
- PBMC blood draw (~ 90 mL)
- Cyclophosphamide accountability
- Directed Physical examination
- Injection site evaluation (for injection #1 SD7 and injection #2 SD28)

After these assessments, the subject will be administered a 0.1 mL maintenance injection as detailed in Section 6.1.3. Vital signs will be collected approximately 15 +/- 5 minutes after injection.

For subjects whose CT scan and biopsy were not scheduled early at SD70 & SD77-SD83, a CT scan will be scheduled for SD91 and a tumour biopsy will be scheduled between SD98 - SD104.

7.4.7 Visit 7 (SD91)

The following assessments will be conducted at this study visit prior to infusion:

- Procedures listed in Section 7.4
- Complete or Directed Physical examination*
- Injection site evaluation (for injection #1 SD7, injection #2 SD28 and injection #3 SD84)
- CT Scan**
- Bone Marrow Aspirate & Trephine** *(only if results were positive at Screening)*

After these assessments, the infusion of 200 mg pembrolizumab will begin. The infusion will take place over 30 minutes (-5, +10 mins).

* For subjects who had an early CT and Tumour biopsy, complete only a directed physical exam at this visit

**Required for subjects that did not have an early CT at SD70. Reminder to book tumour biopsy between SD98– SD104.

7.4.8 Visit 8 (SD 112)

At this visit, subjects will be re-staged using the same procedures outlined in Section 7.3.2. The following assessments will be conducted at this study visit prior to infusion:

- Procedures listed in Section 6.4
- Directed physical examination
- Re-staging of disease. See Section 7.3.2
- Injection site evaluation (for injection #1 SD7, injection #2 SD28 and injection #3 SD84)

After these assessments, the infusion of 200 mg pembrolizumab will begin. The infusion will take place over 30 minutes.

7.4.9 Visit 9 (SD133)

The following assessments will be conducted at the start of the visit prior to infusion:

- Procedures listed in Section 7.4
- Directed physical examination
- Injection site evaluation (for injection #1 SD7, injection #2 SD28 and injection #3 SD84)

After these assessments, the infusion of 200 mg pembrolizumab will begin. The infusion will take place over 30 minutes.

7.4.10 Visit 10 (SD140)

The following assessments will be conducted at the start of the visit prior to injection:

- Procedures listed in Section 7.4
- PBMC blood draw (~ 90 mL)
- Directed physical examination
- Injection site evaluation (for injection #1 SD7, injection #2 SD28 and injection #3 SD84)

After these assessments, the subject will be administered a 0.1 mL maintenance injection. Vital signs will be collected approximately 15 +/- 5 minutes after injection.

7.4.11 Visit 11 (SD 154)

The following assessments will be conducted at this study visit prior to infusion:

- Procedures listed in Section 7.4
- Directed physical examination
- Injection site evaluation (for injection #1 SD7, #2 SD28, #3 SD84 and #4 SD140)

After these assessments, the infusion of 200 mg pembrolizumab will begin. The infusion will take place over 30 minutes (-5, +10 mins).

Reminder to book a routine CT scan for SD175.

7.4.12 Visit 12 (SD 175)

The following assessments will be conducted at the start of the visit prior to infusion:

- Procedures listed in Section 7.4
- Directed physical examination
- Injection site evaluation (for injection #1 SD7, #2 SD28, #3 SD84 and #4 SD140)
- CT Scan
- Bone Marrow Aspirate & Trephine *(only if results were positive at Screening)*

After these assessments, the infusion of 200 mg pembrolizumab will begin. The infusion will take place over 30 minutes (-5, +10mins).

7.4.13 Visit 13 (SD 196)

At this visit, subjects will be re-staged using the same procedures outlined in Section 7.3.2. The following assessments will be conducted at this study visit prior to infusion:

- Procedures listed in Section Section 7.4
- PBMC blood draw (~ 90 mL)
- Complete physical examination
- Re-staging of disease. See Section 7.3.2

- Injection site evaluation (for injection #1 SD7, #2 SD28, #3 SD84 and #4 SD140)

After these assessments, the subject will be administered a 0.1 mL maintenance injection. Vital signs will be collected approximately 15 +/- 5 minutes after injection.

At least thirty minutes after the injection, the infusion of 200 mg pembrolizumab will begin. The infusion will take place over 30 minutes (-5, +10mins).

7.4.14 Visit 14 (SD217)

The following assessments will be conducted at the start of the visit prior to infusion:

- Procedures listed in Section 7.4
- Directed physical examination
- Injection site evaluation (for injection #1 SD7, #2 SD28, #3 SD84, #4 SD140 and #5 SD196)

After these assessments, the infusion of 200 mg pembrolizumab will begin. The infusion will take place over 30 minutes (-5, +10mins).

7.4.15 Visit 15 (SD238)

The following assessments will be conducted at the start of the visit prior to infusion:

- Procedures listed in Section 7.4
- Directed physical examination
- Injection site evaluation (for injection #1 SD7, #2 SD28, #3 SD84, #4 SD140 and #5 SD196)

After these assessments, the infusion of 200 mg pembrolizumab will begin. The infusion will take place over 30 minutes (-5, +10mins).

7.4.16 Visit 16 (SD252)

The following assessments will be conducted at the start of the visit prior to injection:

- Procedures listed in Section 7.4
- PBMC blood draw (~ 90 mL)
- Complete Physical exam
- Injection site evaluation (for injection #1 SD7, #2 SD28, #3 SD84, #4 SD140 and #5 SD196)

After these assessments, the subject will be administered a 0.1 mL maintenance injection. Vital signs will be collected approximately 15 +/- 5 minutes after injection.

7.4.17 Visit 17 (SD259)

The following assessments will be conducted at the start of the visit prior to infusion:

- Procedures listed in Section 7.4
- Directed physical examination
- Injection site evaluation (for injection #1 SD7, #2 SD28, #3 SD84, #4 SD140, #5 SD196 and SD#6 SD252)

After these assessments, the infusion of 200 mg pembrolizumab will begin. The infusion will take place over 30 minutes (-5, +10mins).

7.4.18 Visit 18 (SD280)

The following assessments will be conducted at the start of the visit prior to infusion:

- Procedures listed in Section 7.4
- Directed physical examination
- Injection site evaluation (for injection #1 SD7, #2 SD28, #3 SD84, #4 SD140, #5 SD196 and SD#6 SD252)

After these assessments, the infusion of 200 mg pembrolizumab will begin. The infusion will take place over 30 minutes (-5, +10mins).

7.4.19 Visit 19 (SD301)

The following assessments will be conducted at the start of the visit prior to infusion:

- Procedures listed in Section 7.4
- Directed physical examination
- Injection site evaluation (for injection #1 SD7, #2 SD28, #3 SD84, #4 SD140, #5 SD196 and SD#6 SD252)

After these assessments, the infusion of 200 mg pembrolizumab will begin. The infusion will take place over 30 minutes (-5, +10mins).

7.4.20 Visit 20 (SD308)

The following assessments will be conducted at the start of the visit prior to injection:

- Procedures listed in Section 7.4
- PBMC blood draw (~ 90 mL)
- Directed physical examination
- Injection site evaluation (for injection #1 SD7, #2 SD28, #3 SD84, #4 SD140, #5 SD196 and SD#6 SD252)

After these assessments, the subject will be administered a 0.1 mL maintenance injection. Vital signs will be collected approximately 15 +/- 5 minutes after injection.

7.4.21 Visit 21 (SD322)

The following assessments will be conducted at the start of the visit prior to infusion:

- Procedures listed in Section 7.4
- Directed physical examination
- Injection site evaluation (for injection #1 SD7, #2 SD28, #3 SD84, #4 SD140, #5 SD196 and SD#6 SD252 and #7 SD308)

After these assessments, the infusion of 200 mg pembrolizumab will begin. The infusion will take place over 30 minutes (-5, +10mins).

7.4.22 Visit 22 (SD343)

The following assessments will be conducted at the start of the visit prior to infusion:

- Procedures listed in Section 7.4
- Directed physical examination
- Injection site evaluation (for injection #1 SD7, #2 SD28, #3 SD84, #4 SD140, #5 SD196 and SD#6 SD252 and #7 SD308)

After these assessments, the infusion of 200 mg pembrolizumab will begin. The infusion will take place over 30 minutes (-5, +10mins).

