MSK PROTOCOL COVER SHEET

Pilot study of pembrolizumab in untreated extranodal, NK/T cell lymphoma, nasal type

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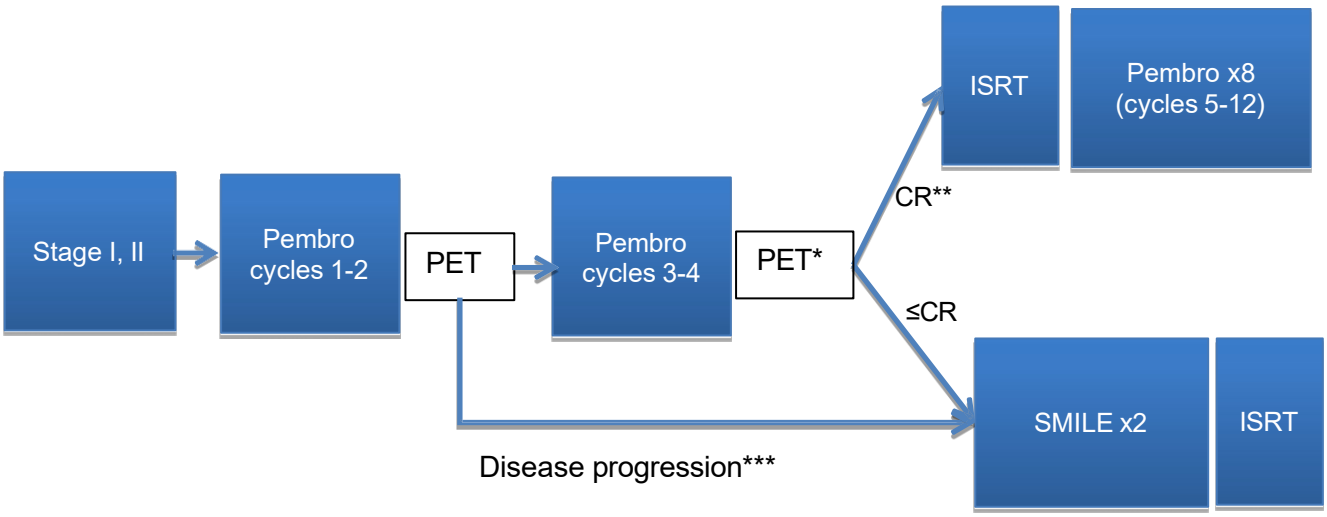
Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

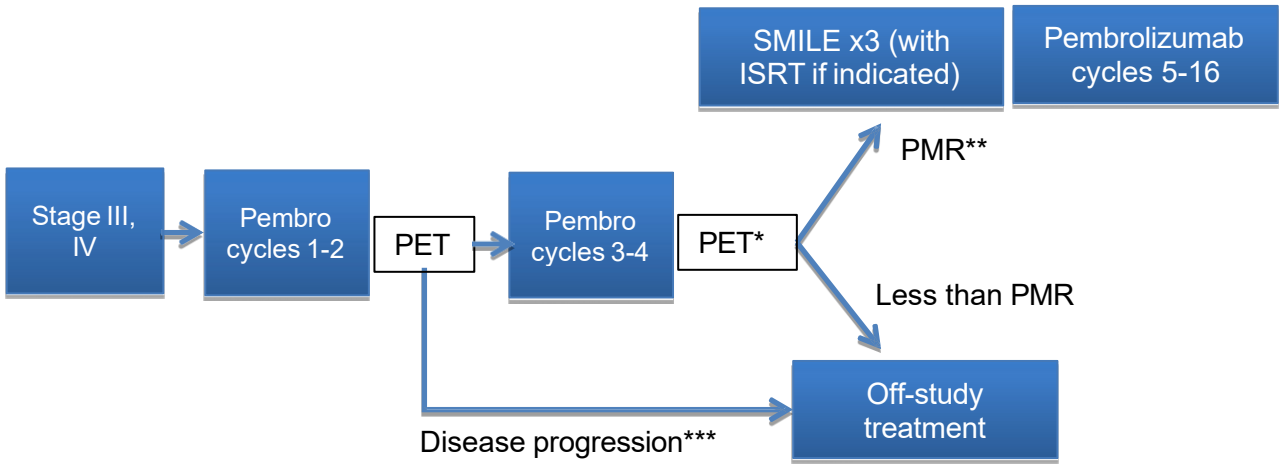
This is a pilot study evaluating front-line treatment with pembrolizumab in extranodal NK ("natural killer")/T-cell lymphoma (ENKTL). The primary endpoint is to assess the complete response rate after 4 cycles of pembrolizumab in untreated ENKTL. Treatment will differ for early stage (stage I or II) and advanced stage (stage III or IV) patients as outlined below. This study will enroll a total of 19 patients (regardless of stage).

Stage I, II:



*PET-positive patients will undergo biopsy to evaluate for persistent disease
**Or biopsy showing no evidence of lymphoma
***Patients with an "indeterminant response" by the LYRIC criteria (evidence of disease progression on PET but with clinical improvement) can be considered for another 2 cycles of pembrolizumab after discussion with the MSK PI.[1] See section 9.1 for details.
Abbreviations: ISRT (involved site radiation therapy), SMILE (steroids, methotrexate, ifosfoamide, asparaginase, etoposide)

Stage III, IV:



*Patients with PET showing less than partial metabolic response may undergo biopsy to evaluate for persistent disease after discussion with PI.
**Or biopsy showing no evidence of lymphoma
***Patients with an "indeterminant response" by the LYRIC criteria (evidence of disease progression on PET but with clinical improvement) can be considered for another 2 cycles of pembrolizumab after discussion with the MSK PI.[1] See section 9.2 for details.
Abbreviations: ISRT (involved site radiation therapy), SMILE (steroids, methotrexate, ifosfoamide, asparaginase, etoposide), PMR (partial metabolic response)

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objectives:

- Assess the complete response rate of pembrolizumab in untreated ENKTL.

Secondary objectives:

- Assess safety of pembrolizumab as front line therapy for ENKTL.
- Assess the partial response rate and overall response rate of pembrolizumab in untreated ENKTL.
- Assess response after 2 cycles of pembrolizumab according to the LYRIC criteria[1]
- Determine 2-year progression free survival and overall survival for newly diagnosed ENKTL treated with pembrolizumab-based therapy
- Explore mechanism of action and markers of response and resistance through assessment of baseline and on-treatment biopsies
- Evaluate plasma Epstein-Barr virus (EBV) PCR as a marker of response to therapy and/or early predictor of relapse.

3.0 BACKGROUND AND RATIONALE

Extranodal NK/T-cell lymphoma

ENKTL is a rare, aggressive lymphoma characterized by extranodal presentation (commonly but not always the upper aerodigestive tract), association with Epstein-Barr virus (EBV), and higher prevalence in Asia, South America, and Central America.[2] ENKTL has traditionally been associated with poor prognosis, with 5-year overall survival of 49%.[3] Poor outcomes are largely due to resistance to conventional chemotherapy, such as CHOP, due to overexpression of P-glycoprotein leading to multidrug resistance (MDR). Modern ENKTL regimens, such as SMILE (steroids, methotrexate, L-asparaginase, and etoposide), were designed to overcome the MDR phenotype, and as a result produce higher response rates than previously observed with CHOP-like regimens.[4] Building upon the high efficacy observed with SMILE, since 2009 our practice has been to treat with a modified version of SMILE in patients with untreated early stage and advanced stage ENKTL.[5] Early stage patients are treated with 2 cycles of modified SMILE followed by consolidation with involved-field radiation therapy; advanced stage patients receive 3 to 4 cycles of SMILE following by consideration for autologous or allogeneic stem cell transplant. In a recent analysis of patients with ENKTL treated at our institution from 1996 through 2014, the 2-year progression free survival for early stage and advanced stage patients were 56% and 18% respectively.[6] Among the 26 early stage patients, introduction of SMILE was associated with improved outcomes. Of the 11 early stage patients who received SMILE, 2-year progression free survival was 83%, significantly better than observed for patients who received CHOP ($p=0.03$). On the contrary, despite high response rates, the impact of SMILE was disappointing for advanced stage patients in our series. Among 17 advanced stage patients, 9 received SMILE of whom only 1 remained progression-free at 1 year. While the outcomes for our early stage patients are excellent, SMILE chemotherapy is associated with considerable toxicity such as neutropenic fever, renal insufficiency related to methotrexate, ifosfamide induced encephalopathy, as well as significant nausea and vomiting; therefore, strategies to reduce toxicity while maintaining excellent outcomes for early stage patients are warranted. For advanced stage patients, outcomes are poor despite incorporation of SMILE and transplant. Strategies to improve treatment efficacy in the advanced stage setting are therefore greatly needed.

