*A Phase I/II study to determine feasibility and safety pembrolizumab (MK-3475) alone or in combination with copanlisib in relapsed or refractory NK and T-cell Non-Hodgkin lymphoma*

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## 1.0 TRIAL SUMMARY

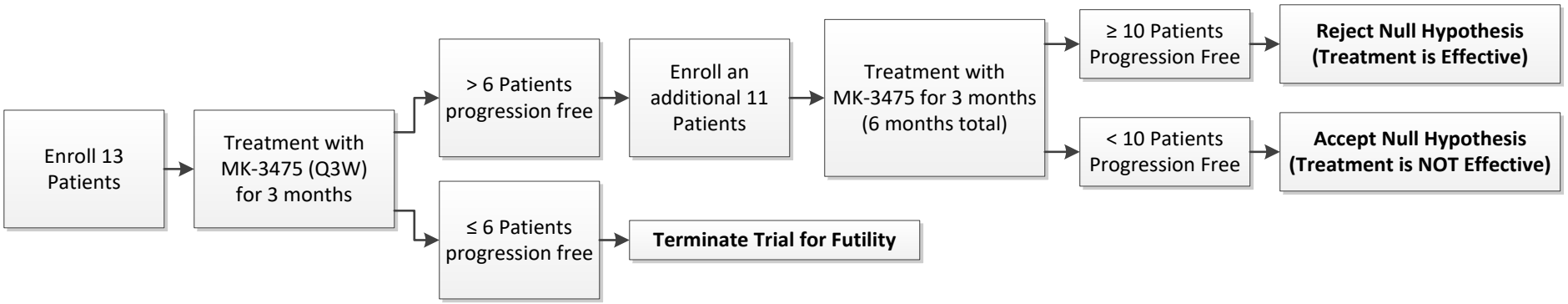
| | |
|---|---|
| Abbreviated Title | Pembrolizumab alone or in combination with copanlisib for Relapsed or Refractory Peripheral T-cell Lymphoma |
| Trial Phase | *Phase 1/2* |
| Clinical Indication | Relapsed or refractory NK or T cell lymphoma |
| Trial Type | Multicenter, open-label single arm |
| Type of control | None |
| Route of administration | Pembrolizumab is given intravenously at a fixed dose of 200mg every 3 weeks<br>Copanlisib is given intravenously at RP2D determined from Phase I study |
| Trial Blinding | None |
| Treatment Groups | Single arm |
| Number of trial subjects | 18 in cohort 1 (pembrolizumab alone; completed); up to 30 in Cohort 2; 4-12 in cohort 2a (phase I); 18 in cohort 2b (phase II). Total up to 48 |
| Estimated duration of trial | *3.5 years* |
| Duration of Participation | 2 years |

## 2.0 TRIAL DESIGN

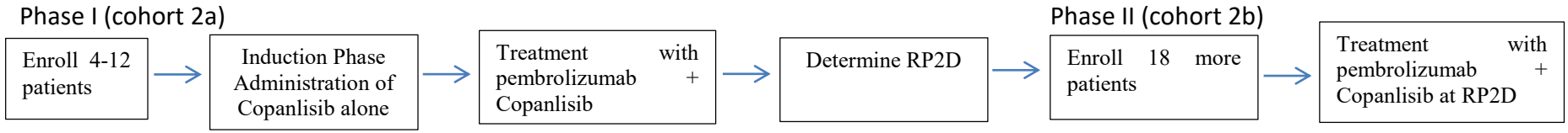
This is a multicenter, single-arm, open label, study consisting of two cohorts. Patients with relapsed or refractory (RR) NK and T-cell Lymphoma (NKTCL), who have received at least 1 prior systemic therapy, were enrolled in cohort 1. The study design for cohort 1 was a single arm phase II 2-stage design, to explore monotherapy with the PD-1 antibody pembrolizumab (or MK-3475) given intravenously at a fixed dose of 200 mg every 3 weeks for up to 36 cycles. Enrollment to this cohort has been completed. Cohort 2 explores the combination of copanlisib and pembrolizumab in patients with relapsed or refractory NKTCL, who have received at least 1 prior systemic therapy. Cohort 2 will include a phase 1 portion (cohort 2a) to determine the recommended phase 2 dose (RP2D) utilizing a standard 3+3 design, followed by a phase II portion where patients will be treated at the RP2D (cohort 2b). The primary endpoint for cohort 1 was progression-free survival; the primary endpoint for cohort 2a will be to determine RP2D for the combination therapy; and overall response rate at the end of 4 treatment cycles for cohort 2b. Patients will be assessed for response with PET CT or CT every 12 weeks using the revised Cheson criteria. Correlative endpoints will be exploratory and assess PD-1 expression on peripheral blood lymphocytes; peripheral blood T-cell and NK-cell functional assays; PD-1 and PD-L1 expression on tumor tissue; tumor infiltrating lymphocytes and gene expression panels using the nanostring technology as prognostic and predictive biomarkers, as well as monitoring of minimal residual disease via high-throughput sequencing of cell free tumor DNA.

### 2.1 Trial Schema

Cohort 1 (enrollment completed)




Cohort 2a and 2b



## 3.0 OBJECTIVES

### 3.1 Cohort 1

#### 3.1.1 Primary Objective Cohort 1

To estimate the progression-free survival (PFS) defined as time elapsed from date of registration to disease progression or death in patients with relapsed or refractory NKTCL treated with single agent pembrolizumab.

#### 3.1.2 Secondary Objectives Cohort 1

1. To assess the safety and tolerability of single agent pembrolizumab
2. To estimate the overall response rate (ORR: complete response plus partial responses) as defined by the revised Response Criteria for Lymphoma (Cheson criteria)[1]
3. To estimate the ORR as defined by the Lugano criteria[2]
4. To estimate overall survival (OS) and PFS at 6 months and 1 year
5. To estimate duration of response

#### 3.1.3 Exploratory Objective Cohort 1

1. To assess expression of PD-1, PD-L1 and extent of tumor infiltrating lymphocytes (TILs) in the primary tumor at the time of relapse
2. To compare PD-1 expression and leukocyte activation markers on circulating lymphocytes pre-treatment, at weeks 3 and 6, and at time of disease progression
3. To compare functional responses (degranulation and IFN gamma production) by NK and T cells pre-treatment, at weeks 3 and 6, and at end of treatment
4. To explore the association of the degree of tissue PD-1 and PD-L1 expression with the rate of CR
5. To explore the association of the degree of tissue PD-1 and PD-L1 expression with 1-year PFS and OS
6. To explore the association of changes in circulating PD-1 positive lymphocytes with disease status
7. To assess cell free tumor DNA analysis as minimal residual disease marker in NKTCL
8. To assess gene expression profiles using the nanostring platform as prognostic or predictive biomarker

### 3.2 Cohort 2

#### 3.2.1 Primary Objective Cohort 2

3.2.1.1 Cohort 2a (Phase I portion)**: To determine the recommended phase II dose (RP2D) of the combination of pembrolizumab and Copanlisib in patients with RR NK/T-cell lymphoma**