7.4.23 Visit 23 (SD364)

The following assessments will be conducted at the start of the visit prior to injection:

- Procedures listed in Section 7.4
- PBMC blood draw (~ 90 mL)
- Physical exam
- Injection site evaluation (for injection #1 SD7, #2 SD28, #3 SD84, #4 SD140, #5 SD196 and SD#6 SD252 and #7 SD308)
- CT Scan

After these assessments, the subject will be administered a 0.1 mL maintenance injection. Vital signs will be collected approximately 15 +/- 5 minutes after injection.

At least thirty minutes after the injection, the infusion of 200 mg pembrolizumab will begin. The infusion will take place over 30 minutes (-5, +10mins).

7.4.24 End of Study (EOS) Visit

This visit can occur under two different circumstances: (1) after subjects have completed one year of treatment (SD364/V23), or (2) sooner for any subject who progresses during the study or withdraws early for any reason. In both instances, an EOS visit should be scheduled 30 days after a DPX-Survivac injection unless the subject progresses and needs immediate and urgent treatment.

7.4.24.1 Suspected Disease Progression/pseudo-progression

When disease progression is *suspected*, but the subject is not in urgent need of immediate treatment, they should remain on study protocol and have a CT scan performed at the time of suspected progression ***and again*** approximately 4 weeks after the first documented progression to rule out pseudo-progression.

7.4.24.2 Confirmed Disease Progression

For subjects who have confirmed progression, either by CT scan or other assessment, and need immediate and urgent treatment, every attempt should be made to conduct the EOS visit in conjunction with a CT scan before new treatment begins. The EOS visit may occur less than 30 days beyond the last injection, so that new treatment can begin quickly.

7.4.24.3 immune-related Response Criteria

To document irRC, a CT scan should be performed approximately 4 weeks after disease progression, if the subject consents, and has not started another form of cancer therapy.

At an EOS visit, all subjects will be re-staged using the same procedures outlined in Section 7.3.2. The following assessments will be conducted for the EOS visit:

- Procedures listed in Section 7.4
- PBMC blood draw (~ 90 mL)
- Complete Physical exam
- Re-staging of disease. See Section 7.3.2
- Injection site evaluation (for injection #1 SD7, #2 SD28, #3 SD84, #4 SD140, #5 SD196 and SD#6 SD252, #7 SD308 and #8 SD364)
- CT scan*
- Bone Marrow Aspirate & Trephine *(only if results were positive at Screening)*
- ^{18}F-FDG PET scan**
- Tumour Biopsy***

* When possible. Not required for subjects who have completed trial and received a CT scan at SD364

** This should be performed if there is equivocal evidence of disease at EOS, and is considered necessary in the opinion of the investigator.

*** Not required. Samples are to be obtained *if:* (1) the participant consents to sharing and (2) in the judgment of the investigator, a tumour biopsy is needed to better determine next course of therapy for that participant. The biopsy should be done before the start of a new treatment.

7.4.25 Follow-up Visits

Information on disease progression, general health and survival will be collected at each follow-up visit. These visits are recommended to be completed in person, but may also be completed by phone call or chart review, as per the consent requests of the subject.

7.4.25.1 For Subjects that Completed Treatment/ Did Not Progress on Study

After the EOS visit, subjects *who did not progress* will be followed every 2 months for 1 year, or until progression and the start of a new therapy, whichever occurs first. Whenever possible, the following should be collected:

- Procedures listed in Section 7.4*
- Physical exam
- Injection site evaluation (for injection #1 SD7, #2 SD28, #3 SD84, #4 SD140, #5 SD196 and SD#6 SD252, #7 SD308 and #8 SD364)
- Disease Status
- Tumour therapy
- Subject Status (survival)

**Procedures in Section 7.4 are only to be followed as appropriate. For example: pregnan*cy questions asked for 120 days *after last pembrolizumab infusion, AEs and Concomitant Medications to be collected until the start of a new therapy, etc.*

7.4.25.2 Follow-up Visits for Discontinued/Withdrawn Subjects

It is recommended that for subjects who; progress while on treatment, are discontinued from the study due to an adverse event or condition (defined in Section 5.5.1), or who withdraw from the study for any reason, be followed-up every 2 months if possible. At month 6 and month 12, after EOS/study discontinuation, the following should be collected:

- Procedures listed in Section 7.4
- Physical exam
- Injection site evaluation (for any and all injections received)
- Disease Status*
- Tumour therapy*
- Subject Status (survival)*

* May be collected from a chart review depending on subject consent and ability to successfully contact.

7.4.25.3 Follow-Up for Subjects of Childbearing Potential

As part of the expected follow-up, *questions regarding pregnancy* for both female participants of childbearing potential, and male participants with partners of childbearing potential, should only continue for 120 days (4 months) after last pembrolizumab infusion.

7.4.25.4 Follow-Up Visits for Subject Safety

All subjects, regardless of trial status (completion or withdrawal), will require a follow up visit at 30 days after receiving their last injection and last infusion, which may be the same as their EOS visit or different. An additional follow-up will be conducted at 90 days after receiving their last infusion of pembrolizumab, to assess the occurrence of any Serious Adverse Events. This is only to be completed as per subject consent requests *and* if the subject is not on another form of treatment.

It is also recommended that if an ^{18}F-FDG PET was performed, that the subject be contacted, as per institutional guidelines, to determine if there are any adverse events to report from the procedure.

7.5 Unscheduled Study Visits

It is possible that a subject requires a visit in addition to those outlined in Section 7.4. These visits include, but are not limited to; adverse events (including injection site reactions); serious adverse events (or other reasons for hospitalization); medical imaging performed for reasons not related to study procedures, such as MRI, DVT, CT Scan, Ultrasound, etc.; reasons related to study procedures, such as a previously omitted injection or infusion; imaging, specialist appointments, etc. not previously identified as being necessitated in the subject's medical history at Screening; additional laboratory test(s) or imaging directly related to study procedures.

Unscheduled study visits do not need to be attended, or requested, by study staff to be considered significant or relevant to the study.

Imaging, laboratory results, appointments or conditions being followed by a specialist, and not previously identified in a subject's medical history, whereby results can be obtained by study staff, should be reviewed by the investigator for clinical significance. If the visit or the results are deemed clinically significant by the site investigator, all attempts should be made to document the details in the Source **and** eCRF as appropriate. If the unscheduled visit, and or results, are deemed not clinically significant by the investigator, it should be noted as such in Source only.

7.6 Pregnancy Visit(s)

The Sponsor should be notified within 24 hours of site awareness in the case of a pregnancy in either a female subject, or the partner of a male subject.

If a female subject inadvertently becomes pregnant while on study, the subject will immediately be withdrawn from the study.

The site will contact the subject, or the subject's partner (when possible) on a monthly basis to document the pregnancy and outcome. The outcome of the pregnancy will be reported to the Sponsor within 24 hours of site awareness. The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the subject and newborn/fetus to the Sponsor.

The Sponsor will notify the Data Safety Monitoring Board (DSMB) within 24 hours awareness of a pregnancy and *if at which time, the outcome is a serious adverse experience for the mother or newborn/fetus* (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication). Additional reporting requirements can be found in Section 8.4.1.

7.7 Protocol Deviations

It is the responsibility of the investigator to ensure that only investigative procedures, as outlined in this protocol are performed on study participants; the occurrence of deviations from the protocol are limited; and compliance with the regulations is maintained. Planned deviations from the protocol must not be implemented without prior agreement from the Sponsor and approval from the local REB/ethics committee (EC), as required, unless to eliminate an immediate hazard to a participant.

Planned or unplanned deviations may occur on the part of the subject, the investigator, or study research team. In resolution to a deviation, corrective/preventative actions are to be developed and implemented in a timely manner. Protocol deviations will be documented and reported as required and assessed where necessary during analysis.

8 ASSESSMENT OF SAFETY

The safety of research participants is foremost and should always be considered throughout the conduct of research.

8.1 Adverse Events

An adverse event (AE) means any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment, and includes an adverse drug reaction (ADR).

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e. any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of either DPX-Survivac or pembrolizumab, is also an adverse event.