Rationale for Pembrolizumab and ISRT in ENKTL

Virus-associated lymphomas are known to up-regulate PD-L1 on tumor cells and/or tumor associated macrophages, likely imparting reduced immune surveillance in these diseases. Five out of 6 ENKTLs (83%) evaluated by immunohistochemical staining expressed PD-L1, indicating the potential for PD-1 blockade in this disease.[7] Impressive results for 7 patients with relapsed or refractory ENKTL treated with pembroliuzmab was initially presented by Dr. Yok-Lam Kwong at the T-cell lymphoma Forum in January 2017 and recently published in Blood.[8] All patients had failed prior L-asparaginase containing therapies and 2 patients previously underwent allogeneic stem cell transplant. Furthermore, 5 of the 7 patients had evidence of hemophagocytic syndrome at the time of treatment. All patients responded to therapy, with 5 patients achieving CR or near CR and 2 patients achieving PR.

Based upon the observed efficacy of pembrolizumab in relapsed and refractory ENKTL, we believe that pembrolizumab has the potential to fundamentally alter the treatment paradigm for newly diagnosed ENKTL. Since this population will likely not have had prior radiation therapy, we propose here a pilot study incorporating pembrolizumab in untreated ENKTL for both early and advanced stage patients, followed by involved site radiation therapy (ISRT) when appropriate. Since radiation promotes anti-tumor immunity by causing increased antigen release from irradiated tumor tissue, the combination of pembrolizumab with ISRT can enhance pembrolizumab's impact on ant-tumor immunity. We aim to establish pembrolizumab's efficacy in untreated ENKTL, evaluate for markers of response and resistance, and explore its mechanism of action.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a pilot study evaluating front-line treatment with pembrolizumab in extranodal NK/T-cell lymphoma (ENKTL). The treatment will differ based upon stage as outlined below.

4.2 Intervention

Early Stage (Stage I, II) ENKTL

Newly diagnosed patients with early stage disease will initially receive 2 cycles of single-agent pembrolizumab, 200mg IVPB every 3 weeks followed by reassessment by PET. Patients with no evidence of disease progression will receive another 2 cycles of pembrolizumab. In addition, patients with an "indeterminant response" by the LYRIC criteria (evidence of disease progression on PET but with clinical improvement) can be considered for another 2 cycles of pembrolizumab after discussion with the MSK PI.[1] Patients who progress to stage III or IV ENKTL will come off treatment and receive subsequent standard of care treatment at the discretion of the treating physician. After 4 cycles of pembrolizumab, patients achieving complete response will receive involved site radiation (ISRT) and an additional 6 months of maintenance pembrolizumab. Patients who do not achieve complete response to pembrolizumab will undergo a biopsy. Those with pathologic complete response to treatment will receive the same treatment as those achieving complete response on PET (involved site radiation and an additional 6 months of maintenance pembrolizumab). Patients with less than complete response by PET or biopsy after 4 cycles of pembrolizumab will proceed to 2 cycles of SMILE chemotherapy and involved site radiation.

(Refer to Stage I, II Schema in Section 1.0 Protocol Summary)

Advanced Stage (Stage III, IV) ENKTL

Newly diagnosed patients with advanced stage disease will initially receive 2 cycles of single-agent pembrolizumab, 200mg IVPB every 3 weeks followed by reassessment by PET. Patients with no evidence of disease progression will receive another 2 cycles of pembrolizumab. In addition, patients with an "indeterminant response" by the LYRIC criteria (evidence of disease progression on PET but with clinical improvement) can be considered for another 2 cycles of pembrolizumab after discussion with the MSK PI.[1] After 4 cycles of pembrolizumab, those who achieve a partial metabolic response (PMR) to pembrolizumab will proceed to 3 cycles of SMILE chemotherapy, involved site radiation therapy (if indicated and according to institutional standards), followed by 10 months maintenance therapy with pembrolizumab. Patients who do not achieve partial metabolic response to pembrolizumab will undergo biopsy. Those with biopsy showing persistent lymphoma will come off study and receive treatment per discretion of treating physician. If the biopsy shows pathologic complete response to therapy, patients will receive the same treatment as those with PMR.

(Refer to Stage III, IV Schema in Section 1.0 Protocol Summary)

Hemophagocytic lymphohistiocytosis (HLH)

Subjects with HLH may be considered for study regardless of the hematological criteria specified in Section 6.1. Cytopenias including hemoglobin <90 g/L, platelets <100 x 10^9/L, or neutrophils <1.0 x 10^9/L are characteristic of HLH per HLH-2004 diagnostic criteria. For patients with HLH at baseline, dexamethasone is recommended with pembrolizumab administration. Patients with HLH should have enhanced blood count monitoring throughout the study. Patients with suspected HLH will receive dexamethasone 10mg/m2 daily for a minimum of 7 days followed by taper over 1-4 weeks as tolerated.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Pembrolizumab

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information. See Pharmacy Manual for detail information on handling and administration.

5.1.1 Dispensing

The study drug, pembrolizumab, will be supplied by Merck. Pembrolizumab will be shipped by Merck directly to each participating site. Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site. The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

5.1.2 General Information:

Generic Name: Pembrolizumab
Commercial Name: Keytruda ® Solution for Infusion, 100mg/4mL vial

Pembrolizumab (previously known as MK-3475 and SCH 9000475) 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 without ADCC or CDC activity.

5.1.3 Formulation

Pembrolizumab is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for intravenous infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.

5.1.4 Clinical Pharmacology

Mechanism of Action:

PD-1 is an immune-checkpoint receptor that limits the activity of T lymphocytes in peripheral tissues. The PD-1 pathway is an immune control checkpoint that may be engaged by tumor cells to inhibit active T-cell immune surveillance. Pembrolizumab is a high affinity antibody against PD-1, which exerts dual ligand blockade of the PD-1 pathway, including PD-L1 and PD-L2, on antigen presenting or tumor cells. By inhibiting the PD-1 receptor from binding to its ligands, Pembrolizumab reactivates tumor-specific cytotoxic T lymphocytes in the tumor microenvironment and thereby also reactivates anti-tumor immunity.

5.1.5 Pharmacokinetics and Drug Metabolism

Absorption: Pembrolizumab is dosed via the IV route and therefore is immediately and completely bioavailable.

Distribution: Consistent with a limited extravascular distribution, the volume of distribution of pembrolizumab at steady state is small (approximately 7.7 L; Coefficient of Variation (CV): 14%). As expected for an antibody, pembrolizumab does not bind to plasma proteins in a specific manner.

Metabolism: Pembrolizumab is catabolized through non-specific pathways; metabolism does not contribute to its clearance.

Excretion: The systemic clearance of pembrolizumab is - approximately 0.2 L/day (CV: 28%) and the terminal half-life (t½) is approximately 26 days (CV: 24%).

Exposure to pembrolizumab as expressed by peak concentration (Cmax) or area under the plasma concentration time curve (AUC) increased dose proportionally

within the dose range for efficacy. Upon repeated dosing, the clearance of pembrolizumab was found to be independent of time, and systemic accumulation was approximately 2.1-fold when administered every 3 weeks. Steady-state concentrations of pembrolizumab were reached by 18 weeks; the mean Cmin at steady-state was 23 mcg/mL during a regimen of 2 mg/kg every 3 weeks.

5.2 SMILE

Refer to package insert for the drugs included in SMILE: methotrexate, leucovorin, ifosfamide, MESNA, etoposide, PEG-asparaginase, pegfilgrastim.

5.3 Involved Site Radiation Therapy (ISRT) Guidelines

5.3.1 ISRT Volume

ISRT will be employed according to the published ILROG guidelines for using ISRT for extranodal lymphomas.[10] The pre-pembrolizumab gross tumor volume (pre-pembro GTV) will be determined using information from the initial PET/CT SIM. PET/CT SIM will be preferably performed with CT IV contrast with a 5-point mask and after a dental consultation. Body and arms position, immobilization, and use of Deep Inspiration Breath Hold will be determined by the attending Radiation Oncologist. Post-pembrolizumab/post-SMILE gross tumor volume (GTV) will be determined with information derived from the post-pembrolizumab/SMILE PET/CT SIM performed at the same conditions as the initial PETCT-SIM. Clinical treatment volume (CTV) and when relevant internal target volume (ITV) will always include the post-pembrolizumab/SMILE GTV and will account for pre-pembrolizumab GTV according to the quality of response to pembrolizumab (+/- SMILE), presence of organs at risk (OAR), and quality of imaging information. CTV will not include normal tissues like lung, heart, kidney, bowel, bone muscle or breast that are no longer involved after response to pembrolizumab (+/- SMILE). Planning treatment volume (PTV) will account for set-up variability and beam characteristics. Radiation treatment plan will be approved by an attending radiation oncologist. Intensity Modulated Radiation Therapy (IMRT) and 3-D conformal planning using photons and or electrons is allowed.