#### 3.2.1.2 Cohort 2b (Phase II portion): To determine the overall response rate [ORR: complete and partial response] by 4 cycles of the combination of pembrolizumab and copanlisib in patients with RR NK/T-cell lymphoma

### 3.2.2 Secondary Objectives Cohort 2

1. To assess the safety and tolerability of the combination of pembrolizumab and copanlisib
2. To estimate overall survival (OS) and PFS at 6 months and 1 year
3. To estimate duration of response
4. To identify potential pretreatment biomarkers of response to clinical outcome
5. To identify copanlisib-induced changes in immune cell biomarkers

## 4.0 BACKGROUND & RATIONALE

### 4.1 Background

### 4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades.[3] Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies.[4-8] In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4, which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2).[9,10] The structure of murine PD-1 has been resolved.[11] PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70, which are involved in the CD3 T-cell signaling cascade.[9,12-14] The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4, as both molecules regulate an overlapping set of signaling proteins.[15,16] PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells.[17,18] Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells.[19] The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors.[15,20-22] Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells

found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues.[15] Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL).[23] This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab (previously known as SCH 900475) 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.

The phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway is one of the prominent pathways that promote cellular survival and constitutively is activated in many types of cancers (11, 12). Class I PI3K is downstream of most cancer-associated tyrosine kinase growth factor receptors (such as epidermal growth factor receptor [EGFR]/ human epidermal growth factor receptor [HER], insulin-like growth factor 1 receptor [IGF-1R], platelet-derived growth factor receptor [PDGFR], vascular endothelial growth factor [VEGF], c-KIT or mesenchymal epithelial transition factor [Met]).

Four of these PI3K isoforms (PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ) are categorized as class I enzymes because they can use phosphatidylinositol-4,5-bisphosphate (PI-4,5-P2) as a substrate to generate phosphatidylinositol-3,4,5-trisphosphate (PIP3). Elevated PIP3 in cellular membranes drives several hallmarks of the cancer phenotype: cell proliferation, survival, metabolic reprogramming, and migration. PI3Kα and β are ubiquitous; PI3Kγ and δ are expressed mostly in hematopoietic tissues.

As expected from its pharmacological properties, copanlisib, a small molecule pan-class 1 PI3K inhibitor with predominant activity against PI3Kα and PI3Kδ isoforms, demonstrated anti-tumor activity in pre-clinical models characterized by activating genetic aberrations of the PI3K pathway.

Copanlisib exhibits potent kinase inhibitory effect on all four isoforms with biochemical IC50 values of 0.5 nM, 0.7 nM, 3.7 nM and 6.4 nM for PI3Kα, PI3Kδ, PI3Kβ and PI3Kγ, respectively. Copanlisib also potently regulates nuclear localization of the forkhead family members resulting in the induction of transcriptional programs that lead to rapid cell death by apoptosis.

For additional background information, please refer to the Investigator's Brochure.

### 4.1.2 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for Preclinical and Clinical data for each agent.

## 4.2 Rationale

### 4.2.1 Rationale for the Trial and Selected Subject Population

The peripheral T-cell lymphomas (PTCL) are a diverse group of mature T-cell and natural killer (NK) cell neoplasms accounting for 10-15% of non-Hodgkin lymphoma (NHL) diagnoses in the United States.[24-26]

The number of diagnoses has increased nearly 3-fold over the past 2 decades.[27] In the WHO classification, the diverse mature T-cell and NK-cell neoplasms are listed individually. The PTCL histologies include PTCL-NOS, angioimmunoblastic T-cell Lymphoma (AITL), anaplastic large cell lymphoma (ALC) ALK positive and negative (the 3 most common histologies in the US), as well as the less common extranodal NK/T-cell lymphoma, nasal type, enteropathy-associated T-cell lymphoma (EATL), hepatosplenic T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma and adult T-cell leukemia/lymphoma (ATLL).[28,29] Therapy for the PTCLs is largely based on aggressive B-cell lymphoma regimens. Outcomes though are generally worse when compared to B-cell NHL with 5-year survival rates of 35-43% and for the rarer PTCLs 22%-24%.[30] A recent analysis showed that the median time from initial diagnosis to relapse or progression after primary therapy is only 6.7 months.[31]

In the absence of hematopoietic stem cell transplantation (HSCT) treatment is usually palliative in the relapsed/refractory setting with a median overall survival (OS) and progression-free survival (PFS) after relapse or progression of only 5.5 and 3.1 months, respectively.[31] Even with high-dose therapy followed by autologous stem cell transplantation for chemosensitive disease, survival is poor (PFS <12 months; OS <18 months).[32] There is currently no accepted standard of care for the treatment of r/r PTCL. Multiple combination and single agent regimens have been studied with limited success. The two most recently FDA approved agents for this indication are pralatrexate and romidepsin based on an overall response rate (ORR) of 29% and 25%, respectively.[33,34] Overall survival appears only marginally better in patients who receive chemotherapy at relapse (6.5 vs. 3.7 months, respectively)[31] identifying an unmet need.

PD-L1 expression has been demonstrated for a variety of B- and T-cell lymphomas, specifically for the PTCL subtypes ALC, ATLL and extranodal NK-T-cell NHL.[35-37] PD-L1 is also highly expressed in malignant lymphocytes of patients with cutaneous T-cell lymphomas.[38] Additionally, expression of PD-1 peripheral blood CD4+ and CD8+ lymphocytes is markedly elevated in patients with lymphomas, including T-cell NHL, especially at the time of relapse.[39] These findings, in addition to the observation that reconstitution of an immune anti-lymphoma effect following allogeneic stem cell transplantation ("graft-versus-lymphoma" effect) can result in durable remissions for patients with PTCL,[40,41] indicate the essential role of an effective immune response for lymphoma control.

Whilst multiple trials exploring PD-1 blockade in hematological malignancies are ongoing, published data supports its safety and efficacy. A phase 1 trial by Berger et al demonstrated that PD-1 blockade is safe in patients with hematological malignancies, even after allogeneic stem cell transplantation.[42] Since then two other larger phase 2 studies with the PD-1 antibody pidilizumab for patients with diffuse large B-cell lymphoma following ASCT and follicular lymphoma have shown that PD-1 blockade is not only safe, but also has promising efficacy in lymphomas.[43,44] The same appears to be the case for PD-L1 and CTLA-4 blockade.[45,46] While "active" immunotherapy by immune checkpoint blockade might not be applicable to all subtypes of PTCL, an additional anti-lymphoma effect of PD-1 antibodies by "passive" immune mechanisms could be postulated for T-cell NHL with high PD-1 expression (e.g. AITL).[47-49] For this subgroup of patients with high PD-1 expression, binding of the PD-1 monoclonal antibody (mAb) could lead to direct cytotoxicity, although with an IgG4 mAbs such as pembrolizumab less antibody-dependent (ADCC) or complement mediated cytotoxicity is expected than with IgG1 mAbs.[50]

In conclusion, strong preliminary evidence warrants the exploration of the PD-1 antibody pembrolizumab in patients with r/r PTCL.