- Adverse events may occur during the course of the use of DPX-Survivac, pembrolizumab, or cyclophosphamide in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.
- Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.
- Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.
- Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

8.1.1 **Assessment of an Adverse Event**

To assess the severity of an adverse event the investigators will use the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 4.03 (Appendix E). The Investigator's opinion of the following should be documented on an Adverse Event Log:

8.1.1.1 Relationship (Causality/Relatedness)

The causality assessment is the determination, according to the investigator's clinical judgment, of the existence of a reasonable possibility that the study drug caused or contributed to an adverse event.

If the site investigator is unsure about whether or not the study drug caused or is related to the event, then the event will be handled as “related” to the study drug for reporting purposes of the trial. If the causality assessment is "unrelated” to the study drug, this should be clearly documented in the source documents.

The site investigator is obligated to estimate the relationship between the study drugs listed in Section 6.1 and the occurrence of each AE or SAE using their best clinical judgment. Other causes, such as the history of the underlying disease, concomitant therapy, other risk factors, and the temporal relationship of the event to the study drug will be considered and investigated. The site investigator will also consult the Investigator Brochure (IB) or Product Monograph (PM) in the determination of the assessment. If more information is needed to determine “relatedness”, the site should contact the Sponsor for guidance.

When reporting an SAE, the causality assessment is one of the criteria used to determine regulatory reporting requirements and should not be left blank. The site investigator may change his or her opinion of the causality in light of follow-up information, amending the SAE report.

8.1.1.2 Expectedness

Events are classified as unforeseen or unexpected if the nature, severity or frequency is not consistent with the risk information set out in IB or PM.

An expected AE is one that is consistent with the known risk information described in current IB or PM, therefore and ***unexpected*** AE is defined as any AE where the specificity or severity of which ***is not consistent*** with the known risk information described in current IB or PM.

Expectedness will be determined by the site investigator with discussion with the global principal investigator as required.

8.1.1.3 Seriousness

Events are classified as serious if associated with effects threatening the life or physiological functions of a participant. Refer to the definition for “Serious Adverse Events” in Section 8.2. All adverse events, regardless of grade, must also be evaluated for seriousness.

8.1.1.4 Severity

The term "severe" is often used to describe the intensity (severity) of a specific event (e.g. mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on participant/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. The terms “serious” and “severe” are not synonymous. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

To assess the severity of an adverse event the investigators will use the NCI CTCAE v 4.03 (Appendix E).

8.1.2 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI CTCAE v 4.03 (Appendix E). Any adverse event which changes grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets. See Table 10 for additional guidance.

All adverse events regardless of grade must also be evaluated for seriousness.

The investigator will also attempt to establish a diagnosis of the event based on the signs, symptoms, or other clinical information. In such cases, the diagnosis, not the individual signs and symptoms, should be documented on the appropriate eCRF as the AE or SAE Report Form – CIOMS I.

8.2 Serious Adverse Events

A serious adverse event is any adverse event occurring from the time 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 pembrolizumab or DPX-Survivac or at any dose during the any use of pembrolizumab or DPX-Survivac, that:

- Results in death;
- Is life threatening*;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is another important medical event
- Progression of cancer under study *only if it results in hospitalization or death*

*The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

Hematological adverse events (such as low absolute neutrophil count or low white blood cell count) identified as a serious adverse event based grading of lab values obtained for study purposes, are in fact common, known and expected in this disease population, and should not be considered a serious adverse event. See Section 8.5: Events of Clinical Interest for further instruction.

Any serious adverse event must be reported within 24 hours to the Sponsor using the SAE Report Form – CIOMS I, and within 1 working day to the Manufacturer. Additionally, any serious adverse event, considered by an investigator, who is a qualified physician, to be related to pembrolizumab or DPX-Survivac that is brought to the attention of the investigator at any time,

even if outside of the time period specified in the trial design, must also be reported immediately to the Sponsor.

8.2.1 **Unexpected Adverse Event**

An unexpected adverse event is any AE that is not identified in nature, severity or frequency in the current Investigator's Brochure or Product Monograph

8.2.2 **Unexpected Adverse Drug Reaction (ADR)**

An ADR is an adverse reaction, the severity of which is not consistent with the applicable Investigator's Brochure or Product Monograph. All noxious and unintended responses to a medicinal product related to any dose should be considered an ADR.

The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

The expression "causal relationship" is meant to convey that in general there are facts, evidence or arguments to suggest a reasonable causal relationship, a Serious Unexpected Adverse Drug Reaction (SUADR). All SUADRs will have expedited reporting to regulatory agencies following ICH-GCP and local regulatory requirements.

8.2.3 **Follow-up of SAEs**

After the initial SAE report, the site investigator is required to follow the subject and provide further information with regards to the subject's condition. All SAE(s) will be followed until:

- Resolution;
- The condition stabilizes;
- The event is otherwise explained;
- Death;
- The subject is lost to follow-up;

Or to a maximum of 90 days after onset, whichever occurs first

Once the event is resolved, the SAE Report Form – CIOMS I and the eCRF will be updated. The site investigator will also ensure that the follow-up includes any supplemental information, excluding source documents that may explain the causality of the event(s).
New or updated information will be recorded on the originally completed SAE Report Form – CIOMS I, with all changes signed and dated by the site investigator or designee. The updated SAE Report Form - CIOMS I will then be signed by the investigator and resubmitted to the Sponsor.

8.3 Investigational Product Overdose: pembrolizumab

For purposes of this trial, an overdose will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose) of pembrolizumab. 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 Pembrolizumab, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.*

If a dose of pembrolizumab meeting the protocol definition of "overdose" is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as an *Event of Clinical Interest* (Section 8.5), using the terminology "**accidental or intentional overdose without adverse effect**."

All reports of overdose with or without an associated adverse event must be reported within 24 hours to the Sponsor.

Table 10 Evaluating Adverse Events

V4.03 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any IP use that:	
	Results in death; or	
	Is life threatening; or places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	Results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or	
	Results in or prolongs an existing inpatient hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	Is a congenital anomaly/birth defect (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer;** (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment,	

	the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a ❖).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause IP to be discontinued?	
Relationship to test drug	Did IP cause the adverse event? The determination of the likelihood that IP caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between IP and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely IP caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to IP such as: reliable history, acceptable compliance assessment (pill count, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of IP? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)), or other host or environmental factors
	Dechallenge	Was IP discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. *(Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of IP; or (3) the trial is a single-dose drug trial); or (4) IP only used one time.)*

Relationship to IP (continued)	**The following components are to be used to assess the relationship between IP and the AE: (continued)**	
	Rechallenge	Was the subject re-exposed to IP in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. *(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) IP is/ used only one time).* NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY PEMBROLIZUMAB, OR IF REEXPOSURE TO PEMBROLIZUMAB POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE PRINCIPAL INVESTIGATOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding IP or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of IP relationship).**	
Yes, there is a reasonable possibility of IP relationship.	There is evidence of exposure to IP. The temporal sequence of the AE onset relative to the administration of IP is reasonable. The AE is more likely explained by IP than by another cause.	
No, there is not a reasonable possibility IP relationship	Subject did not receive IP OR temporal sequence of the AE onset relative to administration of IP t is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)	

8.4 Adverse Event Recording/Reporting

Adverse events will be recorded from the time the consent form is signed through the end of study participation (completion or withdrawal) and includes follow-up visits outlined in the trial design, or through 90 days following cessation of pembrolizumab. Information on all adverse events should be recorded promptly in the source document, and assessed by an investigator in a timely manner allowing sufficient time to meet required reporting timelines for SAEs and SUADRs as described. Adverse event logs should be completed using source documents by a delegated research team member in a timely manner. Additional instructions on reporting timelines can be found in the study Manual of Operations.

8.4.1 **Reporting of Pregnancy and Lactation to the Sponsor**

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, including that of a male subject's female partner. The Sponsor should be notified within 24 hours of site awareness of such instances which occur 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.

The outcome of the pregnancy will be reported to the Sponsor within 24 hours of site awareness. The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the subject and newborn/fetus to the Sponsor.

All subjects and female partners of male 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 Sponsor.