5.3.2 ISRT Dose

ISRT will be given once daily using fractions of 1.8 Gy. Total dose will be 45 Gy (25 daily treatments) for patients who achieve a CR post-pembrolizumab (+/- SMILE). For patients who achieve less than CR, the dose may be increased to 50.4 Gy (28 daily treatments).

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Histologic diagnosis of extranodal NK/T, nasal type cell lymphoma at the enrolling institution
- 18 years of age on day of signing informed consent.
- Have a performance status of ≤ 1 on the ECOG Performance Scale.
- Have measurable disease by PET/CT.
- Demonstrate adequate organ function as defined in Table 2.0 below.

Table 2.0 Adequate Organ Function

System	Laboratory Value
Renal	
Serum creatinine **OR** Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤ 1.5 X upper limit of normal (ULN) **OR** ≥ 60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR** ≤ 3 X ULN for subjects with liver metastases
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN OR ≤ 5 X ULN for subjects with liver metastases
Cardiac	
Ejection fraction	≥ 50%
Pulmonary	
Hemoglobin-adjusted diffusing capacity for carbon monoxide	≥ 50%

- Women of childbearing potential (WOCBP)* must have a negative urine or serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to receiving the first dose of study medication.
    - *A woman of childbearing potential is a sexually mature female who has not undergone a hysterectomy or bilateral oophorectomy; or has not been naturally postmenopausal for at least 24 consecutive months (i.e. has had menses at any time in the preceding 24 consecutive months)
- Women of childbearing potential must be willing to use an adequate method of contraception
    - Must agree to practice 2 effective methods of contraception from the time of signing the informed consent form through 120 days after the last dose of study therapy, or agree to completely abstain from heterosexual intercourse

- Male subjects of childbearing potential must agree to use an adequate method of contraception.
    - Male subjects, even if surgically sterilized (i.e. status post vasectomy) must agree to 1 of the following:
        - Practice effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study therapy, or agree to completely abstain from heterosexual intercourse

6.2 Subject Exclusion Criteria

- Received prior treatment for extranodal NK/T cell lymphoma
- Medical illness unrelated to lymphoma, which, in the opinion of the treating physician and/or institutional principal investigator, makes participation in this study inappropriate.
- Has received a live vaccine or live-attenuated vaccine within 30 days prior to the first dose of study drug. Administration of killed vaccines is allowed.
- Has a known additional malignancy that is progressing or has required active treatment within the past 2 years. Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g. breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.
- Has known active CNS metastases and/or carcinomatous meningitis.
- Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.
- Has 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.
- Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
- Has an active infection requiring systemic therapy.
- Has a known history of Human Immunodeficiency Virus (HIV).
- Has active Hepatitis B (defined as HBV DNA is detected) or known active Hepatitis C virus (defined as HCV RNA is detected) infection.
- Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
- Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
- Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of trial treatment.

- Has had an allogenic tissue/solid organ transplant.

7.0 RECRUITMENT PLAN

The clinical trial will be listed on the clinicaltrials.gov website.

Patients seen in the inpatient or outpatient setting who meet eligibility criteria will be recruited to this study. At MSK, patients will be recruited through the Lymphoma Disease Management Teams. The Lymphoma Disease Management Team holds weekly interdepartmental meetings to identify study participants for open clinical trials. The principal investigator will be available to all patients for further questions and information through a contact number, which will be provided on the consent form. Similar recruitment procedures will be conducted at participating institutions. An attending physician of the Lymphoma or Hematology service will evaluate all patients.

All eligible patients, regardless of sex and race, will be approached for participation. The investigators are aware of the NIH policy concerning inclusion of women and minorities in clinical research populations.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. Participation in the study is completely voluntary. Patients will be required to read, agree to, and sign an IRB-approved informed consent form prior to registration on this trial. Patients will not receive payment for their participation on this study. Patients are free to withdraw from the study without consequence at any time.

A total of 19 participants will be enrolled on this study. Participants will be accrued at Memorial Sloan Kettering Cancer Center (MSK) and an external participating institution. Approximately 10 participants will participate from MSK.

8.0 PRETREATMENT EVALUATION

Within 6 months of initiating treatment:

- Hepatitis B surface antigen, core antibody
- Hepatitis C antibody
- HIV I/II antibodies

Prior to initiation of treatment:

- Patients will be required to have a biopsy that confirms extranodal NK/T cell lymphoma. If a biopsy is already done, 20 unstained slides from archived tissue will be requested for correlative studies.
    - Please refer to Section 10.1 Correlative Studies for more information on planned correlatives.

Within 4 weeks prior to initiation of treatment:

- Referral to Radiation Oncology
  - MSK patients will be referred to MSK Main center
- FDG-PET/CT Simulation [only for early stage patients who will receive radiation]
  - MSK patients will be referred to MSK Main center
  - Optional for advanced stage patients who will receive radiation
- MRI nasal cavity (only for patients with nasal cavity disease)
- PET/CT [only for patients not receiving radiation and being referred to Radiation Oncology]
- Echocardiogram
- Pulmonary function tests
- ECG

Within 14 days prior to initiation of treatment:

- CBC
- Comprehensive metabolic panel

9.0 TREATMENT/INTERVENTION PLAN

9.1 Stage I, II ENKTL

Newly diagnosed patients with early stage disease will initially receive the following study treatment:

- Baseline FDG-PET/CT simulation will be done following an initial consultation in Radiation Oncology (main center) and prior to starting therapy
- 2 cycles of single-agent pembrolizumab, 200mg IVPB every 3 weeks
- Reassessment by PET after 2 cycles of pembrolizumab
  - If no evidence of disease progression, another 2 cycles of pembrolizumab.
  - Patients with an “indeterminant response” by the LYRIC criteria (evidence of disease progression on PET but with clinical improvement) can be considered for another 2 cycles of pembrolizumab after discussion with the MSK PI.[1]
  - Patients with progression of disease without evidence of clinical improvement will proceed to 2 cycles of SMILE chemotherapy and ISRT.
  - Patients who progress to stage III or IV ENKTL will come off treatment and receive subsequent standard of care treatment at the discretion of the treating physician.
- Reassessment by PET after 4 cycles of pembrolizumab
  - If CR response on PET, patients will begin 45 Gy of involved site radiation (ISRT) and an additional 6 months of maintenance pembrolizumab. ISRT will begin 2-6 weeks after cycle 4 of pembrolizumab.
  - Patients with less than CR will undergo a biopsy. If biopsy shows no evidence of lymphoma, patients will proceed with same treatment as those with PET CR.

- Patients with less than complete response by PET and persistent evidence of disease on biopsy after 4 cycles of pembrolizumab will proceed to 2 cycles of SMILE chemotherapy and ISRT.

9.2 Stage III, IV ENKTL

Newly diagnosed patients with advanced stage disease will obtain baseline FDG-PET/CT simulation after a Radiation Oncology consultation. They will initially receive 2 cycles of single-agent pembrolizumab, 200mg IVPB every 3 weeks followed by reassessment by PET. Patients with no evidence of disease progression will receive another 2 cycles of pembrolizumab. In addition, patients with an "indeterminant response" by the LYRIC criteria (evidence of disease progression on PET but with clinical improvement) can be considered for another 2 cycles of pembrolizumab after discussion with the MSK PI.[1] After 4 cycles of pembrolizumab, those who achieve a partial metabolic response (PMR) to pembrolizumab will proceed to 3 cycles of SMILE chemotherapy, up to 50.4 Gy of involved site radiation therapy (if determined to be appropriate by a Radiation Oncology Attending and according to institutional standards), followed by 10 months maintenance therapy with pembrolizumab. Patients who do not achieve partial metabolic response to pembrolizumab will undergo biopsy. Those with biopsy showing evidence of lymphoma will come off study and receive treatment per discretion of treating physician. If the biopsy shows no evidence of lymphoma, patients will receive the same treatment as those with PMR.

9.3 Pembrolizumab

Dosing

Dosing of pembrolizumab is outlined in Table 3.0 below. Pembrolizumab will be administered every 3 weeks (21 days) (+/-3 days).

Table 3.0 Pembrolizumab Dosing

Drug	Dose/Potency	Route of Administration	Regimen/Treatment Period
Pembrolizumab	200mg Flat	IVPB over 30 minutes	Once every 21 days

Administration

Pembrolizumab should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Schedule of Assessments (Section 10.0). Study treatments will be administered on an outpatient basis. Study treatment may be administered up to 3 days before or after (+/- 3 days) the scheduled Day 1 of each cycle. Subjects may be dosed with pembrolizumab no less than 17 days from the previous dose. Treatment related toxicity requiring treatment delay of 6 weeks or more would require removal from the study unless after discussion with the PI it is felt to be clinically appropriate for the patient to remain on study.

Supportive Care/Premedications

There are no premedications routinely recommended unless patient has experienced previous infusion reaction. Subjects should be carefully monitored for infusion reactions during pembrolizumab administration. If an acute infusion reaction is noted, subjects should be managed according to 7.0 in Section 11.6.