### 4.2.2 Rationale for Dose Selection/Regimen/Modification (cohort 1)

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

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

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

### 4.2.3 Rationale for pembrolizumab and copanlisib combination treatment (cohort 2)

Enrollment to cohort 1, where patients with RR NKTCL were enrolled and treated with single agent pembrolizumab, has been completed. Out of 18 enrolled patients, all patients were evaluable for toxicity and 15 were evaluable for response. Four patients achieved a complete response, and 1 patient achieved partial response resulting in a 27% complete response (CR) rate (95% CI 5%-49%) and overall response rate (ORR) of 33% (95% CI 9-55%). Remissions were durable with 2 patients remaining on study (1 patient >12 months, 1 patient >10 months) as of February 2018. Only 3 came off study for toxicity (17%, 95% CI 0%-34%; pneumonitis n=1; vasculitis, n=1; hyperbilirubinemia, n=1). However, although the response rate with single agent pembrolizumab is comparable to other approved agents in this setting, as only 5 pts had not progressed by 3 months, the futility endpoint was not met and enrollment to cohort 1 was halted early for futility as per original statistical design.

Copanlisib similarly demonstrated single agent activity in T-cell NHL with an overall response rate of 21%.[52]

While both agents alone have moderate activity, there is preclinical evidence that supports synergy between PD1-inhibitors and PI3K inhibitors. Inhibition of PI3Kβ, PI3Kγ, and PI3Kδ enhances antitumor immunity and susceptibility to immune checkpoint inhibitors and can potentially overcome resistance to either drug alone.[53-57] furthermore, inhibition of the PI3K pathway may abrogate a possible disease flare with PD-1/PDL-1 blockade in NKTCL.[58]

We hypothesize that the combination of the PD1-inhibitor pembrolizumab with the copanlisib will be safe and result in synergistic efficacy in the treatment of mature NK/T-cell NHL. **Therefore, Cohort 2 has been added to the original study to explore the combination treatment**

#### 4.2.3.1 Study design for cohort 2

As the recommended phase II dose of Copanlisib in combination with pembrolizumab (MK-3475) has not been established, there will be a phase 1 part (cohort 2a), during which the recommended phase 2 dose (RPTD) of the combination of pembrolizumab and copanlisib will be determined. This will be followed by a phase 2 portion (cohort 2b), which will explore safety and efficacy of the combination. The phase 1 part follows a classical '3+3' dose escalation/de-escalation design with up to 3 dose levels (-1, 0, and 1). Based on preclinical data, the copanlisib dose and dosing frequency will change with dose levels (dose level -1: 45 mg on day 1 q21d; dose level 0: 45 mg days 1 & 8 q21d; dose level 1: 60 mg days 1 & 8 q21d), while the pembrolizumab dose will remain a flat dose of 200 mg on day 1 of every 21 day cycle for each dose level. In the initial cohort up to 3 patients will be treated on dose level 0. Should less than 1 patient experience a dose-limiting toxicity (DLT) during cycle 1, then the next 3 patients will be treated at dose level 1. However, should 1 out of 3 of the initial patients treated on dose level 0 experiences a DLT, 3 more patients will be enrolled on the same dose level. Should no further patient experience a DLT, we will proceed to dose level 1, where 3 patients will be treated. If 0 out of 3 experience a DLT, 3 more patients will be added. However, should at any time 2 patients on dose level 0 experience a DLT, the dose will be de-escalated to dose level -1, where up to 6 patients will be treated. If 2 or more patients on dose level -1 experience a DLT, the trial will be terminated. The highest dose level, at which ≤1/6 patients experience a DLT will be defined as the RP2D.

**Dose levels for Phase 1 portion of Cohort 2**

| Dose Level | Pembrolizumab | Copanlisib |
|---|---|---|
| -1 | 200 mg D1 | 45 mg D1 |
| 0 | 200 mg D1 | 45 mg D1 and D8 |
| +1 | 200 mg D1 | 60 mg D1 and D8 |

**D-day; cycle length: 21 days**

**Maximum Tolerated Dose:** The maximum tolerated dose (MTD) is defined as the highest dose tested in which none or only one patient experienced DLT attributable to the study drug(s), when 6 patients have been treated at that dose and are evaluable for toxicity.

**Recommended Phase II dose (RP2D):** MTD will be considered as the RP2D, unless there are other safety concerns.

#### 4.2.3.2 DLT definition

DLT window for the phase I portion of this study is 21 days or 1 cycle.

DLT will be defined as any of the below AE occurring during cycle 1 that are considered by the investigator as at least possibly related to study treatment with copanlisib and pembrolizumab:

- CTCAE grade 4 neutropenia lasting > 7 days despite growth factor support
- CTCAE grade 4 febrile neutropenia
- CTCAE grade 3 thrombocytopenia with bleeding that requires transfusion therapy

- Treatment delays by treatment-related toxicity causing > 14 days in the start of a subsequent cycle of treatment
- Non-hematologic toxicities of CTCAE ≥ grade 3 except for the following:
    - Alopecia of any grade
    - CTCAE grade 3 fatigue for < 72 hours,
    - Isolated, asymptomatic grade 3 changes in biochemistry laboratory values that last for ≤ 7 days. This includes electrolyte abnormalities that respond to medical intervention. Exceptions are Bilirubin elevation ≥ CTCAE grade 3; and Bilirubin ≥ grade 2 with ALT ≥ CTCAE grade 3 – those count as DLT.
    - ≥ CTCAE grade 3 vomiting or nausea that can be controlled (i.e. <grade 3) within 72h with optimal anti-emetic treatment
    - ≥ CTCAE grade 3 diarrhea that can be controlled within 72h (i.e. <grade 3) with the use of optimal anti-diarrheal treatment
    - ≥ CTCAE grade 3 hypothyroidism/hyperthyroidism
    - ≥ CTCAE grade 3 hyperglycemia that resolves within 7 days
    - CTCAE grade 3 arthralgias/myalgias that resolve within 7 days with the use of anti-inflammatory drugs
    - CTCAE grade 3 infusion reactions that resolve within 6 hours with appropriate management in the absence of steroid and antihistamine prophylactic premedication

AEs occurring in the "induction phase" of copanlisib only treatment (i.e. days -1 to day -21 of the induction phase) will not be considered a DLT in terms of determining the RPTD. Treatment-related AE ≥ CTCAE grade 3 or grade 2 treatment-related AE that lead to dose interruption of >6 weeks and that occur after cycle 1 may be considered a DLT after discussion with the sponsor/study chair. Patients who come off during the induction phase for any reason will be replaced.

#### 4.2.3.3 Phase II portion of Cohort 2

We will enroll up to 18 patients treated at the RPTD in the phase II portion in order to define safety and feasibility of the combination of pembrolizumab and copanlisib (total of 24 patients treated at the RPTD in the phase I and II portions combined). Furthermore, there will be a "induction phase" treatment with 2 weekly doses of copanlisib (days -21 and -14) starting 3 weeks prior to day 1 of cycle 1 in order to assess potential copanlisib induced changes in peripheral blood immune cell biomarkers. Patients who come off during the induction phase for any reason will be replaced and not included in the futility analysis.