8.4.2 **Investigator Reporting**

In all instances of SUADRs, the investigator should record and report to the REB in accordance with local reporting requirements and timelines and to the Sponsor in 24 hours.

Reporting for SUADRs should include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. The minimum information required includes at least one identifiable subject, one identifiable reporter, one serious reaction, and one suspect product.

Additionally, a Suspect Adverse Reaction Report – CIOMS I Form must be completed by the investigator and forwarded to the Sponsor within 24 hours of site awareness. Information on other possible causes of the event, such as concomitant medications and illnesses should also be provided as soon as is made available.

8.4.3 **Sponsor Reporting of SUADRs and ECIs**

The regulatory Sponsor is responsible for reporting all relevant SAEs, overdoses, pregnancies and Events of Clinical Interest to Merck and IMV Inc. in 2 working days of learning of the event;

- Report by Fax to Merck Canada Inc. : Attn: Worldwide Product Safety; FAX 1-800-369-3090
- Report to IMV Inc.: Attn: Safety Reporting; FAX 902-492-0888.

The regulatory Sponsor is also responsible for reporting SUADRs to regulatory authorities in accordance with local expedited reporting requirements and timelines. In addition, the Sponsor will complete the ADR Expedited Reporting Summary Form and submit this form in conjunction with the completed CIOMS Form to the appropriate Health Canada directorate.
The regulatory Sponsor is responsible for distributing blinded expedited reports of SUADRs to each investigator for submission to local Ethics Committees within 15 days of Sponsor awareness.

8.4.4 **Reporting and Entry Timelines of Site to Sponsor**

8.4.4.1 SAE's

All deaths and immediately life-threatening events, whether related or unrelated, will be recorded and reported to the Sponsor within 24 hours of site awareness.

Serious adverse events other than death and immediately life-threatening events, regardless of relationship, will be reported to the Sponsor within 24 hours of site awareness.

Serious adverse event information will be entered into the eCRF in a timely manner (**within 72 hours)** from the time the investigator becomes aware of the event.

8.4.4.2 AE's

Adverse event information will be entered into the eCRF in a timely manner and **no later than 15 days** from the time the investigator becomes aware of the event.

8.5 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 Log and reported within 24 hours to the Sponsor. Events of clinical interest for this trial include:

- An overdose of pembrolizumab, as defined in Section 8.3 with or without symptoms.
- An elevated AST or ALT lab 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 with 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.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Manual of Operations.

8.6 Data and Safety Monitoring Board (DSMB)

Data and Safety Monitoring Board (DSMB) will comprise of clinician scientists with pertinent expertise, and who are considered independent of the study Sponsor. DSMB members will meet to assess at regular intervals the progress of a trial, the safety data and the critical efficacy endpoints and will recommend to the Principal Investigator whether to continue, modify or stop the trial. The roles and the responsibilities of the DSMB will be defined in the form of a charter. This Charter will serve as the Standard Operating Procedure (SOP) for the DSMB.

8.7 Steering Committee

A steering committee will be established. This will consist of investigators, other experts not otherwise involved in the trial and representatives of the Sponsors. The steering committee will oversee the maintenance of the quality of study conduct, monitoring of toxicities and AEs, determining the need and generation of trial amendments and coordinating writing of publications. They will also generate idea's around extension or additional related studies that may be conducted. All publications and presentations pertaining to this trial and any future/extension trials must first be approved by the Steering Committee.

9 SITE MONITORING, AUDITING AND INSPECTING

9.1 Site Monitoring Plan

Site monitoring is conducted to ensure the safety of human study subjects and the protection of their rights and well-being. Monitoring also verifies that collected study data is accurate, complete and verifiable by source documentation and that the study is conducted in accordance with the protocol and operating procedures.

Monitoring for this study is the responsibility of the Sponsor. The delegated monitor will evaluate study processes and documentation based on the approved protocol/amendment(s), Part C, Division 5 of the Food and Drug Regulations, the International Council for Harmonisation (ICH), E6: Good Clinical Practice guidelines (GCP) and institutional policies.

The extent and nature of monitoring will be outlined in the Monitoring Plan. The monitoring plan specifies the frequency of monitoring, monitoring procedures, the level of site monitoring activities (e.g., the percentage of subject data to be reviewed), and the distribution of monitoring reports. Monitoring activities will be performed both in person and remotely. Reports of findings identified during monitoring activities will be provided to sites detailing any required actions. Documentation of monitoring activities and findings will be provided to the site study team and the study QI. The institution and/or local REB reserves the right to conduct independent audits as necessary.

The Investigator is responsible for ensuring monitors and/or quality assurance reviewers are given access to all study-related documents noted above and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and have adequate space to conduct the monitoring visit or audit.

9.2 Auditing and Inspecting

The investigator will provide direct access to source data/documents for the purposes of study-related monitoring, audits, and inspections by the REB, the Sponsor, and applicable regulatory bodies. The investigator will permit the review of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.) and will ensure access to applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

10 STATISTICAL CONSIDERATIONS

10.1 Study Hypotheses

We hypothesize that combining DPX-Survivac and metronomic cyclophosphamide with pembrolizumab in patients with measurable or recurrent DLBCL will result in a clinically significant objective response level that will be at least 24%.

We also hypothesize that combining DPX-Survivac and metronomic cyclophosphamide with pembrolizumab in patients with measurable or recurrent DLBCL will enhance the activation of the polyfunctional T cells in the peripheral blood activated by DPX-Survivac and increase the infiltration of tumour sites with lymphocytes compared to pre-treatment biopsies. This will be evidence that both mechanisms of anti-tumour activity are elicited by this combination immunotherapy.

10.2 Populations of Interest

Patients with recurrent or refractory DLBCL, both de novo and transformed disease, post primary, secondary or subsequent regimens will be enrolled. Patients must not be eligible for alternative curative strategies and must meet the inclusion and exclusion criteria. Subjects will be continuously monitored. Data from all subjects entered will be presented and summarized. The safety population is defined as all subjects who receive at least one immunization. The efficacy population is defined as all subjects who received at least three injections and four infusions of pembrolizumab.

10.3 Planned Interim Analyses

An initial interim report based upon immunologic and/or safety results may be performed after the first four subjects have received at least three injections. The primary function of this analysis is to document safety profile and immunologic responses.

An additional interim analysis will be performed once 12 subjects are enrolled, to further assess safety and immunological responses and also review efficacy of the approach.

The DSMB and Steering Committee will review the interim reports. There is no plan to interrupt recruitment during the planned interim analysis. Based on study progression, safety or immunologic results analysis may occur at different time points.

If, after the first few subjects are evaluated, the immune responses are not at the level expected then, after consultation with the steering committee, 0.5 mL maintenance doses of DPX-Survivac may be considered for subsequent subjects.

There will be a lead-in cohort of 6 patients. If 2 or more grade 3 injection site ulcerations occur then the priming two doses of DPX-Survivac will be decreased to 0.25 mL each. Patient accrual will not be held after the 6th patient is treated in the lead-in cohort but the dose will be reduced as above for patients entered after the second grade 3 injection site ulceration is documented.

10.3.1 **Safety Review**

Safety will be assessed by using NCI CTCAE v 4.03 (Appendix E). The safety assessments up to the final study visit (EOS) will be based on reported adverse events and the results of vital sign measurements, physical examinations, and clinical laboratory tests. The incidence of adverse events will be tabulated and reviewed for potential significance and clinical importance. A subject will be considered evaluable for safety if treated with at least one dose of DPX-Survivac.

10.3.2 **Efficacy Review**

The primary objective is to determine the objective response rate to treatment with DPX-Survivac and low dose cyclophosphamide and pembrolizumab, in patients with recurrent survivin-expressing B cell lymphomas, using Modified Cheson criteria (Appendix C). The response rate will also be calculated for all subjects for descriptive purposes.

Secondary objectives are to document evidence of tumour regression using clinical and radiologic criteria for waterfall analysis. The duration of response will be determined using routine clinical and radiologic criteria (Modified Cheson criteria – Appendix C) as well as using irRC (Appendix D).