Dose modifications of Pembrolizumab are discussed in Section 11.5.

9.4 SMILE

The SMILE regimen will be administered as per institutional guidelines and is outlined in the table below. SMILE will begin at the discretion of the treating physician following the last dose of pembrolizumab and is administered every 21-28 days.

Table 4 SMILE regimen

Drug	Dose/Potency	Route of Administration	Regimen/Treatment Period
Methotrexate	2000 mg/m2	IVPB over 6 hours	Day 1
Leucovorin	25mg FLAT	IVPB q 6 hours	Begin 30 hours after start of Methotrexate
Ifosfamide	1500mg/m2	IVPB over 1 hour	Days 2, 3, 4
MESNA	300mg/m2	IVPB over 15 min	30 min prior to chemo, then 4 and 8 hours post chemo
Etoposide	100mg/m2	IVPB over 1 hour	Days 2, 3, 4
Dexamethasone	40mg	IVPB	Days 2, 3, 4
PEG-asparaginase	1500-2000 units/m2	IM or IVPB over 1 hour	Between day 5 and 8
Pegfilgrastim	6mg	SC	Between day 5 and 8

9.5 Involved site radiation

Patients with stage I or II disease will undergo involved site radiation therapy (ISRT) according to published ILROG guidelines for using ISRT for extranodal lymphomas.[10] A total dose of 45 Gy (25 daily treatments) will be given with the option of increasing it to 50.4 Gy (28 daily treatments) for patients who have PET-positive disease after pembrolizumab. Involved site radiation therapy will begin 2-6 weeks following cycle 4 of pembrolizumab. Cycle 5 of pembrolizumab will begin 3-6 weeks following completion of radiation. Patients with advanced stage disease may receive ISRT if indicated. ISRT may be administered between cycles of SMILE or after SMILE and will be performed according to institutional standards.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1 Evaluations during treatment for stage I, II patients:

Study Calendar, Stage I, II

Assessment Period	**Screening** [2]	**Cycle 1**		**Cycle 2**		**If PD with no clinical improvement, proceed to 2 cycles of SMILE chemotherapy and ISRT (Involved Site Radiation Therapy (see footnote 16]**	**Cycle 3**	**Cycle 4**		**Involved Site Radiation Therapy (ISRT) OR SMILE, then ISRT [see footnote 17]**	**Cycles 5 – Cycle 12**		**Post-Treatment**	
Study Days	**Day -28 to 1**	**Day 1**	**Day 8-20**	**Day 1**	**Day 14-21**		**Day 1**	**Day 1**	**Day 14-21**		**Day 1**	**Day 14-21**	**End of Treatment**	**Follow up**[18]
Visit Window [1]	*-28 days*	*- 3 days*		*+/- 3 days*			*+/- 3 days*	*+/- 3 days*	*+/- 3 days*		*+/- 3 days*			*+/- 1 month*
Informed consent	X													
Medical History	X													
Review of concomitant medications		X		X			X	X			X		X	
Review of adverse events		X		X			X	X			X		X	
Physical Examination [3]		X		X			X	X			X		X	X
Vital Signs [4]		X		X			X	X			X		X	X
ECOG/KPS		X		X			X	X			X		X	X
Hematology [5] and Chemistry [6]		X		X			X	X			X		X	X
HIV, Hepatitis B and Hepatitis C [7]	X													
Pregnancy test [8]		X												
EBV PCR [9]		X		X				X			X		X	X
Referral to radiation oncology	X													
FDG-PET/CT simulation[10]	X													
MRI nasal cavity *(only for patients with nasal cavity disease)*	X													
ECHO	X													

ECG	X													
Pulmonary function tests [11]	X													
Baseline Biopsy or archive tissue [12]	X													
Research Tumor Biopsy [13]			X						X[13]					
PET/CT	X[19]				X				X		Cycle 8 & Cycle 12[20]	X	X	
Tumor assessment [14]					X				X		Cycle 8 & Cycle 12			
cfDNA[21]		X						X			X		X	X[21]
Pembrolizumab [15]		X		X			X	X			X			

1. Each cycle is 21 days in length.
2. **Screening assessments** must be completed prior to initiation of treatment. HIV, Hep B and C tests must be done within 6 months of start of treatment. Baseline biopsy must be done prior to treatment. All other assessments must be done within 28 days of treatment, except for laboratory tests which must be done within 14 days of treatment. Lab tests CBC and comp must be repeated within 3 days of C1D1. Pregnancy test is required for females of child-bearing potential and must be done within 7 days of initiating treatment.
3. **Physical Examination** must include height and weight. The patient's weight in kilograms must be determined before the start of each cycle.
4. **Vital signs** include: pulse, blood pressure, temperature, respiratory rate, and oxygen saturation.
5. **Hematology** must include CBC with differentials. Screening CBC done within 14 days of start of treatment. Must be repeated within 3 days of C1D1.
6. **Chemistry** must include comprehensive metabolic panel (albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium) magnesium, phosphorus amylase, lipase, thyroid function tests (fT4, and TSH) and LDH. Screening comp done within 14 days of start of treatment. Must be repeated within 3 days of C1D1. Screening magnesium, phosphorus, amylase, lipase, thyroid function tests (fT4 and TSH) and LDH must be done within 7 days of starting treatment.
7. **HIV, Hep B and Hep C tests** include: HIV I/II antibodies, Hepatitis B surface antigen, core antibody and Hepatitis C antibody. Must be done within 6 months of initiating treatment.
8. **Pregnancy test** includes: serum β-HCG or urine pregnancy test for women of child-bearing potential. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Screening pregnancy tests must be performed within 7 days of starting treatment.
9. **EBV PCR:** screening EBV PCR must be done within 7 days of starting treatment. It is done on Cycle 2 Day 1, Cycle 4 Day 1, then odd cycles only starting in Cycle 5.
10. **Baseline FDG-PET/CT** simulation will be done following an initial consultation in Radiation Oncology and prior to starting therapy. Only required for patients who will be receiving radiation therapy.
11. **Pulmonary Function tests** include: DLCO at minimum.
12. **Baseline tumor biopsy:** all study participants will be required to have a biopsy that confirms extranodal NK/T cell lymphoma. If a biopsy is already done, 20 unstained slides from archived tissue will be requested for correlative studies if possible. The biopsy must be done prior to initiation of treatment.
13. **Research biopsies:** on-treatment biopsies are mandatory for all study participants. Biopsies will be done Cycle 1 (between days 8-20), and Cycle 4 (between days 8-20), except in cases where due to the location of disease, biopsy would be associated with unnecessary risk to the patient.

14. **Tumor Assessment:** is the response assessment after PET scans. Refer to Section 12.0 Criteria for Therapeutic Response/Outcome Assessment.
15. **Pembrolizumab**: Pembrolizumab is administered every 3 weeks (21 days) on Day 1 of each cycle, ± 3 days. Pembrolizumab is given 200m via IVPB infusion over 30 minutes (+/- 5 minutes).
16. **Reassessment by PET after 2 Cycles of pembrolizumab:** If there is no evidence of disease progression, participant will receive another 2 cycles of pembro. If evidence of disease progression on PET but with clinical improvement, participant can be considered for another 2 cycles of pembro after discussion with the study PI. Patients with progression of disease without evidence of clinical improvement will proceed to 2 cycles of SMILE chemotherapy and ISRT.
17. **Reassessment by PET after 4 Cycles of pembrolizumab**: If Complete Response (CR) by PET, patients will begin 45 Gy of involved site radiation (ISRT), and an additional 6 months (8 cycles) of maintenance pembrolizumab. ISRT will begin 2-6 weeks after Cycle 4 of pembrolizumab. Patients with less than CR will undergo a biopsy. If biopsy shows no evidence of lymphoma, patients will proceed with same treatment as those with PET CR. Patients with less than CR by PET and persistent evidence of disease on biopsy after 4 cycles of pembro will proceed to 2 cycles of SMILE chemotherapy and ISRT.
18. **Follow-up** includes: standard clinic visit and laboratory tests (CBC, comp only). EBV PCR every 3 months for 3 years. Imaging to be obtained every 6 months for 2 years post treatment. cfDNA to be collected 6 months, 1 year, and 2 years into follow up or until a new therapy is initiated.
19. PET/CT to be completed at baseline only if the patient will not be receiving radiation therapy.
20. Patients will be followed by PET/CT (skull apex to midthigh). If PET/CT is not feasible, patients may be followed with CT CAP plus CT nasal cavity (for patients with nasal cavity disease) after discussion with MSK PI. If followed by PET/CT, additional diagnostic CT is NOT required.
21. cfDNA to be collected at C1D1, C4D1, after SMILE or at C5D1 of pembrolizumab, end of treatment, and 6 months, 1 year, and 2 years into follow up or until a new therapy is initiated.