### 4.2.4 Rationale for Endpoints

#### 4.2.4.1 Efficacy Endpoints

The objective of this trial is to explore the safety and efficacy of pembrolizumab in patients with NKTCL (Cohort 1). We will assess efficacy by evaluating progression-free survival (PFS), overall survival (OS) and response rate. For cohort 2 the objective is to determine RP2D in phase I portion of the study and then to determine objective response rate using the combination therapy in phase II portion. Classical

response criteria such as defined by the RECIST,[59] the revised Cheson criteria[1] or the Lugano criteria[2] may not capture responses seen with immunotherapeutic agents. Therefore, we had chosen PFS as primary endpoint rather than response rate in Cohort 1. However, from our experience in cohort 1, all patients who remained progression free at 3 months had at least stable disease, and durable responses were only seen in patients with at least a partial response on their first response assessment. Therefore, response and not PFS was chosen as primary outcome and efficacy of the combination therapy in cohort 2 will be determined by response as measured by objective response rate defined as complete or partial responses.

Measurement of effect is described in Section 14.3 of the Appendix. While we will use the revised Cheson criteria to assess disease response, we will allow at the first imaging time point (12 weeks after initiating treatment) patients to demonstrate up to 2 new lesions, with sum of all lesions <70% greater than baseline by sum of products of the diameters (SPD), or decreasing in size, if they are clinically stable without evidence of rapid clinical deterioration. In that case patients may continue to be treated with pembrolizumab and clinically observed with imaging repeated after 1 month. If, at that time, there is Progression of Disease (POD) by standard Revised Cheson Response Criteria, patients will be removed from study. For a more detailed description see Appendix – Section 14.3.5 Response Endpoints.

#### 4.2.4.2 Biomarker Research

##### 4.2.4.2.1 PD-1, PD-L1 and tumor infiltrating lymphocytes (TIL)

We will assess expression of PD-1, PD-L1 and tumor infiltrating lymphocytes (TIL) in pre-treatment tumor specimens in order to assess their ability to predict response to pembrolizumab therapy and serve as a potential prognostic or predictive biomarker. Multiple studies have implicating expression of PD-1, PD-L1, in the tumor or tumor microenvironment as well as presence of TIL be associated with outcomes.[60-63]

##### 4.2.4.2.2 Immune cell biomarkers

Additionally, we will assess PD-1 expression and leukocyte activation markers on circulating lymphocytes as well as NK- and T-cell function pre-treatment, during treatment as well as at time of relapse in order to assess potential associations with treatment response and outcome. In addition, we will also assess PD-L1 and PD-L2 on the surface of peripheral tumor cells when detectable. Preliminary studies of immune cell biomarkers, including PD-1, on peripheral blood mononuclear cells in renal cell carcinoma by our group have indicated that PD-1 expression on fresh peripheral blood leukocytes may provide a useful marker for disease progression. Furthermore, the results suggest that measuring PD-1 levels in peripheral blood may assist in identifying patients likely to respond to PD-1 blocking antibodies.[64]

##### 4.2.4.2.3 Non-invasive disease monitoring

High-throughput sequencing (HTS) is an emerging technology enabling quantitative measurement of cell-free DNA in peripheral blood.[65,66] It is highly sensitive and has been shown to assist with non-invasive monitoring of disease status in diffuse large B cell lymphoma[66,67] and follicular lymphoma.[68] Not only is this technology non-invasive, but it provides an opportunity for earlier detection of relapse than traditional imaging techniques.[67] HTS of the T-cell receptor (TCR) has been utilized for disease monitoring in other hematologic malignancies including cutaneous T cell lymphoma,[69] acute lymphoblastic

leukemia,[70] and chronic lymphocytic leukemia.[65] HTS can be used to identify clonal evolution[68] as well as early disease relapse, which has been shown to predict survival[70] and may inform therapeutic intervention.[65,71] This technology has not yet been studied in peripheral T-cell lymphoma, signifying an unmet need for investigation.

We will utilize HTS commercialized by ImmunoSEQ™ to measure pre-treatment levels of circulating cell free DNA as well as at pre-determined intervals during treatment. We will investigate the relationship between pre-treatment level with PFS and OS. In addition, we will examine the association of circulating cell free DNA levels during treatment with disease response to therapy.

Genomic DNA from PBMC will be collected and stored for possible future research.

#### 4.2.4.2.4 Exploration of predictive biomarkers using gene expression profiling via Nanostring technology

In order to explore biomarkers predictive of response to pembrolizumab we will perform gene expression profiling via Nanostring technology using the nCounter® PanCancer Immune Profiling Panel as well as the nCounter® PanCancer Pathway Panel on tumor tissue. This will allow us to better characterize a) the immune milieu of the tumor microenvironment and b) deregulated pathways in PTCL.

We hypothesize that patterns of differential gene expression as described by the above panels will provide gene signatures predictive of response to pembrolizumab.

Additionally, we will design a nanostring gene expression panel composed of up to 30 genes of interest in PTCL based on the available literature and preliminary work performed by researchers at the Fox Chase Cancer Center. Examples include DLX5, a gene encoding a transcription factor, which is up regulated in up to 40% of T cell lymphoid malignancies and associated with aggressive behavior.[72,73] Others include Rpl22, a ribosomal protein gene, and Lin28b, a gene encoding a "stemness" factor and others to be potentially involved in T-cell lymphomagenesis and prognosis.[74-77]

We hypothesize that above analysis can potentially identify additional pathways whose roles in pathogenesis or disease progression have previously not been recognized or well described.

#### 4.2.4.2.5 Identification of copanlisib induced changes in peripheral blood immune cell biomarkers

We will assess the copanlisib induced changes in the immune cell biomarkers. For this the patients will be treated with copanlisib alone at day -21 and -14 during the induction phase prior to cycle 1 day 1. The blood sample will be collected before drug administration (day -21) and day -7 during the induction phase and then for research on cycle 1 day 1 prior to drug administration. The copanlisib induced changes in immune biomarkers will also be correlated to the clinical outcome to identify biomarkers of response to clinical outcome.

## 5.0 METHODOLOGY

### 5.1 Entry Criteria

#### 5.1.1 Subject Inclusion Criteria

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

1. Have a histologically or cytologically confirmed relapsed/refractory mature T-cell lymphoma that has progressed after a minimum of 1 systemic therapy with any of the following T-cell histologies: Peripheral T-cell NHL, not otherwise specified (PTCL, NOS); Anaplastic large cell T-cell lymphoma (ALCL) anaplastic lymphoma kinase positive or negative; angioimmunoblastic T-cell lymphoma; subcutaneous panniculitis like T-cell lymphoma; primary cutaneous gamma-delta T cell lymphoma; enteropathy associated T-cell lymphoma; follicular T-cell lymphoma; nodal peripheral T-cell lymphoma with TFH phenotype; monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL); hepatosplenic T-cell lymphoma; extranodal NK/T-cell lymphoma, nasal type; unclassifiable PTCL; and transformed cutaneous T-cell lymphoma (CTCL) to PTCL with systemic involvement (not local skin transformation).
2. Be willing and able to sign written informed consent for the trial.
3. Be $\geq$ 18 years of age on day of signing informed consent.
4. Have measurable disease based as defined by at least one lesion that can be measured in least 2 perpendicular dimensions and measures at least 1.5 cm in its long axis.
5. Have provided tissue from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion obtained within 28 days prior to study enrollment.
6. Have a performance status of 0 or 1 on the ECOG Performance Scale.
7. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 10 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