Exploratory analyses will be included in interim analyses when available. Exploratory efficacy analysis will look at the percentage of subjects with a positive immune response to one or more antigens in the drug. Survivin-peptide specific T cell immune response will be measured in the peripheral blood primarily by ELISpot assay, by stimulating subject PBMC with pooled as well as HLA-matched survivin peptides. Other exploratory immunologic assessments may be performed on remaining blood samples. The rate of immune response is defined as the percentage of subjects with a positive immune response to one or more epitopes in the drug. For ELISpot analysis, antigen-specific response rate greater than Mean±2SD value obtained from pre-treatment and/or unstimulated/background cells will be considered a positive response.

Tumour biopsy samples will be obtained pre-treatment and on-treatment to assess for changes in lymphocyte infiltrates, lymphocyte subsets, and gene expression profiles with treatment. Other novel biomarkers may be evaluated as they become available. If an injection site biopsy is required for clinical management during the course of this trial, portions of this biopsy may be studied for evidence of antigen specific T cell infiltrates, other biomarkers or immune activity.

10.4 Stopping Rules

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse events that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; or (3) any new information becomes available during the trial that necessitates stopping the trial.

10.5 Final Analysis Plan

A one-stage design requires treating and evaluating 25 subjects for response. The intended sample size is 25 evaluable subjects. Subjects who are survivin positive (>10% survivin

expression) and who that have received at least 4 doses of pembrolizumab, 3 injections of DPX-Survivac and have an on-treatment CT scan (between SD70 and SD104) will be considered evaluable. Other analyses addressing total patients enrolled (evaluable and non-evaluable) will also be explored particularly to indentify factors that may predict the likelihood of identifying evaluable versus non evaluable enrolled patients.

If objective responses are observed in at least 6 of 25 subjects, the treatment will be considered worthy of further testing. The design has more than 90% power to conclude that the treatment is effective if its true response rate were equal to 35% or more. The design also has less than 5% probability to conclude that the treatment is effective if its true response rate were equal to 10% or less. (If the power is 0.5 then the trial has a less than 5% chance to conclude that the trial is ineffective if its true response rate is greater than 10%).

Standard descriptive statistical methods will be used to summarize the data. The response rate will be estimated along with its exact 95% confidence interval.

Secondary objectives are to document evidence of tumour regression using clinical and radiologic criteria for waterfall analysis. Tumour volume recorded at baseline imaging will be compared to interim and end of study imaging. The degree of change/volume of response will be plotted on a waterfall plot to demonstrate the degree of individual responses. The duration of response will be determined using routine clinical and radiologic criteria (modified Cheson criteria) as well as using irRC. Evidence of toxicity will be assessed at each visit and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE v 4.03).

Exploratory endpoints will be evaluated as per Section 3.3 and will be important in determining whether the treatment is promising and worthy of further clinical evaluation assuming activity (i.e. minimal response rate of 24%, or 6 responses among 25 patients). We expect that both previously documented mechanisms of immune activity should be elicited by this immunotherapy combination. That is we would expect to see evidence of increases in circulating survivin specific T cells in the majority of patients. We would also expect to see increases in lymphocyte infiltration and gene expression in at least 24% of patients (i.e. 6 of 25 patients). Quantitative assessments of both of these parameters will be obtained and standard paired t-tests will be used to compare pre- and post-treatment assessments. Descriptive analyses will be used to describe the levels of Survivin in the plasma pre and during treatment.

Analyses will be performed to identify baseline and/or on-treatment clinical, immune and biologic parameters that predict for patients likely to have long clinical responses to the treatment versus those with no or shorter clinical responses. Similary these parameters will also be used to identify patients more likely to have peripheral and intra-tumour immune responses to survivin or to the tumour.

The final report will be conducted once 25 patients have reached evaluable or if the trial has been terminated early.

11 DATA HANDLING AND RECORD KEEPING

11.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the extent permitted by all applicable provincial, local, and federal data protection/privacy laws and/or regulations, and will not be made publicly available. Where consent is required, each subject must be informed of the following:

- What PHI will be collected during this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator may use all information collected prior to the revocation of subject authorization. For subject that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

11.2 Source Documents

Source data/documents are original documents, data and records in a clinical study that are necessary for the reconstruction and evaluation of the study. Examples of these original documents and data records include, but are not limited to:

- Worksheets
- hospital records
- medical records
- memorandum
- subjects' diaries or evaluation checklists
- pharmacy dispensing records
- recorded data from automated instruments (i.e. ECGs)
- copies or transcriptions certified after verification as being accurate and complete
- subject files and records kept at the pharmacy
- entries entered directly into the printed CRF

Each participating site will maintain appropriate medical and research records for this study, in addition to regulatory and institutional requirements for the protection of confidentiality of subjects. If electronic source data documents are printed, it should be signed and dated by the investigator to confirm content and filed with other source documents.

The investigator(s) and research team members listed on the Task Delegation Log (TDL) will have access to subject medical records and will collect only the information needed for the study. Sponsor delegated monitors, representatives of institutional committees and regulatory authority representatives of the country in which the study is being conducted will also have

access to examine records for the purposes of quality assurance reviews, audits and evaluation of study safety and progress.

11.3 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study personnel under the supervision of the investigator. All source documents and applicable laboratory reports should be reviewed as needed and used to ensure that data collected for the purposes of the study are accurate and complete. Contemporaneous review of laboratory results and the assessment of clinical significance for those results considered out of range should be documented by means of dated signature by the reviewing investigator. Study personnel, including data entry team members, should use source documents to complete case report forms (eCRFs).

As part of the safety plan for this study, the investigator will review individual study subject records to ensure that appropriate mechanisms to protect the safety of study subjects are being followed, that protocol requirements are being adhered to, and that data is accurate, complete, and secure. Subject records include, but are not limited to: consent forms, case report forms, data forms, laboratory specimen records, inclusion/exclusion forms, and medical charts. All study data will be collected by a member of the study research team and recorded in accordance with applicable procedures.

11.4 Data Capture

11.4.1 Case Report Forms

Data collection for this protocol is done using an electronic data capture (EDC) system and the clinical study sites will be provided with instructions for accessing the EDC system using a controlled unique username and password. eCRFs will be completed by the study site in a timely fashion following the subject visits according to the instructions in the eCRF Completion Guidelines. All data corrections will be made by the investigational site within the EDC system. It is the responsibility of the investigator to make sure each page of the eCRF accurately reflects the subject's medical record.

CRFs or eCRFs will be reviewed and source verified by the study monitor during periodic site visits. Prior to or between visits, the study monitor and/or data management group may request copies of the CRFs or study monitor may review the eCRFs for preliminary medical review. Once the CRFs or eCRFs are complete and source-verified, the investigator must sign and date all required pages, verifying the accuracy of all data contained within the CRF or eCRF.

Only the subject number and subject initials will be recorded on the CRF or eCRF, and if the subject name appears on any other document, it must be hidden or masked and replaced by subject number and initials before a copy is supplied to a data management group. Any discrepancies found will be sent to the sites for clarification.

11.5 Records Retention

Study essential documents must be maintained in a secure and confidential manner for participating Canadian sites for a period of 25 years. For the purposes of this study, the start date of the retention period is the date of the final report of the trial. Exceptions may be made for sites that close prematurely, wherein the start date for the retention period will be the date of notification to Health Canada of the sites closure. Sites conducting this study outside of Canada must maintain study records for the required retention period as stipulated by local regulatory authorities. All study records are then to be destroyed according to local and national policy and requirements. It is the investigator's responsibility to request authorization for destruction at the completion of the retention period and/or for the Sponsor to inform the investigator/institution when these documents may be destroyed.

11.6 Clinical Trial Registration

In accordance with Health Canada's Notice "Registration and Disclosure of Clinical Trial Information, November 30, 2007", the Sponsor will be responsible for registering the study on Clinicaltrials.gov (*www.clinicaltrials.gov*), a publically available registry that conforms to international standards for registries.

12 QUALITY CONTROL AND QUALITY ASSURANCE

As per ICH-GCP and local regulations, the Sponsor is responsible for ensuring the implementation and maintenance of systems that support quality assurance and quality control.