10.2 Evaluations during treatment for stage III, IV patients:

Assessment Period	Screening [2]	Cycle 1		Cycle 2		Cycle 3	Cycle 4		SMILE, Cycles 1-3; ISRT if indicated [see footnote 16]	SMILE	Cycles 5 – Cycle 16		Post-Treatment	
Study Days	**Day -28 to 1**	**Day 1**	**Day 8-20**	**Day 1**	**Day 14-21**	**Day 1**	**Day 1**	**Day 14-21**		**Post-Cycle 1-3 [20]**	**Day 1**	**Day 14-21**	**End of Treatment**	**Follow up[17]**
Visit Window [1]	*-28 days*	*- 3 days*		*+/- 3 days*		*+/- 3 days*	*+/- 3 days*	*+/- 3 days*			*+/- 3 days*			*+/- 1 month*
Informed consent	X													
Medical History	X													
Review of concomitant medications		X		X		X	X			X	X		X	
Review of adverse events		X		X		X	X			X	X		X	
Physical Examination [3]		X		X		X	X			X	X		X	X
Vital Signs [4]		X		X		X	X				X		X	X
ECOG/KPS		X		X		X	X			X	X		X	X
Hematology [5] and Chemistry[6]		X		X		X	X				X		X	X
HIV, Hepatitis B and Hepatitis C [7]	X													
Pregnancy test [8]		X												
EBV PCR [9]		X		X			X				X		X	X
Referral to Radiation Oncology	X													
FDG-PET/CT simulation[10]	X													
MRI nasal cavity *(only for patients with nasal cavity disease)*	X													
ECHO	X													
ECG	X													
Pulmonary function tests [11]	X													

Baseline Biopsy or archive tissue [12]	X													
Research Tumor Biopsy [13]			X					X						
PET/CT	X[18]				X			X	X[20]		Cycle 8[19] Cycle 12[19] Cycle 16[19]	X	X
Tumor assessment [14]					X			X			Cycle 8[19] Cycle 12[19] Cycle 16[19]		
cfDNA[21]		X					X			X[21]		X	X
Pembrolizumab [15]		X		X		X	X			X			

1. Each cycle is 21 days in length.
2. **Screening assessments** must be completed prior to initiation of treatment. HIV, Hep B and C tests must be done within 6 months of start of treatment. Baseline biopsy must be done prior to treatment. All other assessments must be done within 28 days of treatment, except for laboratory tests which must be done within 14 days of treatment. Pregnancy test is required for females of child-bearing potential and must be done within 7 days of initiating treatment.
3. **Physical Examination** must include height and weight. The patient's weight in kilograms must be determined before the start of each cycle.
4. **Vital signs** include: pulse, blood pressure, temperature, respiratory rate, and oxygen saturation.
5. **Hematology** must include CBC with differential. Screening CBC done within 14 days of start of treatment. Must be repeated within 3 days of C1D1.
6. **Chemistry** must include comprehensive metabolic panel (albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, magnesium, phosphorus), amylase, lipase, and thyroid function tests (fT4, and TSH) and LDH. Screening comp done within 14 days of start of treatment. Must be repeated within 3 days of C1D1. Screening amylase, lipase, thyroid function tests (fT4 and TSH) and LDH must be done within 7 days of start of treatment.
7. **HIV, Hep B and Hep C tests** include: HIV I/II antibodies, Hepatitis B surface antigen, core antibody and Hepatitis C antibody. Must be done within 6 months of initiating treatment.
8. **Pregnancy test** includes: serum β-HCG or urine pregnancy test for women of child-bearing potential. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Screening pregnancy tests must be performed within 7 days of starting treatment.
9. **EBV PCR:** screening EBV PCR must be done within 7 days of start of treatment. It is done on Cycle 2 Day 1, Cycle 4 Day 1, then odd cycles only starting in Cycle 5.
10. **Baseline FDG-PET/CT** simulation will be done following an initial consultation in Radiation Oncology and prior to starting therapy. Only required for patients who will be receiving radiation therapy.
11. **Pulmonary Function tests** include: DLCO at minimum
12. **Baseline tumor biopsy:** all study participants will be required to have a biopsy that confirms extranodal NK/T cell lymphoma. If a biopsy is already done, 20 unstained slides from archived tissue will be requested for correlative studies if possible. The biopsy must be done prior to initiation of treatment.
13. **Research biopsies:** on-treatment biopsies are mandatory for all study participants. Biopsies will be done Cycle 1 (between days 8-20), and Cycle 4 (between days 8-20), except in cases where due to the location of disease, biopsy would be associated with unnecessary risk to the patient.
14. **Tumor Assessment:** is the response assessment after PET scans. Refer to Section 12.0 Criteria for Therapeutic Response/Outcome Assessment.

15. **Pembrolizumab**: Pembrolizumab is administered every 3 weeks (21 days) on Day 1 of each cycle, ± 3 days. Pembrolizumab is given 200m via IVPB infusion over 30 minutes (+/- 5 minutes).
16. **Reassessment by PET after 4 Cycles of pembrolizumab**: If Partial Metabolic Response (PMR) by PET, patients may begin 45 Gy of involved site radiation (ISRT) if indicated, and an additional 6 months (8 cycles) of maintenance pembrolizumab. ISRT will begin 2-6 weeks after Cycle 4 of pembrolizumab. Patients with less than PMR will undergo a biopsy. If biopsy shows no evidence of lymphoma, patients will proceed with same treatment as those with PET CR. Patients with less than PMR by PET and persistent evidence of disease on biopsy after 4 cycles of pembro will be taken off study.
17. **Follow-up** includes: standard clinic visit and laboratory tests (CBC, comp only). EBV PCR every 3 months for 3 years. Imaging to be obtained every 6 months for 2 years post treatment. cfDNA to be collected 6 months, 1 year, and 2 years into follow up or until a new therapy is initiated.
18. PET/CT to be completed at baseline only if the patient will not be receiving radiation therapy.
19. Patients will be followed by PET/CT (skull apex to midthigh) If PET/CT is not feasible, patients may be followed with CT CAP plus CT nasal cavity (for patients with nasal cavity disease) after discussion with MSK PI. If followed by PET/CT, additional diagnostic CT is NOT required.
20. PET/CT to be done after last cycle of SMILE only – may be done prior to treatment on C5D1. All other assessments marked should be done for every cycle of SMILE.
21. cfDNA to be collected at C1D1, C4D1, C5D1 of pembrolizumab, end of treatment, and 6 months, 1 year, and 2 years into follow up or until a new therapy is initiated.

10.3 Correlatives

We propose a series of correlative studies to evaluate for pre-treatment and post-treatment predictors of response or resistance to pembrolizumab in ENKTL:

Tissue biopsies

Pre-treatment biopsies will be required prior to initiation of study treatment unless archival tissue is available. On-treatment biopsies will be performed during Cycle 1 (between days 8-20), except in cases where due to the location of disease, biopsy would be associated with unnecessary risk to the patient. In addition, biopsies will be performed after 4 cycles of pembrolizumab for patients who do not achieve complete metabolic response. Tissue will be collected, processed, and stored for planned correlative studies including;

1. **Immunohistochemistry** for MHC-I, MHC-II, B2M, PD-1, PD-L1, PD-L2, FoxP3, CD68, CD4, and CD8 to evaluate for both cell autonomous and non-cell autonomous markers of immune evasion and elucidate mechanisms of action.
2. Molecular profiling by MSK IMPACT assay to evaluate for mutations and altered expression profiles associated with disease response and resistance. In most cases, patients will have this as done as part of their clinical workup.

Blood Collection

Additionally, based upon prior reports regarding the prognostic and predictive value of plasma EBV DNA levels in ENKTL[9], we will evaluate EBV DNA levels by PCR at baseline and during therapy to clarify its significance for patients with ENKTL treated with checkpoint inhibitors. We are collecting blood for analysis of EBV DNA levels by PCR at baseline, C2D1, C4D1, and then odd cycles starting Cycle 5. Following completion of treatment, EBV PCR will be evaluated every 3 months for 3 years.

Cell-free DNA

Cell-free DNA (cfDNA) will be extracted from serum samples obtained at C1D1, C1D4, after completion of SMILE or C5D1 of pembrolizumab, EOT, and 6 months, 1 year and 2 years into follow-up or until a new therapy is initiated. Shallow whole genome sequencing be used to detect copy number alterations in order to confirm tumor vs host origin and quantify tumor-specific cell-free DNA. Targeted resequencing using the MSKCC HemePACT assay will be performed on cell-free DNA to identify genomic alterations present at baseline, on treatment, and in follow-up.

10.4 MSK IMPACT Testing

The consent indicates that samples and genetic information collected may be shared with other qualified researchers and placed in online databases. An example of an online database is the NIH dbGAP database, which is monitored by the National Institutes of Health, and may be made accessible to investigators approved by the U.S. government.