| System | Laboratory Value |
|---|---|
| **Hematological** | |
| Absolute neutrophil count (ANC) | ≥1,500 /mcL, **OR**<br>≥1,000 /mcL if lymphomatous bone marrow involvement |
| Platelets | ≥70,000 / mcL, **OR**<br>≥50,000 / mcL if lymphomatous bone marrow involvement<br>Patients with documented marrow involvement may be transfused to this value. |
| Hemoglobin | ≥9 g/dL or ≥5.6 mmol/L<br>Patients with documented marrow involvement may be transfused to this value. |
| **Renal** | |
| Serum creatinine **OR**<br>Measured or calculated[a] creatinine clearance<br>(GFR can also be used in place of creatinine or CrCl) | ≤1.5 X upper limit of normal (ULN) **OR**<br><br>≥40 mL/min for subject with creatinine levels > 1.5 X institutional ULN |
| **Hepatic** | |
| Serum total bilirubin | ≤ 1.5 X ULN **OR** |
| | Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN |
| AST (SGOT) and ALT (SGPT) | ≤ 2.5 X ULN **OR**<br>≤ 5 X ULN for subjects with liver involvement by lymphoma |
| **Other** | |
| Lipase | ≤ 1.5 X ULN |
| **Coagulation** | |
| International Normalized Ratio (INR) or Prothrombin Time (PT)<br><br>Activated Partial Thromboplastin Time (aPTT) | ≤1.5 X ULN unless subject is receiving anticoagulant therapy<br>as long as PT or PTT is within therapeutic range of intended use of anticoagulants<br>≤1.5 X ULN unless subject is receiving anticoagulant therapy<br>as long as PT or PTT is within therapeutic range of intended use of anticoagulants |
| [a]Creatinine clearance should be calculated per institutional standard. | |

8. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.5.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
9. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

### 5.1.2 Subject Exclusion Criteria

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

1. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 2 weeks of the first dose of treatment.
2. Patients diagnosed with Adult T-cell Leukemia/Lymphoma (ATLL) or T-cell PLL
3. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
4. Has had a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
5. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

- Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
- Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

6. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
7. Has known active intraparenchymal lymphomatous central nervous system (CNS) lesions and/or lymphomatous meningitis. Subjects with previously treated CNS involvement by lymphoma may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain lesions, and are not using steroids for at least 7 days prior to trial treatment.
8. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjoegren's syndrome will not be excluded from the study.
9. Has evidence of interstitial lung disease or has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis
10. Has an active infection requiring systemic therapy.
11. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
12. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
13. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
14. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
15. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
16. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
17. Has received a live vaccine within 30 days prior to the first dose of trial treatment.
18. Cohort 2a: Has received an allogeneic stem cell transplant.
    For cohort 2b, patients within the first 100 days of having undergone an allogeneic stem cell transplant will be excluded. Otherwise, patients who have received an allogeneic stem cell

transplant are allowed as long as they have no evidence of active GVHD or are not taking immunosuppressive therapy

19. Uncontrolled arterial hypertension despite optimal medical management
20. Uncontrolled Type I or II diabetes mellitus as deemed appropriate by the investigator. Suggested guidelines for uncontrolled diabetes: HbA1c > 8.5%
21. Anti-arrhythmic therapy (beta blockers or digoxin are permitted)
22. Use of CYP3A4 inhibitors and inducers. Copanlisib is primarily metabolized by CYP3A4. Therefore, concomitant use of strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, clarithromycin, ritonavir, indinavir, nelfinavir and saquinavir), and strong inducers of CYP3A (e.g. rifampin, phenytoin, carbamazepine, phenobarbital, St. John's Wort) are not permitted from Day -14 of Cycle 1 until the Safety follow up visit. See Table in Appendix 5 for complete list
23. Concurrent diagnosis of pheochromocytoma
24. Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within 3 months before the start of study medication
25. Prior exposure to PI3K inhibitors, unless on PI3K inhibitor therapy more than 6 months ago AND reason for discontinuation of prior PI3K inhibitor therapy was other than progression or toxicity.
26. Patients with detectable CMV viremia are excluded

### 5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 2A and 2B

Table 2A Trial Treatment (Cohort 1)

| Drug | Dose/Potency | Dose Frequency | Route of Administration | Regimen/Treatment Period | Use |
|---|---|---|---|---|---|
| Pembrolizumab | 200 mg (fixed dose) | Every 3 weeks (Q3W) | IV infusion | 36 cycles (2 years) | Experimental |
| The pembrolizumab dosing interval may be increased due to toxicity as described in Section 5.2.1.2, but there are no dose reductions allowed for pembrolizumab. | | | | | |

Table 2B Trial Treatment (Cohort 2)

| Drug | Dose/Potency | Dose Frequency | Route of Administration | Regimen/Treatment Period | Use |
|---|---|---|---|---|---|
| Pembrolizumab | 200 mg (fixed dose) | Every 3 weeks (Q3W) | IV infusion | 2 years | Experimental |
| Copanlisib | RP2D | Day 1 +/- day 8 of every 3 weeks | IV infusion | 2 years | Experimental |
| The pembrolizumab and copanlisib dosing interval may be increased due to toxicity as described in Section 5.2.1.2, but there are no dose reductions allowed for pembrolizumab. Dose reductions are allowed for copanlisib depending upon RP2D | | | | | |

Trial treatment should begin within 7 days of the date on which treatment is assigned. Cohort 2 will have a 21 day long induction phase prior to the beginning of treatment (numbered day -1 to -21, followed immediately by Cycle 1 Day 1) cycles during which subjects will receive 2 doses of copanlisib alone, first one on day -21 and second dose on day -14 of the induction phase.

During treatment cycles, on the days both pembrolizumab and copanlisib are administered, copanlisib must be administered first, followed by pembrolizumab.

### 5.2.1 Dose Selection/Modification

The attribution of causality of any AE to the test drugs specifically may be difficult. However, in Phase I and II trials, certain toxicities were seen only in relation to copanlisib, e.g., transient increases in glucose and blood pressure. If a particular AE is attributed to pembrolizumab or copanlisib then the specific drug can be interrupted according to the dose modification criteria while the other may continue. Both drugs may need to be interrupted if attribution is not clear. If toxicity is not resolved such that the drug/s cannot be administered 21 days beyond their scheduled administration the patient will be off treatment. If the toxicity that results in treatment discontinuation is clearly due to one of the drugs, then the patient can be treated on monotherapy after discussion with the sponsor-investigator. Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

#### 5.2.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale.

The dose amount required to prepare the pembrolizumab and copanlisib infusion solution will be a fixed dose (i.e. not dependent upon patient’s weight).