The study must be conducted in compliance with the study protocol and all data collected must be accurate and verifiable by source document(s). For the purpose of monitoring and auditing by the Sponsor, and inspection by regulatory authorities, the site will provide direct access to all study related source data/documents. The Sponsor will verify that the study is conducted and data has been collected, documented (recorded), and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

Data for the study will be centrally stored and managed by the Centre for Clinical Trial Support (CCTS). To ensure the quality of study data, quality assurance and control systems will be implemented using validated electronic quality control checks within the electronic data capture system. These verification measures will identify missing data, inconsistencies and/or data anomalies. Both electronic and manual queries will be generated for resolution and review by sites.

Access to secure and validated electronic systems used for the purposes of this study will be controlled by the Sponsor. Access will only be granted to individual research team members upon review of training and qualification and authorization by delegation of the investigator.

Quality assurance and control measures will be implemented to ensure training for specific trial–related tasks beyond the usual scope of practice.

For the purposes of this study, “research equipment” is defined as equipment used solely for the purposes of this study and that are unrelated to the delivery of standard-of-care treatment or procedures. In accordance with this definition, performance verification and /or calibration documentation will only be maintained for the following pieces of research equipment:

- Fridges, Freezers and Liquid Nitrogen tanks where biological specimens are stored
- Fridges where investigational products are stored
- Centrifuges used in biological sample processing

13 ETHICS CONSIDERATIONS

13.1 Ethical Standard

The investigator will ensure that this study is conducted in accordance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Participants of Research, and codified in the Tri-Council Policy Statement and/or the ICH E6.

13.2 Research Ethics Board (REB)

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the REB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is screened. Any amendment to the protocol will require review and approval by the REB before the changes are implemented in the study, unless to eliminate an immediate hazard.

13.3 Consent

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. A consent form describing in detail the study procedures and risks will be reviewed with and given to each participant. Consent forms will be REB-approved, and the participant is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the participant and answer any questions that may arise. The participant will sign the informed consent document prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to participants for their records.

Prior to involvement in any study-related activities, consent must be obtained in writing for each participant using the current REB approved informed consent from. It is the responsibility of the investigator to ensure that all advertisements and written information, including the informed consent form, disseminated to participants has been approved by the local REB prior to use. The ethics approved Informed Consent Form (ICF) and any other written information, must be provided to each participant, allowing ample time to ask and have answered any questions prior to making a decision regarding participation. Neither the investigator nor study staff should unduly influence or coerce a participant to participate in the study.

The ICF will be signed and dated by the participant and individual obtaining consent. The consent process will be documented in the clinical or research record.

The original ICF, in its entirety, will be maintained by the site, and a complete copy of the signed ICF provided to the participant. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study. The provision of consent is an ongoing process and should be maintained throughout the duration of the study. Participants may withdraw consent at any time throughout the course of the study.

14 PUBLICATION/DATA SHARING POLICY

The Steering Committee will lead and/or approve the generation of any publications obtained from this study. Authorship on study publications will adhere to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals of the International Committee of Medical Journal Editors. These requirements state “Authorship credit should be based on:

1) Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;

2) Drafting the article or revising it critically for important intellectual content; and

3) Final approval of the version to be published.

Authors should meet conditions 1, 2, and 3.” Where journal policies permit, all study site investigators who played a contributing role in the trial, including to its accrual, will be included in an Acknowledgement section.

15 LITERATURE REFERENCES

1. Higano CS, Schellhammer PF, Small EJ, et al. Integrated data from 2 randomized, double-blind, placebo-controlled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer. *Cancer*. 2009;115(16):3670-3679.
2. Berinstein NL. Strategies to enhance the therapeutic activity of cancer vaccines: using melanoma as a model. *Ann N Y Acad Sci*. 2009;1174:107-117.
3. Buckstein R, Kerbel RS, Shaked Y, et al. High-Dose celecoxib and metronomic "low-dose" cyclophosphamide is an effective and safe therapy in patients with relapsed and refractory aggressive histology non-Hodgkin's lymphoma. *Clin Cancer Res*. 2006;12(17):5190-5198.
4. Lindauer A, Valiathan CR, Mehta K, et al. Translational Pharmacokinetic/Pharmacodynamic Modeling of Tumor Growth Inhibition Supports Dose-Range Selection of the Anti-PD-1 Antibody Pembrolizumab. *CPT Pharmacometrics Syst Pharmacol*. 2017;6(1):11-20.
5. Wilson M, Villella JA, Berinstein NL, et al. Phase I/Ib clinical and immunologic assessment of immunotherapeutic vaccine, DPX-Survivac in women with ovarian, Fallopian tube, or peritoneal cancer (OC). *Journal of Clinical Oncology*. 2014;32(15_suppl):5555-5555.
6. Disis ML. Immune regulation of cancer. *J Clin Oncol*. 2010;28(29):4531-4538.
7. Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. *Annu Rev Immunol*. 2005;23:515-548.
8. Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. *Proc Natl Acad Sci U S A*. 2001;98(24):13866-13871.
9. Zhang X, Schwartz JC, Guo X, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. *Immunity*. 2004;20(3):337-347.
10. Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. *J Immunol*. 2004;173(2):945-954.
11. Sheppard KA, Fitz LJ, Lee JM, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. *FEBS Lett*. 2004;574(1-3):37-41.
12. Riley JL. PD-1 signaling in primary T cells. *Immunol Rev*. 2009;229(1):114-125.
13. Parry RV, Chemnitz JM, Frauwirth KA, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. *Mol Cell Biol*. 2005;25(21):9543-9553.
14. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. *Immunol Rev*. 2010;236:219-242.
15. Agata Y, Kawasaki A, Nishimura H, et al. Expression of the PD-1 antigen on the surface of stimulated mouse T and B lymphocytes. *Int Immunol*. 1996;8(5):765-772.
16. Vibhakar R, Juan G, Traganos F, Darzynkiewicz Z, Finger LR. Activation-induced expression of human programmed death-1 gene in T-lymphocytes. *Exp Cell Res*. 1997;232(1):25-28.
17. Nishimura H, Honjo T, Minato N. Facilitation of beta selection and modification of positive selection in the thymus of PD-1-deficient mice. *J Exp Med*. 2000;191(5):891-898.
18. Brown JA, Dorfman DM, Ma FR, et al. Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production. *J Immunol*. 2003;170(3):1257-1266.
19. Sharpe AH, Freeman GJ. The B7-CD28 superfamily. *Nat Rev Immunol*. 2002;2(2):116-126.

20. Hamanishi J, Mandai M, Iwasaki M, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. *Proc Natl Acad Sci U S A*. 2007;104(9):3360-3365.
21. Gao Q, Wang XY, Qiu SJ, et al. Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. *Clin Cancer Res*. 2009;15(3):971-979.
22. Thompson RH, Dong H, Lohse CM, et al. PD-1 is expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. *Clin Cancer Res*. 2007;13(6):1757-1761.
23. Fourcade J, Kudela P, Sun Z, et al. PD-1 is a regulator of NY-ESO-1-specific CD8+ T cell expansion in melanoma patients. *J Immunol*. 2009;182(9):5240-5249.
24. Karkada M, Weir GM, Quinton T, et al. A novel breast/ovarian cancer peptide vaccine platform that promotes specific type-1 but not Treg/Tr1-type responses. *J Immunother*. 2010;33(3):250-261.
25. Velculescu VE, Madden SL, Zhang L, et al. Analysis of human transcriptomes. *Nat Genet*. 1999;23(4):387-388.
26. Vermeij R, Daemen T, de Bock GH, et al. Potential target antigens for a universal vaccine in epithelial ovarian cancer. *Clin Dev Immunol*. 2010;2010.
27. Friedrichs B, Siegel S, Andersen MH, Schmitz N, Zeis M. Survivin-derived peptide epitopes and their role for induction of antitumor immunity in hematological malignancies. *Leuk Lymphoma*. 2006;47(6):978-985.
28. Kanwar JR, Shen WP, Kanwar RK, Berg RW, Krissansen GW. Effects of survivin antagonists on growth of established tumors and B7-1 immunogene therapy. *J Natl Cancer Inst*. 2001;93(20):1541-1552.
29. Ciesielski MJ, Apfel L, Barone TA, Castro CA, Weiss TC, Fenstermaker RA. Antitumor effects of a xenogeneic survivin bone marrow derived dendritic cell vaccine against murine GL261 gliomas. *Cancer Immunol Immunother*. 2006;55(12):1491-1503.
30. Andersen MH, Pedersen LO, Becker JC, Straten PT. Identification of a cytotoxic T lymphocyte response to the apoptosis inhibitor protein survivin in cancer patients. *Cancer Res*. 2001;61(3):869-872.
31. Gu X, Lin HL. [Analysis of survivin expression in subtypes of lymphoma]. *Ai Zheng*. 2004;23(6):655-661.
32. Adida C, Haioun C, Gaulard P, et al. Prognostic significance of survivin expression in diffuse large B-cell lymphomas. *Blood*. 2000;96(5):1921-1925.
33. Markovic O, Marisavljevic D, Cemerikic-Martinovic V, et al. Survivin expression in patients with newly diagnosed nodal diffuse large B cell lymphoma (DLBCL). *Med Oncol*. 2012;29(5):3515-3521.
34. Altieri DC. The case for survivin as a regulator of microtubule dynamics and cell-death decisions. *Curr Opin Cell Biol*. 2006;18(6):609-615.
35. Lennerz V, Gross S, Gallerani E, et al. Immunologic response to the survivin-derived multi-epitope vaccine EMD640744 in patients with advanced solid tumors. *Cancer Immunol Immunother*. 2014;63(4):381-394.
36. Berinstein NL, Karkada M, Oza AM, et al. Survivin-targeted immunotherapy drives robust polyfunctional T cell generation and differentiation in advanced ovarian cancer patients. *Oncoimmunology*. 2015;4(8):e1026529.
37. Barve M, Bender J, Senzer N, et al. Induction of immune responses and clinical efficacy in a phase II trial of IDM-2101, a 10-epitope cytotoxic T-lymphocyte vaccine, in metastatic non-small-cell lung cancer. *J Clin Oncol*. 2008;26(27):4418-4425.