Such information will not include identifying information such as name. It is also stated in the Research Authorization that research data (e.g. genomic sequence) may be shared with regulators. The requirements for submission of genotype/phenotype data into the NIH dbGAP or any other public database will be followed as per the MSK IRB SOP for Genomic Data Sharing.

In the course of this research it is possible that some patients whose tumors are analyzed through investigational “next-generation” profiling in a research (non-CLIA) environment will be found to have somatic or germline mutations in genes that are known to be associated with an increased risk of cancer or other diseases. It will be stated in the consent that the participants will not receive any specific results from research tests. The consent will tell participants that if they wish to have genetic testing done for personal reasons than they should make an appointment with the MSK Clinical Genetics Service or Clinical Genetics Service at their site.

If in the course of this research a research finding is obtained that, in the opinion of the investigator, may be critical to the preventive care of the participant or their family, the investigator can communicate that finding to the MSK IRB Genomic Advisory Panel (GAP). The finding will be reviewed by the GAP to determine whether the incidental finding should be discussed with the participant. For MSK patients, in the event that the GAP determines that the finding should be discussed with the participant, and the participant has consented to be re-contacted, then the treating/consenting physician shall be contacted by the panel and asked to refer the participant to the Clinical Genetics Service for further discussion of the research finding.

The following information must be provided to GAP for review:

- Participant Name/MRN #
- Type of Biospecimen (tissue, blood, saliva)
- Incidental Finding
- Collection Protocol #
- Contact: ocrgapirb@mskcc.org

For non-MSK patients being treated at one of the participating institutions, in the event the GAP determines that the finding should be discussed with the participant, and the participant has consented to be re-contacted, the findings will be returned to the Site Principal Investigator. Site policies on returning these research findings to the patient should be followed.

10.5 Future Unspecified Use of Biospecimens

The protocol includes an informed consent document and research authorization that meets statutory guidelines. Each participating site will have its own consent form meeting the requirements described in this section. The consent form will inform patients of the purpose of the bank, their rights in relation to it, and the safeguards in place to protect the

confidentiality of their health information. The consent will state that some of the biospecimens will be saved to use for future research.

Type of future use

The consent specifically describes the types of future research that may be performed, including use of tissues to develop new drugs with cancer-associated molecular targets, development of cell lines, future use of cell lines to define cancer phenotype and (somatic) genotype, DNA sequence analysis of tumor compared to normal and identification of tumor-associated proteins as diagnostic or prognostic markers. It will be stated that researchers at MSK may either keep indefinitely or dispose of any leftover blood or tissues or other samples, including DNA that the samples contain. Blood and tissues will be stored with identifiers in secure tissue or fluid banks. It is stated that the samples could be lost or ruined because of mechanical failure, and that MSK cannot guarantee that samples will be stored indefinitely. The samples will be stored for as long as deemed useful for research purposes.

Consent for future use and re-contact

Patients are asked in a series of check boxes at the end of the consent if 1) they permit their biospecimen samples to be stored and used in future research to learn about or prevent cancer or side effects of treatment, or to develop new treatments; 2) if they permit their samples to be stored and used in future research to learn about, prevent, or treat diseases other than cancer; or 3) if they permit their samples, with personal identifiers protected, to be used for research about inherited genetic factors, 4) if they permit their samples to be used for genetic analysis of the tumor and normal tissue to learn about the causes of cancer, 5) participants are asked if they agree to be contacted in the future as part of research studies for additional health information or to be asked to participate in future biospecimen research studies and 6) if they consent to be contacted to discuss research findings which may come from their sample. Finally, if not available (e.g. deceased), if they wish to have their designee designated on the consent to be contacted.

Participants will not be provided with specific results of research tests performed on their collected human biologic specimens.

Use of identifiable information for genetic studies

In the course of this research it is possible that some patients whose tumors are analyzed through investigational “next-generation” profiling in a research (non-CLIA) environment will be found to have somatic or germline mutations in genes that are known to be associated with an increased risk of cancer or other diseases. It will be stated in the consent that the participants will not receive any specific results from research tests. The consent will tell participants that if they wish to have genetic testing done for personal reasons than they should make an appointment with the MSK Clinical Genetics Service or Clinical Genetics Service at their site.

If in the course of this research a research finding is obtained that, in the opinion of the investigator, may be critical to the preventive care of the participant or their family, the investigator can communicate that finding to the MSK IRB Genomic Advisory Panel (GAP). The finding will be reviewed by the GAP to determine whether the incidental finding should

be discussed with the participant. For MSK patients, in the event that the GAP determines that the finding should be discussed with the participant, and the participant has consented to be re-contacted, then the treating/consenting physician shall be contacted by the panel and asked to refer the participant to the Clinical Genetics Service for further discussion of the research finding.

The following information must be provided to GAP for review:

- Participant Name/MRN #
- Type of Biospecimen (tissue, blood, saliva)
- Incidental Finding
- Collection Protocol #
- Contact: ocrgapirb@mskcc.org

For non-MSK patients being treated at one of the participating institutions, if the GAP determines the finding to be reportable to the participant and the participant has consented to be re-contacted, results will be returned to the Site Principal Investigator via the study team. Site policies on returning these research findings to the patient should be followed.

We anticipate that other research assays may be incorporated into this protocol as technology evolves.

Voluntariness of research participation

It is stated that taking part in this tissue and blood bank is voluntary and patients have the right to withdraw at any time. Participation in the study will not impact on the clinical care patients receive.

Withdrawal

Participants may decide at a later date that they do not want identified blood and tissue samples to be stored in the tissue bank and /or used for future research. If participants decide to withdraw from the study, specimens that have not yet left the specimen archive will not be used in new studies and any remaining portions of samples that have not been used for research will be used only for clinical purposes or, if requested by the patient, destroyed. For specimens already shipped out from the archive, it may not be possible to locate the samples or stop already ongoing research. When a participant withdraws from the protocol, the MSK study team should be notified immediately. If a non-MSK participant withdraws from the study, the MSK study staff member will notify the MSK database teams. The withdrawal request will be documented in CRDB and the system updated accordingly. In addition, a note-to-file documenting the patient withdrew must be filed in his/her medical records.

Rights after death

The consent states that if the research participant dies or is unable to make his/her wishes known, all of their rights to decide about future uses of the blood or tissues will pass to the authorized representative of the estate. If there is no representative of the estate, the rights pass to the next of kin.

Risks of research participation

The greatest risk is release of information from health or research records in a way that violates privacy rights. MSK and any participating sites will protect records so that name, address, phone number, and any other information that identifies the participant will be kept private. It will be stated to the participant that the chance that this information will be given to an unauthorized individual without the participant's permission is very small.

Costs/compensation

There is no cost to the participant to enroll in this research. Tissue or blood obtained in this research may be used to make a cell line, and these may be patented or licensed and thus may have significant commercial value. The participant is informed that there are no plans to provide financial compensation for use of their human biologic specimens, nor are there plans for the participant to receive money for any new products, tests, and discoveries that might come from this research.

Biospecimen Privacy

Medical information is confidential. The participant's personal identity will not be used in reports that are written about the research. The MSK IRB/PB will review all requests for research performed involving biospecimens ascertained through this protocol. Blood and tissue samples may be stored with a code linked to the patient's medical record. The results of any research using blood or tissues will not be placed in the medical record.

The consent indicates that samples and genetic information collected may be shared with other qualified researchers and placed in online databases. An example of an online database is the NIH dbGAP database, which is monitored by the National Institutes of Health, and may be made accessible to investigators approved by the U.S. government. Such information will not include identifying information such as name. It is also stated in the Research Authorization (HIPAA Authorization) that research data (e.g. genomic sequence) may be shared with regulators. The requirements for submission of genotype/phenotype data into the NIH dbGAP or any other public database will be followed as per the IRB SOP for Genomic Data Sharing.

Use of banked samples (at MSK)

When samples are to be analyzed, the individual investigator needs to write an IRB biospecimen protocol. This protocol is fast-tracked through MSK Research Council review and is reviewed at the MSK IRB by the expedited review process. This protocol is only for research that will be done on biospecimens obtained under identified protocols and their informed consent and research authorization that include the institutional future use questions. The consent and research authorization for the use of the biospecimens will be waived as per 45 CFR 46.116(d) and 45 CFR 164.512(i)(2)(ii).

11.0 TOXICITIES/SIDE EFFECTS

11.1 Adverse Events Definitions

An AE is any untoward medical occurrence in a study subject and does not necessarily have a causal relationship with this treatment.

An AE therefore can be any unfavorable and unintended sign (including laboratory finding), symptom or disease temporally associated with participation in an investigational study, whether or not considered drug-related. In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs after the subject signs a consent form for participation is considered an AE. This includes any side effect, injury, toxicity, or sensitivity reaction.

Whenever possible, the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 should be used to describe the event and for assessing the severity of AEs. Any events representing a change in the CTCAE Grade need to be reported in CRDB. This includes any change in laboratory values.