#### 5.2.1.2 Pembrolizumab (MK-3475) and copanlisib Dose Modification (Escalation/Titration/Other) for immune-related events

Adverse events (both non-serious and serious) associated with pembrolizumab and/or copanlisib exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening immune-related AEs as per Table 3 below. For guidelines on the management of adverse events with potential immunological etiology see Section 5.4 Supportive Care and Management of Immune-related Adverse Events, including use of corticosteroids.

Table 3: Dose Modification Guidelines for Immune Related Adverse Events

| Toxicity | Grade | Timing for Restarting Treatment | Treatment Discontinuation |
|---|---|---|---|
| Diarrhea/Colitis | 2-3 | Hold until toxicity resolves to Grade 0-1. Restart MK3475 and copanlisib once until Grade ≤1 and decrease copanlisib by one dose level[3]. | Discontinue both drugs if toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks. |
| | 4 | Permanently discontinue | Permanently discontinue |
| AST, ALT, or Increased Bilirubin | 2 | Hold until toxicity resolves to Grade 0-1. Restart MK3475 and copanlisib once Grade ≤1 and decrease copanlisib by one dose level[3]. | Discontinue both if toxicity does not resolve within 12 weeks of last dose. |
| | 3-4 | Permanently discontinue (see exception below)[1] | Permanently discontinue |
| Type 1 diabetes mellitus (if new onset) or hyperglycemia | T1DM new or 3-4 associated with evidence of β-cell failure | Hold treatment and resume pembrolizumab and copanlisib when patients are clinically and metabolically stable. | |
| Hypophysitis | 2 | Hold until toxicity resolves to Grade 0-1. | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks. |
| | 3-4 | Hold until toxicity resolves to Grade 0-1 or permanently discontinue at the discretion of the treating Physician | Permanently discontinue at the discretion of treating Physician |
| Hyperthyroidism | 3-4 | Hold or Permanently discontinue at the discretion of treating Physician | Permanently discontinue at the discretion of treating Physician |
| Hypothyroidism | 2-4 | Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted | Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted. |
| Infusion Reaction | 3-4 | Permanently discontinue | Permanently discontinue |
| Pneumonitis | 2 | Hold until toxicity resolves to Grade 0-1. Restart MK3475 and copanlisib once Grade ≤1 and decrease copanlisib by one dose level[3] | Discontinue both if toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks. |
| | 3-4 or recurrent Grade 2 | Permanently discontinue | Permanently discontinue |
| Renal Failure or Nephritis | 2 | Hold until toxicity resolves to Grade 0-1 | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks. |
| | 3-4 | Permanently discontinue | Permanently discontinue |
| Myocarditis | 1-2 | Hold until toxicity resolves to Grade 0. Restart MK3475 and copanlisib once Grade <1 and decrease copanlisib by one dose level[3]. | Discontinue both if toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks. |
| | 3-4 | Permanently discontinue study treatment | |

| Toxicity | Grade | Timing for Restarting Treatment | Treatment Discontinuation |
|---|---|---|---|
| Dermatological | | | |
| Grade 1 | Any appearance | No change | No change |
| Grade 2[b] | 1st appearance | Interruption until Grade ≤1 | No change |
| | 2nd appearance | Interruption until Grade ≤1. Restart MK3475 and copanlisib once Grade ≤1 and decrease copanlisib by one dose level[3] | |
| | 3rd appearance | Interruption until Grade ≤1. Restart MK3475 and copanlisib once Grade ≤1 and decrease copanlisib by one dose level[3] | |
| | 4th appearance | Permanently discontinue | Permanently discontinue copanlisib and MK3475 |
| Grade 3[b] | 1st appearance | Interruption until Grade ≤ 1. Restart MK3475 and copanlisib once Grade ≤1 and decrease copanlisib by one dose level[3] | |
| | 2nd appearance | Interruption until Grade ≤1. Restart MK3475 and copanlisib once Grade ≤1 and decrease copanlisib by one dose level[3] | |
| | 3rd appearance | Permanently discontinue | Permanently discontinue copanlisib and MK3475 |
| Grade 4 | 1st appearance | Permanently discontinue | Permanently discontinue copanlisib and MK3475 |
| All Other immune-Related Toxicity[2] | Intolerable /persistent Grade 2 | Hold until toxicity resolves to Grade 0-1 | |
| | 3 | Hold until toxicity resolves to Grade 0-1. Restart MK3475 and copanlisib once Grade ≤1 and decrease copanlisib by one dose level[3]. | Discontinue both if toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks. |
| | 4 or recurrent Grade 3 | Permanently discontinue | Permanently discontinue |

**Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.**

[1] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[2] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

[3] Not applicable to dose level -1 of copanlisib. In that case, patient has the option of continuing on pembrolizumab alone.

#### 5.2.1.3 Copanlisib Dose Modifications

Treatment interruptions for copanlisib must be done according to the guidelines in hematological toxicity and non-hematological toxicity sections (5.2.1.3.1 and 5.2.1.3.2) except for immune related adverse events, in which case, instruction from section 5.2.1.2 and Table 3 should be followed. The investigator may judge a more conservative dose modification if appropriate. If dose reduction below 30mg is required, the patient has the option of continuing on pembrolizumab alone. Furthermore, if copanlisib is discontinued due to non-immune-related toxicities or toxicities clearly related to copanlisib

alone, the patient has the option of continuing on pembrolizumab alone. Patients can continue with pembrolizumab while copanlisib is being held.

| Dose Level | Copanlisib |
|---|---|
| -1 | 30 mg |
| 0 | 45 mg |
| +1 | 60 mg |

#### 5.2.1.3.1 Hematological Toxicities

Neutropenia and febrile neutropenia are listed in the current version of IB as expected adverse events. The guidelines described below should be followed.

Dose modification of copanlisib for hematological toxicity

| Hematological toxicity (any of the following) | Study treatment action (for any toxicity) |
|---|---|
| • CTCAE Grade ≥ 3 thrombocytopenia (platelet < 50,000/mm$^3$)<br>• Febrile neutropenia [a]<br>• CTCAE Grade ≥ 3 neutropenia (ANC < 1000/mm$^3$)<br>• INR or PTT CTCAE Grade ≥3 with bleeding [b]<br>• CTCAE Grade ≥ 3 anemia (Hb < 8 g/dL) | Delay infusion until criteria displayed in Table: 'Laboratory test criteria for Day 1 dose of subsequent cycles are met'.[d] (section 5.2.2.2) Patient can be treated at one dose level lower at the investigator's discretion.[c] If more dose reductions are required than allowed per protocol, discontinue copanlisib permanently. The lowest dose level is 30 mg. |

ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria of Adverse Events, version 5; Hb = hemoglobin; INR = international normalized ratio; PTT = partial thromboplastin time

a: These patients should recover from neutropenia (Table 1), without fever

b: International normalized ratio (INR) and partial thromboplastin time (PTT) should have returned to ≤ 1.5 and ≤ 1.5 x ULN, respectively, with no signs of bleeding

c: After having fully recovered from toxicity and in the absence of any criteria for further dose reduction or study drug discontinuation, re-escalation to dose level -1 or 1 is allowed at the investigator's discretion

d: Treatment with transfusion or growth factors is allowed at the investigator's discretion