38. Ghiringhelli F, Menard C, Puig PE, et al. Metronomic cyclophosphamide regimen selectively depletes CD4+CD25+ regulatory T cells and restores T and NK effector functions in end stage cancer patients. *Cancer Immunol Immunother*. 2007;56(5):641-648.
39. Greten TF, Ormandy LA, Fikuart A, et al. Low-dose cyclophosphamide treatment impairs regulatory T cells and unmasks AFP-specific CD4+ T-cell responses in patients with advanced HCC. *J Immunother*. 2010;33(2):211-218.
40. Veltman JD, Lambers ME, van Nimwegen M, et al. Low-dose cyclophosphamide synergizes with dendritic cell-based immunotherapy in antitumor activity. *J Biomed Biotechnol*. 2010;2010:798467.
41. Gebbia V, Boussen H, Valerio MR. Oral metronomic cyclophosphamide with and without methotrexate as palliative treatment for patients with metastatic breast carcinoma. *Anticancer Res*. 2012;32(2):529-536.
42. Borne E, Desmedt E, Duhamel A, et al. Oral metronomic cyclophosphamide in elderly with metastatic melanoma. *Invest New Drugs*. 2010;28(5):684-689.
43. Penel N, Clisant S, Dansin E, et al. Megestrol acetate versus metronomic cyclophosphamide in patients having exhausted all effective therapies under standard care. *Br J Cancer*. 2010;102(8):1207-1212.
44. Lord R, Nair S, Schache A, et al. Low dose metronomic oral cyclophosphamide for hormone resistant prostate cancer: a phase II study. *J Urol*. 2007;177(6):2136-2140; discussion 2140.
45. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007;25(5):579-586.
46. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res*. 2009;15(23):7412-7420.
47. Lesokhin AM, Ansell SM, Armand P, et al. Nivolumab in Patients With Relapsed or Refractory Hematologic Malignancy: Preliminary Results of a Phase Ib Study. *J Clin Oncol*. 2016;34(23):2698-2704.
48. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649-655.
49. *https://www.fda.gov:80/FDAgov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm182668.htm*

16 APPENDICES

APPENDIX A: Schedule of Events for Screening Period

Table A1: Screening Procedures for SD-21 to SD-1

Type of Visit	Screening
Procedure/Test	**SD-35 to SD-1**
Informed Consent	**X**
Inclusion/Exclusion Criteria	**X**
Demographics	**X**
Complete Medical History	**X**
β-HCG	**X**
Urinalysis	**X**
T3, T4, TSH	**X**
Organ function lab tests see Table 2	**X**
ECOG Performance Scale	**X**
Hematology and Clinical Chemistry see Table 9	**X**
Concomitant Medications	**X**
Physical Examination	**X**
Vital Signs and Weight	**X**
Routine CT Scan	**X**
Tumour Biopsy*	**X**
Disease Staging	**X**
Bone Marrow Aspirate & Trephine**	**X**
Lumbar Puncture with CSF analyses†	**X**
Adverse Events	**X**

* Archived tumour samples may also be assessed for evidence of survivin expression but will not replace the pre-treatment biopsy unless obtained less than 3 months prior to SD0 and unless at least 10 FFPE slides or a tumour block are available.
Note: The timeline for pre-treatment biopsies is 3 months + 7 days for subject eligibility and enrollment.

**See Lab manual for sample requirements. See study Manual of Operations for guidance regarding results

† Only required if suspected Central Nervous System (CNS) involvement

APPENDIX B: Schedule of Events for Treatment Visits

Type of Visit	Treatment [a]											
Procedure/Test	**SD0 V1**	**SD7 V2**	**SD28 V3**	**SD49 V4**	**SD70 V5**	**SD84 V6**	**SD91 V7**	**SD112 V8**	**SD133 V9**	**SD140 V10**	**SD154 V11**	**SD175 V12**
ECOG Performance Scale								X				
HLA Testing/Subtyping	X											
Hematology and Clinical Chemistry	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy verification[b]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Examination					X[c]		X[c]					
Directed Physical Examination		X	X	X		X		X	X	X	X	X
Vital Signs and Weight	X	X[d]	X[d]	X	X	X[d]	X	X	X	X[d]	X	X
Routine CT Scan					X[e]		X[e]					X
Bone Marrow Aspirate & Trephine[f]					X[f]		X[f]					X[f]
Tumour Biopsy					X[g]		X[g]					
Disease Staging [h]								X				
Investigational Blood Draw	X	X	X	X		X				X		
0.5 mL Priming Injections		X	X									
0.1 mL Maintenance Injections						X				X		
200 mg Pembrolizumab		X	X	X	X		X	X	X		X	X
ISR Evaluation and Photographs			X	X	X		X	X			X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
^{18}FDG PET[i]												

CT = computed tomography, ECOG = Eastern Cooperative Oncology Group performance status, EOS=End of Study, β-HCG = human chorionic gonadotrophin, HepBsAg = hepatitis B surface antigen, HIV = human immunodeficiency virus, HLA = human leukocyte antigen, ISR = Injection Site Reaction, PBMC = peripheral blood mononuclear cells, SD = Study Day

APPENDIX B: (continued)

Type of Visit	Treatment [a]											EOS	F-U[L]
Procedure/ Test	**SD196 V13**	**SD217 V14**	**SD238 V15**	**SD252 V16**	**SD259 V17**	**SD280 V18**	**SD301 V19**	**SD308 V20**	**SD322 V21**	**SD343 V22**	**SD364 V23**		
ECOG Performance Scale	X											X	
HLA Testing/Subtyping													
Hematology and Clinical Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy screening/verification[b]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	
Complete Physical Examination	X			X							X	X	X
Directed Physical Examination		X	X		X	X	X	X	X	X			
Vital Signs and Weight	X[d]	X	X	X[d]	X	X	X	X[d]	X	X	X[d]	X	X
Routine CT Scan											X	X	
Bone Marrow Aspirate & Trephine[f]												X[f]	
Tumour Biopsy												X[K]	
Disease Staging [h]	X											X	
Investigational Blood Draw	X			X				X			X	X	
0.5 mL Priming Injections													
0.1 mL Maintenance Injections	X			X				X			X		
200 mg Pembrolizumab	X	X	X		X	X	X		X	X	X		
ISR Evaluation		X	X		X	X			X	X		X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
FDG PET[J]												X	