For AEs not adequately addressed in the CTCAE, the severity table (Table 5.0) below may be used:

Table 5.0 AE Severity Table

Severity	Description
GRADE 1 – Mild	Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
GRADE 2 – Moderate	Mild to moderate limitation in activity—some assistance may be needed; no or minimal medical intervention/therapy required.
GRADE 3 – Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.
GRADE 4 – Life-threatening	Extreme limitation in activity, significant assistance required; life-threatening (immediate risk of death); significant medical intervention/therapy required, hospitalization or hospice care probable.
GRADE 5 – Fatal	Death

Any condition, laboratory abnormality, or physical finding with an onset date prior to the subject signing consent for study participation is considered to be pre-existing in nature and part of the subject's medical history.

11.2 Causality

Using the following criteria, the relationship of the AE to the study drug should be assessed as follows:

- Yes: The event is suspected to be related if:
  - There is a clinically plausible time sequence between onset of the AE and administration of study treatment; and/or
  - There is a biologically plausible mechanism for the study treatment to cause or contribute to the AE; and/or

- The event responds to withdrawal of the study intervention (dechallenge) and/or recurs with rechallenge (when clinically feasible); and/or
- The AE cannot be reasonably attributed to concurrent/underlying illness, other drugs, or procedures

- No:
  - The AE is more likely to be explained by the subject's clinical state, underlying disease, concomitant medication, study or non-study procedure; and/or
  - The time of occurrence of the AE is not reasonably related to administration of study treatment; and/or
  - The event is unlikely to be related to the investigational procedures(s)

11.3 Adverse Events Reporting Procedures

All AEs (e.g., any new event or worsening in severity or frequency of a pre-existing condition or laboratory finding) with an onset date after the subject signs consent for study participation must be promptly documented on the appropriate summary. Details of the event must include severity, relationship to study drug, duration, action taken, and outcome.

All AEs that are considered related to study procedures must be followed to resolution or stabilization if improvement is not expected.

AEs should be reported from the time the subject signs consent through 30 days post-last study intervention. In addition, the Investigator should report any AE that may occur after this time period that is believed to have a reasonable possibility of being associated with study intervention. If a subject discontinues study prior to receiving any study intervention, AEs must be reported through the end-of-study visit. AEs which completely resolve and then recur should be recorded as a new AE. For subjects who complete the end of study visit less than 30 days following the last study intervention, a follow up of ongoing AEs should be attempted by telephone and documented in the subject's source. AEs continuing at 30 days post-last treatment should have a comment in the source by the Investigator that the event has stabilized or is not expected to improve.

The Principal Investigator is responsible for evaluating all AEs, obtaining supporting documents, and determining that documentation of the event is adequate. Adverse events will be assigned a severity grade using the NCI CTCAE grading scale v4.0 and recorded. Furthermore, the occurrence of grade 2 or higher immune-related adverse events will be collected and designated as immune-related events of clinical interest (irAEs).

11.4 Pembrolizumab side effects and supportive care

Refer to package insert for frequency of side effects

11.5 Dose Modification and toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce

complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, 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. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 6.

Table 6 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper. Add prophylactic antibiotics for opportunistic infections.	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

				• 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.
AST / ALT elevation or Increased bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3[b] or 4[c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g., 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 (e.g., levothyroxine or liothyroinine)	• Monitor for signs and symptoms of thyroid disorders.

			per standard of care	
Nephritis grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withold	• 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
	Grade2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withold	• 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 AEs	Intolerable/ persistent Grade 2	Withhold [e]	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis, vasculitis and sclerosing cholangitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

[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: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

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

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

11.6 Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 7.

Table 7 Pembrolizumab Infusion Reaction Dose modification and 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 participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** 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 participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 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 participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 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: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.
For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov

Other Considerations

Contraception

Pembrolizumab and the agents in SMILE may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence[†] from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject’s male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

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 of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours to the Sponsor and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to Merck and followed as described above.

Use in Nursing Women

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

11.7 SMILE side effects and supportive care

Refer to product insert for the individual drugs. Dose modifications allowed according to treating physician.

11.8 Radiation side effects and supportive care

Side-effects vary depending on the specific head/neck site(s) treated and total dose administered but can potentially include:

Very Likely:
Sores in the mouth and/or throat
Temporary decrease in taste and/or smell
Thick saliva
Tanning or redness of the skin in the area being treated with radiation
Ear pain and/or pressure
Fatigue
Weight loss
Transient and rarely permanent hair loss in the area treated with radiation

Likely:
Decrease in function of the thyroid gland (if thyroid is in the ISRT field)
Transient odynophagia

Very Rare But Potentially Serious:
Loss of teeth, or cavities in the teeth, if strict dental care is not followed and/or hypersensitivity of teeth
Serious damage to the spinal cord, nerves in the neck, jawbone, voice box, skin, or other parts of the treated area that may require a major operation to correct and although it is rare, it can be life threatening
Temporary pain or scarring around nerves in the shoulder that could cause numbness and/or weakness
Difficulty with swallowing and eating with the possibility of inhaling food and/or liquids into the lungs – which could also result in pneumonia
Serious ear infections and/or hearing loss
Damage to the spinal cord leading to permanent weakness and/or symptoms like a “stroke”.

12.0 CRITERIA FOR STAGING AND THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Patients with ENKTL will be staged using the Ann Arbor criteria prior to initiation of treatment (outlined in Table 8.[10] Response to treatment will be assessed using the Lugano Classification.[11] Definitions for response are outlined in Table 9 below. In addition to the criteria described below, patients with residual PET-avidity, but with a biopsy showing no evidence of lymphoma, will be considered CR. Furthermore, although the Lugano Classification defines partial metabolic response (PMR) simply as “reduced FDG-uptake compared to baseline”, normal variations in FDG-avidity of lesions can be observed between PET scans. To avoid declaring normal variations in SUV as PMR, we will use the definition

of PMR defined by PERCIST which defines PMR as 30% or more reduction in SUV from baseline.[12]

Responses for patients with evidence of disease progression on PET will be further classified using the LYRIC criteria[1] (outlined in Table 10 below) when appropriate.

Table 8 **Ann Arbor Staging Criteria**

ANATOMIC STAGE/PROGNOSTIC GROUPS	
Stage I	Involvement of a single lymphatic site (i.e., nodal region, Waldeyer's ring, thymus, or spleen) (I); or localized involvement of a single extralymphatic organ or site in the absence of any lymph node involvement (IE) (rare in Hodgkin lymphoma).
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II); or localized involvement of a single extralymphatic organ or site in association with regional lymph node involvement with or without involvement of other lymph node regions on the same side of the diaphragm (IIE). The number of regions involved may be indicated by a subscript, as in, for example, II_3.
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which also maybe accompanied by extralymphatic extension in association with adjacent lymph node involvement (IIIE) or by involvement of the spleen (IIIS) or both (IIIE,S). Splenic involvement is designated by the letter S.
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs, with or without associated lymph node involvement; or isolated extralymphatic organ involvement in the absence of adjacent regional lymph node involvement, but in conjunction with disease in distant site(s). Stage IV includes any involvement of the liver or bone marrow, lungs (other than by direct extension from another site), or cerebrospinal fluid.

Table 9 Revised Criteria for Response Assessment[11]

Table 3. Revised Criteria for Response Assessment

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

(continued on following page)

Table 10 LYRIC Criteria for Indeterminate Response (IR)

As with Lugano with the following exceptions: IR IR(1): ≥50% increase in SPD in first 12 weeks IR(2): <50% increase in SPD with a. New lesion(s), or b. ≥50% increase in PPD of a lesion or set of lesions at any time during treatment IR(3): Increase in FDG uptake without a concomitant increase in lesion size meeting criteria for PD

13.0 CRITERIA FOR REMOVAL FROM STUDY

Patients will be followed on study until progression of disease or 2 years following completion of study treatment.

The following patients will be removed from study:

• Patients whose treating physicians determine that it is in their best interest to be removed from the study.

• Patients who develop unacceptable toxicity.

• Patients who request that they be removed from study. This will not compromise the care they receive at this institution.

• Patients who are non-compliant with treatment or follow-up.