#### 5.2.1.3.2 Non-hematological toxicities (non-immune related)

Dose modifications for non-hematologic toxicities attributable to copanlisib except glucose increases, blood pressure increases, and immune related events (see table 3) are outlined in Table below.
Dose modification of copanlisib for non-hematological toxicity (except immune-related events)

| | | | |
|---|---|---|---|
| **Toxicity[a]** | **Occurrence** | **For current course of therapy** | **For next course of therapy** |
| Grade 1-2 | Any appearance | No change | No change |
| Grade 3[b] | 1$^{st}$ appearance | Delay until Grade ≤ 2 | No change |
| | 2$^{nd}$ appearance | Delay until Grade ≤ 2 | Decrease by one dose level[c] |
| | 3$^{rd}$ appearance | Delay until Grade ≤ 2 | Decrease by one dose level[c] |

| | | | |
|---|---|---|---|
| | 4th appearance | Permanently discontinue | |
| Grade 4 | Any appearance | Permanently discontinue | |

a. Toxicities according to CTCAE 5
b. Despite maximum supportive care
c. Not applicable to dose level -1

#### 5.2.1.3.3 Arterial Hypertension

No dose should be given if blood pressure is ≥ 150/90 mmHg. Antihypertensive medication may be given to control the increased blood pressure. Dosing can proceed on the scheduled day if there are at least 2 consecutive measurements <150/90 mmHg apart. Otherwise dosing must be delayed.

If drug-related arterial hypertension (post-dose blood pressure of CTCAE Grade 3 or ≥ 160/100 mmHg) is not manageable with optimal antihypertensive treatment, the dose for the subsequent copanlisib administrations may be reduced by 1 or 2 dose levels at the investigator's discretion. Patients with a post-dose blood pressure that may have life-threatening consequences (e.g. malignant arterial hypertension, transient or permanent neurologic deficit, hypertensive crisis) must permanently discontinue copanlisib.

Table: Dose modification for copanlisib for arterial hypertension

| **Toxicity[a]** | **Study drug action** | **Recommendation** |
|---|---|---|
| Pre-dose Measurements BP≥150/90mmHg | No dose should be given until recovery to < 150/90 mmHg. | Consider BP lowering medication. Dosing can proceed on the scheduled day if after at least 2 consecutive measurements BP returns to < 150/90 mmHg. If BP doesn't return to < 150/90 mmHg, delay dosing until next visit. |
| During infusion: CTCAE hypertension of grade 3 or ⩾ 160/100 mmHg | Infusion can be interrupted or slowed down and administration of BP lowering therapy should be initiated. | Infusion may be resumed when BP has returned to < 150/90 mmHg at the investigator's discretion or skipped.<br>Subsequent study drug administrations may be reduced by 1 dose level at the investigator's discretion.[b] |

| | | |
|---|---|---|
| Post-dose: Drug-related CTCAE hypertension of grade 3 or ⩾ 160/100 mmHg [a] | | Administration of BP lowering therapy should be initiated according to local standard of care.<br>Additional measurements to be performed as clinically indicated until recovery to < 150/90 mmHg.<br>Subsequent study drug administrations may be reduced by 1 dose level at the investigator's discretion.[b] |
| CTCAE hypertension of grade 4 | Permanently discontinue | |

CTCAE = Common Terminology Criteria for Adverse Events V 5.0; BP = Blood pressure

[a]: Not manageable despite optimal antihypertensive treatment.

[b]: The lowest dose level is 30mg.

#### 5.2.1.3.4 Hyperglycemia

| | | | |
|---|---|---|---|
| Pre-dose fasting blood glucose 160 mg/dl or more or random/non-fasting blood glucose of 200 mg/dl or more | Withhold copanlisib until fasting glucose is 160 mg/dl or less, or random/non-fasting blood glucose of 200 mg/dl or less | | |
| Pre-dose or post-dose blood glucose 500 mg/dl or more | On first occurrence withhold copanlisib until fasting glucose is 160 mg/dl or less, or random/non-fasting blood glucose of 200 mg/dl or less. Then dose reduce by one level | On subsequent occurrences, withhold copanlisib until fasting glucose is 160 mg/dl or less, or random/non-fasting blood glucose of 200 mg/dl or less. Then dose reduce by one level | On next occurrence discontinue copanlisib |

Patients who develop infusion related hyperglycemia > 250 mg/dL (13.9 mmol/L) after study drug administration may continue treatment. However, the next infusion must be delayed until the patient's pre-infusion glucose levels return to < 160 mg/dL (8.9 mmol/L) (fasting) or < 200 mg/dL (11.1 mmol/L) (non-fasting).

Persistent infusion related hyperglycemia > 200 mg/dL (11.1 mmol/L) based on repeated laboratory analysis despite glucose lowering therapy after 2 infusions of study drug will require dose reduction by one dose level. Further dose reduction **(where appropriate per study design/population)** is allowed as long as discontinuation criteria was not met.

#### 5.2.1.3.5 Management of hyperlipidemia

As lipids are monitored for the duration of this study it is recommended to treat significant deviations from normal range with standard interventions and therapy in standard doses according to local medical

practice. Goals of therapy are to keep fasting triglycerides < 300 mg/dL (3.4 mmol/L) and low-density lipoproteins (LDL) < 190 mg/dL (4.9 mmol/L) (lower LDL depending on cardiovascular risk) in patients with a life expectancy >1 year. The goals for fasting triglycerides can be raised to < 500 mg/dL (5.6 mmol/L) for patients with life expectancy <1 year. Although there is a paucity of data on the effects of hyperlipidemia and cancer outcomes, these goals have been chosen to decrease risk of established complications of hypertriglyceridemia (pancreatitis) and hypercholesterolemia (cardiovascular events). For evaluation of lipid panels including triglycerides the patient would be required to be fasted for 11 hours prior to sampling. For patients who cannot adhere to these fasting requirements the evaluation of lipid panels including triglycerides and determination of treatment is considered as not feasible.

### 5.2.2 Dose Administration

#### 5.2.2.1 Pembrolizumab

Pembrolizumab should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab will be administered as a 30 minute IV infusion (treatment cycle intervals may be increased due to toxicity as described in Section 5.2.1.2). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The following infusion set materials are compatible with pembrolizumab (MK-3475):

- PVC Infusion set that is plasticized using DEHP
- PVC and tri-(2-ethylhexyl) trimellitate (TOTM) infusion set
- Polyethylene lined PVC infusion set
- PVC Infusion set that is plasticized using Di-2-ethylhexyl Terephthalate (DEHT)
- Polyurethane set.

A sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-line filter made of polyethersulfone (PES) must be used during administration to remove any adventitious particles. If the infusion set does not contain 0.2 to 5 µm in-line filter, it is recommended to use 0.2 to 5 µm add-on filter which may contain an extension line.

Attach the infusion line to the pump and prime the line, either with normal saline (at least 25 mL) or with infusion solution as per local SOP, before starting the infusion.

Infuse pembrolizumab (MK-3475) over approximately 30 minutes, with a window of -5 and +10 minutes, through a peripheral line or indwelling catheter.