[a] visits can occur +/-3 days of the protocol specified day, except for SD0 and SD7; [b] pregnancy verification at SD0 only for subjects of childbearing potential; [c] for subjects receiving an early biopsy (i.e. SD77-83) a physical exam will be completed at SD70 instead of SD91; [d] vital signs at these visits will be collected pre-injection and at 15 ± 5 minutes after injection; [e] most subjects are to complete a routine CT scan at SD91, for subjects with any grade 2 or greater ISR or any injection site ulceration on SD49, the CT scan will be completed early at SD70. Subjects who complete the trial will have a CT scan on SD364, all other subjects will have a CT as part of EOS visit, whichever occurs firs [f] Bone Marrow Aspirate & Trephine to be done as SOC at same visit as CT Scan, *only if results from Screening were positive* [g] most subjects are to complete a post-treatment biopsy between SD98 and SD104, for subjects with any grade 2 or greater ISR or any injection site ulceration on SD49 the biopsy will be completed early, between SD77 and SD83-note CT will be done at visit 5 or 7 but not both depending on whether the patient is experiencing grade 2 ISR or ulceration; [h] disease staging by physical exam and routine radiologic and laboratory assessments; [J] PET scans are optional and should be performed at EOS if there is equivocal evidence of disease; [K] Tumour Biopsy at EOS is not required. Samples can be collected if the subject undergoes the procedure as part of standard of care to determine next best therapy; [L] Follow-up visits for all subjects include safety/adverse event review at 30 & 90 days post pembrolizumab infusion, non-progressors every 2 months up to 1 year or until

progress, for progressors at 6 and 12 months post EOS for survival.

APPENDIX C: Modified Cheson Criteria (2007)

Modified Cheson Criteria[45] will be used in this study for assessment of tumour response, using standard CT imaging.

Table 2. Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

APPENDIX D: Immune Related Response Criteria (IrRC)[46]

Table 1. Comparison between WHO criteria and the irRC

	WHO	irRC
New, measurable lesions (i.e., ≥5 × 5 mm)	Always represent PD	Incorporated into tumor burden
New, nonmeasurable lesions (i.e., <5 × 5 mm)	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining BOR of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than 4 wk apart	Disappearance of all lesions in two consecutive observations not less than 4 wk apart
PR	≥50% decrease in SPD of all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions	≥50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart
SD	50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart

Table 2. Derivation of irRC overall responses

Measurable response	Nonmeasurable response		Overall response
Index and new, measurable lesions (tumor burden),* %	Non-index lesions	New, nonmeasurable lesions	Using irRC
↓100	Absent	Absent	irCR†
↓100	Stable	Any	irPR†
↓100	Unequivocal progression	Any	irPR†
↓≥50	Absent/Stable	Any	irPR†
↓≥50	Unequivocal progression	Any	irPR†
↓<50 to <25↑	Absent/Stable	Any	irSD
↓<50 to <25↑	Unequivocal progression	Any	irSD
≥25?	Any	Any	irPD†

*Decreases assessed relative to baseline, including measurable lesions only (>5 × 5 mm).
†Assuming response (irCR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 wk apart.

APPENDIX E: Common Termiology Criteria for Adverse Events V4.03 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for adverse event reporting. (*http://ctep.cancer.gov/reporting/ctc.html*)

MedDRA v12.0 Code	CTCAE v4.0 SOC	CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
10022095	General disorders and administration site conditions	Injection site reaction	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection.

10033371	General disorders and administration site conditions	Pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	-	-	A disorder characterized by the sensation of marked discomfort, distress or agony
10062466	General disorders and administration site conditions	Edema	Localized to dependent areas, no disability or functional impairment	Moderate localized edema and intervention indicated; limiting instrumental ADL	Severe localized edema and intervention indicated; limiting self-care ADL	-	-	A disorder characterized by swelling due to excessive fluid accumulation at a specific anatomic site
10015277	Skin & subcutaneous tissue disorders	Erythema (erythroderma	-	Erythema covering >90% BSA without associated symptoms; limiting instrumental ADL	Erythema covering >90% BSA with associated symptoms (e.g. Pruritus or tenderness); limiting self-care ADL	Erythema covering >90% BSA with associated fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death	A disorder characterized by generalized inflammatory erythema and exfoliation. The inflammatory process involves >90 of the Body Surface Area
10051837	Skin & subcutaneous tissue disorders	Skin Induration	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration, unable to slide or pinch skin; limiting joint movement; limiting self-care ADL	Generalized; associated with signs and symptoms of impaired breathing or feeding	Death	A disorder characterized by an area of hardness in the skin
10040947	Skin & subcutaneous tissue disorders	Skin Ulceration	Combined area of ulcers <1cm; non-blanchable erythema of intact skin with associated warmth or edema	Combined area of ulcers 1 - 2cm; partial thickness skin loss involving skin or subcutaneous fat	Combined area of ulcers >2cm; full-thickness skin loss involving damage to or necrosis of subcutaneous	Any size ulcer with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting	Death	A disorder characterized by circumscribed, inflammatory and necrotic erosive lesion on the skin

					tissue that may extend down to fascia	structures with or without full thickness skin loss		

APPENDIX F: ECOG Performance Status[48]

Grade	Description
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 G: Dose Modification Guidelines for Drug-Related Adverse Events for Pembrolizumab (July 2019)

Immune Related Adverse Reactions	Severity (Grade)	Treatment Modification
Pneumonitis	Moderate (Grade 2)	Withhold pembrolizumab until adverse reaction recovers to Grade 0-1*
	Severe or life threatening (Grade 3 or 4) or recurrent moderate Grade 2	Permanently discontinue pembrolizumab
Colitis	Moderate or Severe (Grade 2 or 3)	Withhold pembrolizumab until adverse reaction recovers to Grade 0-1*
	Life threatening (Grade 4) or recurrent severe (Grade 3)	Permanently discontinue pembrolizumab
Nephritis	Moderate (Grade 2) with creatinine >1.5 to ≤ 3 times ULN†	Withhold pembrolizumab until adverse reaction recovers to Grade 0-1*
	Severe or life-threatening (Grade 3 or 4) (Grade ≥ 3 with creatinine > 3 times ULN)	Permanently discontinue pembrolizumab
Endocrinopathies	-Severe or life-threatening (Grade 3 or 4) symptomatic hypophystitis -Type I diabetes associated with Grade >3 hyperglycaemia (glucose >250mg/dL or > 13.9 mmol/L) or associated with ketoacidosis -Hyperthyroidism Grade ≥ 3	Withhold pembrolizumab until adverse reaction recovers to Grade 0-1* For patients with severe (Grade 3) or life threatening (Grade 4) endocrinopathy that improved to Grade 2 or lower and is controlled with hormone replacement, if indicated, continuation of pembrolizumab may be considered after corticosteroid taper, if needed. Otherwise treatment

		should be discontinued Hypothyroidism may be managed with replacement therapy without treatment interruption
Hepatitis	Moderate (Grade 2) with asparate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 to 5 times ULN or bilirubin > 1.5 to 3 times ULN	Withhold pembrolizumab until adverse reaction recovers to Grade 0-1*
	-Grade ≥ 3 with AST or ALT >5 ULN or total bilirubin > 3 times ULN -for patients with liver metastasis who begin treatment with moderate (Grade 2) elevation of AST or ALT, if AST or ALT increases ≥ 50% relative to baseline and lasts ≥ 1 week	Permanently discontinue pembrolizumab
Skin Reactions or Stevens-Johnson Syndrome (SJS) or toxic epidermal necrolysis (TEN)	Severe skin reactions (Grade 3) or suspected SJS or TEN	Withhold pembrolizumab until adverse reaction recovers to Grade 0-1*
	Severe skin reactions (Grade 4) or confirmed SJS or TEN	Permanently discontinue pembrolizumab
Other Immune-related adverse reactions	Based on severity and type of reaction (Grade 2 or 3)	Withhold pembrolizumab until adverse reaction recovers to Grade 0-1*
	Severe of life-threatening (Grade 3 or 4) myocarditis, encephalitis, or Guillain-Barre Syndrome	Permanently discontinue pembrolizumab
	Life threatening (Grade 4) or recurrent sever (Grade 3)	Permanently discontinue pembrolizumab

Infusion related reactions	Severe or life-threatening (Grade 3 or 4)	Permanently discontinue pembrolizumab