14.0 BIOSTATISTICS

Primary objectives:

The primary objective of this pilot study is to assess the complete response (CR) rate to pembrolizumab in untreated ENKTL following pembrolizumab. Patients who receive any number of cycles of pembrolizumab and undergo response assessment or come off study before response assessment for disease progression will be evaluable for response. CR will be defined as complete metabolic response or negative biopsy in the setting of residual PET avidity. Although there are marked differences in progression free survival for patients with early stage disease (stage I,II) versus advanced stage disease (stage III, IV), complete response rate to treatment (such as SMILE) is similar regardless of stage.[4] Therefore, for the primary objective, early stage and advanced stage patients will be analyzed together. Early stage disease is more common and thus we expect that 66% of patients enrolled onto this study will have early stage disease. If pembrolizumab is efficacious in untreated ENKTL, the treatment approach evaluated in this study will be evaluated in a larger phase II study. Based

upon expression of PD-L1 in ENKTL and experience in the relapsed/refractory setting, we expect that the clinical or pathologic complete response rate to pembrolizumab in untreated disease will be at least 40%. We plan to enroll 19 patients with untreated ENKTL. Assuming a complete response rate of 40%, the 95% confidence interval with a sample size of 19 is 0.18-0.62, i.e. the width of the interval is 0.44. Patients who are removed prior to the first response evaluation will be counted as non-responders.

This study is expected to enroll 19 patients over 2 years.

Secondary objectives:

The secondary objectives of the study are safety of the treatment program, overall response rate (ORR) and partial metabolic response (PMR) rate to pembrolizumab, progression free survival (PFS), and overall survival (OS). Adverse events related to treatment will be tabulated and analyzed using descriptive statistics. ORR and PMR rates will be assessed after 4 cycles of pembrolizumab and calculated along with an exact 95% confidence interval. Progression free survival (PFS) and overall survival (OS) will be calculated using the method of Kaplan-Meier. Time origin for PFS and OS are time of treatment initiation. PFS and OS will be analyzed separately for early and advanced stage patients.

Exploratory objectives:

1. Explore mechanism of action and markers of response and resistance through assessment of baseline and on-treatment biopsies.

    a. Evaluation of association between expression of MHC-I, MHC-II, B2M, PD-1, PD-L1, PD-L2, FoxP3, CD68, CD4, and CD8 by tumor cells and achievement of complete response to therapy will be assessed by Wilcoxon rank sum test. Due to the small sample size, the association between these biomarkers and PFS will be assessed descriptively by dichotomizing the biomarkers by median and generating Kaplan-Meier curves of PFS for each group and comparing them visually.

    b. Molecular profiling of baseline and on-treatment biopsies and association with response will be assessed by Wilcoxon rank sum test. Due to the small sample size, the association between these biomarkers and PFS will be assessed descriptively by dichotomizing the biomarkers by median and generating Kaplan-Meier curves of PFS for each group and comparing them visually.

2. Evaluate plasma EBV PCR as a marker of response to therapy and/or early predictor of relapse. Associated between EBV DNA and response will be assessed using Wilcoxon rank sum test. Due to the small sample size, the association between this biomarker and PFS will be assessed descriptively by dichotomizing the biomarkers by median and generating Kaplan-Meier curves of PFS for each group and comparing them visually.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study.

Study staff is responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed.

See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration): https://one.mskcc.org/sites/pub/clinresearch/Policies/CR%20401.pdf

15.2 Randomization

N/A

16.0 DATA MANAGEMENT ISSUES

This is a multicenter trial that will be coordinated by the Multi-Site Compliance Office at MSK. An MSK Clinical Research Coordinator (CRC) or equivalent at each participating site, will be assigned to the study at each institution. The responsibilities of the MSK CRC include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team.

The data collected for this study will be entered into a secure database system, Medidata Rave. Source documentation will be available to support the computerized patient record. MSK will be the data coordinating center and will be responsible for reporting to the funding source (as applicable) and governing agencies.

16.1 Quality Assurance

Registration reports will be generated to monitor patient accruals and the completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random sample data quality and protocol compliance audits will be conducted by the study team as on ongoing review process.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html.

The DSM Plans at MSKCC were established and are monitored by the MSK Clinical Research Administration Office. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at:
https://one.mskcc.org/sites/pub/clinresearch/Documents/MSKCC Data and Safety Monitoring Plans.pdf

There are several different mechanisms at MSKCC by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center’s Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

The MSK DSMC will monitor safety and data quality across all participating institutions (MSK and external sites). Regular study teleconferences with all participating institutions will be held to discuss SAEs or other toxicities and study progress.

Final data sets for publication are required to be locked and stored centrally for potential future access requests from outside entities.

17.0 PROTECTION OF HUMAN SUBJECTS

All the patients will be required to sign an IRB-approved informed consent and will have all their questions fully addressed before enrolling in the study. During informed consent, it will be made clear to the patient that participation is voluntary. All the data will be confidential, maintained in a password protected electronic database and will comply with all HIPAA guidelines.

Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patient's name or any other personally identifying information will not be used in reports or publications resulting from this study. The Food and Drug Administration or other authorized agencies (e.g., qualified monitors) may review patients' records and pathology slides, as required.

17.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

For IND/IDE protocols:
The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office

17.2.1 Merck Global Safety Reporting (MSK ONLY)

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject must be reported **within 2 working days** to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study whether or not related to the Merck product, must be reported within 2 working days to Merck Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck Global Safety.

All subjects with serious adverse events must be followed up for outcome.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission.

17.2.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported **within 2 working days** to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229).

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any participant must be reported within 2 working days to Merck Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 2 working days to Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 17.2.3 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. 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 and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*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.

17.2.3 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck

For purposes of this study, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

1. Cheson BD, Ansell S, Schwartz L, Gordon LI, Advani R, Jacene HA, Hoos A, Barrington SF, Armand P. Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy. Blood 2016;128:2489-96.
2. Steven H. Swerdlow EC, Nancy Lee Harris, Elaine S. Jaffe, Stefano A. Pileri, Harald Stein, Jurgen Thiele, and James W. Vardiman, eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon, France: International Agency for Research on Cancer (IARC); 2008.
3. Lee J, Suh C, Park YH, Ko YH, Bang SM, Lee JH, Lee DH, Huh J, Oh SY, Kwon HC, Kim HJ, Lee SI, Kim JH, Park J, Oh SJ, Kim K, Jung C, Park K, Kim WS. Extranodal natural killer T-cell lymphoma, nasal-type: a prognostic model from a retrospective multicenter study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2006;24:612-8.
4. Yamaguchi M, Kwong YL, Kim WS, Maeda Y, Hashimoto C, Suh C, Izutsu K, Ishida F, Isobe Y, Sueoka E, Suzumiya J, Kodama T, Kimura H, Hyo R, Nakamura S, Oshimi K, Suzuki R. Phase II study of SMILE chemotherapy for newly diagnosed stage IV, relapsed, or refractory extranodal natural killer (NK)/T-cell lymphoma, nasal type: the NK-Cell Tumor Study Group study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2011;29:4410-6.
5. Lunning MA, Pamer E, Wintman L, Bhatt V, Yahalom J, Moskowitz AJ, Goldberg JD, Straus DJ, Hamlin P, Zelenetz AD, Horwitz SM. Modified SMILE in the Treatment of Natural Killer T-Cell Lymphoma, Nasal and Nasal Type: A Single Center US Experience. ASH Annual Meeting Abstracts 2011;118:2688-.
6. Qi S, Yahalom J, Hsu M, Chelius M, Lunning M, Moskowitz A, Horwitz S. Encouraging experience in the treatment of nasal type extra-nodal NK/T-cell lymphoma in a non-Asian population. Leukemia & lymphoma 2016;57:2575-83.
7. Chen BJ, Chapuy B, Ouyang J, Sun HH, Roemer MG, Xu ML, Yu H, Fletcher CD, Freeman GJ, Shipp MA, Rodig SJ. PD-L1 expression is characteristic of a subset of aggressive B-cell lymphomas and virus-associated malignancies. Clinical cancer research : an official journal of the American Association for Cancer Research 2013;19:3462-73.
8. Kwong YL, Chan TSY, Tan D, Kim SJ, Poon LM, Mow B, Khong PL, Loong F, Au-Yeung R, Iqbal J, Phipps C, Tse E. PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing l-asparaginase. Blood 2017;129:2437-42.
9. Lei KI, Chan LY, Chan WY, Johnson PJ, Lo YM. Diagnostic and prognostic implications of circulating cell-free Epstein-Barr virus DNA in natural killer/T-cell lymphoma. Clinical cancer research : an official journal of the American Association for Cancer Research 2002;8:29-34.
10. Edge SB, B. D. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010.
11. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, Lister TA, Alliance AL, Lymphoma G, Eastern Cooperative Oncology G, European Mantle Cell Lymphoma C, Italian Lymphoma F, European Organisation for R, Treatment of Cancer/Dutch Hemato-Oncology G, Grupo Espanol de Medula O, German High-Grade Lymphoma Study G, German Hodgkin's Study G, Japanese Lymphorra Study G, Lymphoma Study A, Group NCT, Nordic Lymphoma Study G, Southwest Oncology G, United Kingdom National Cancer Research I. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2014;32:3059-68.
12. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 2009;50 Suppl 1:122S-50S.

20.0 APPENDICES

Appendix A: Multicenter Addendum

Appendix B: Biospecimen Collection and Shipping Manual

Appendix C: Multicenter External Site SAE Report Form