Ensure the entire contents of the bag are dosed and all remaining drug solution in the line is administered according to institutional guidelines for saline flushing.

Document volume administered according to data entry guidelines.

Vital signs will be monitored every 15 minutes during the infusion and for 60 minutes after completion of each infusion.

Whenever possible, the lowest infusion rate should be used that will allow completion of the infusion within the 30 minutes. Maximum rate of infusion should not exceed 6.7 mL/min. through a peripheral line or indwelling catheter. However, when it is necessary to infuse a larger volume (i.e. 250 mL), the flow rate may go as high as 10 mL/min (maximum) in order to keep the infusion within the window as defined above.

#### 5.2.2.2 **Copanlisib**

Before commencing copanlisib, all patients should have CMV status assessed. CMV seronegative patients should receive CMV-negative or filtered blood products. For seropositive patients, CMV quantitative polymerase chain reaction (PCR) testing with every cycle is recommended. Interrupt Copanlisib in patients with evidence of active CMV infection of any grade or viremia until the viremia has resolved. Ganciclovir or valganciclovir should be preemptively initiated in patients with positive CMV PCR and symptoms consistent with CMV infection, patients presenting with fever and no clear source in whom quantitative CMV testing is unavailable, and asymptomatic patients with increasing viral load.

Copanlisib should be administered on Day 1 +/- Day 8 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Day 1 drug administration has a window of +/- 3 days. Copanlisib is supplied as lyophilized preparation in a 6-mL injection vial. The total amount of copanlisib per vial is 60 mg. The solution for IV infusion is obtained after reconstitution of the lyophilisate with 0.9% sodium chloride solution.

Study drug is administered in a normal saline solution, intravenously, over 1 hr. No intravenous glucose preparations should be administered on the days of infusion.

**Induction phase:**

Fasting is required (8 hours minimum) only during the induction phase visits before the first glucose measurement on date of infusion. A low glycemic index meal may be taken 2 hours post-infusion unless the patient needs to have a low glycemic meal and unable to fast for this period of time, then glucose test should be taken prior to meal intake.

It is imperative that the induction phase visits fall on Mon-Thurs during the week so that there is enough time to ship the blood collected for correlative studies to Fox Chase Cancer Center to be processed within the required window (blood may not be processed during the weekend). Also, blood collection must be scheduled so that it reaches Fox Chase Cancer Center on a working day, and not on a holiday.

**All subsequent infusions after Induction phase:**

The decision regarding meal timing can be made by the investigator based on glucose response patterns during prior treatment days.

NOTE: If patient needs to have a low glycemic meal prior to the infusion, then glucose test should be taken prior to the meal and/or at 1-2 hours after the meal.

After the induction phase, a low glycemic index meal may be taken at least 4 h before the start of the study drug infusion for patients who have their infusions scheduled at a later treatment time or due to their age or medical condition when fasting prior to infusion is not viable.

**Fasting requirements and pre-dose glucose levels**

| Period | Fasting ≥ 8 h required before first glucose measurement | Pre-dose glucose levels | Fasting required before study drug infusion |
|---|---|---|---|
| **Day 1 of cycle 1** | Yes | <160 mg/dL (8.9 mmol/L) | Yes[b] |
| **Day 1 of subsequent cycles** | No | <160 mg/dL (fasting) (8.9 mmol/L)<br>< 200 mg/dL (11.1 mmol/L) (non-fasting or random) [c] | Conditional [a, b, d] |
| **Days 8 of each cycle** | No | <160 mg/dL (8.9 mmol/L) (fasting)<br><200 mg/dL(11.1 mmol/L) (non-fasting or random) | Conditional [a, b, d] |

[a]: The decision regarding meal timing and fasting can be made by the investigator based on glucose response patterns during prior treatment days.

[b]: Diabetic patients who take insulin treatment at any cycle visit:

Timing and content of caloric intake on infusion days will be managed by the investigator. Consultation with treating physician or diabetes/endocrinologist is advised.

[c]: In case of non-compliance with the fasting requirement.

[d]. A small, light low glycemic index meal may be taken at least 4 hours before the start of the copanlisib infusion for patients who have their infusions scheduled at a later hour, or due to their age or medical condition when fasting prior to infusion is not viable.

Laboratory test criteria for Day 1 dose of subsequent cycles

| Lab Test | Criteria for Day1 dose (cycle 2 and higher) |
|---|---|
| Glucose | < 160 mg/dL (8.9mmol/L) (fasting) or < 200 mg/dL (11.1 mmol/L) (non-fasting) |
| Hemoglobin | ≥ 8 g/dL [a] |
| ANC | ≥ 1,500/$mm^3$ |
| Platelets | ≥ 75,000/$mm^3$ |
| ALT | <2.5 x ULN [b] |
| AST | <2.5 x ULN [c] |
| Total bilirubin | within normal limits [d] |
| GFR (MDRD) | ≥ 40 mL/min/1.73 $m^2$ |

ANC = Absolute neutrophil count; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; GFR = Glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; ULN = Upper limit of normal.

a: If hemoglobin is < 8 g/dL but ≥ 6 g/dL on the day of planned study drug administration it is permissible to give the study drug dose as scheduled and transfuse within 48 hours after the dose, if the patient is hemodynamically stable and in opinion of investigator benefits outweigh risks. Rationale and treatment should be recorded in source document and eCRF.

b: < 5 x ULN in patients with documented liver involvement by lymphoma or with biliary obstruction due to lymphoma.

c: < 5 x ULN in patients with documented liver involvement by lymphoma or with biliary obstruction due to lymphoma.

d: <3 x ULN in patients with Gilbert syndrome, patients with cholestasis due to compressive adenopathies of the hepatic hilum or documented liver involvement by lymphoma.

A blood count will be performed and assessed prior to study drug infusion on Day 8 of each cycle. On day 8 the dose of copanlisib will be administered if, on the day of scheduled dosing, the laboratory test criteria for **hemoglobin, ANC and platelets** are met.

**Blood pressure measurement on treatment days**

Blood pressure will be measured every 5 – 10 minutes prior to each copanlisib dose (no more than 4 measurements) until there are two consecutive results < 150/90 mmHg. If blood pressure is ≥ 150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. The patient should rest for 5-10 minutes before blood pressure is recorded.

On infusion days, blood pressure will be measured at 0 h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion), and 1 h and 2 hours after the end of infusion

Note: a window of ±10 min is allowed for all BP measurements, except for the 0 h (pre-dose) measurement

### 5.2.3 Participant Registration

Participants may be registered from 8:00 am to 4:00 pm EST excluding holidays by emailing the Investigator-Sponsored Research Unit (ISRU) at: **FCCC.MONITOR@fccc.edu.** Eligible participants will be entered on study centrally once the following items have been received by email:

- Completed registration form
- Consent and HIPAA signature pages
- Eligibility checklist

Following registration, participants must begin protocol treatment within 7 days of registration. Issues that would cause treatment delays must be discussed with the Sponsor-Investigator. If a registered participant does not receive protocol therapy following registration, the participant will be recorded as withdrawn from study. The Study Monitor must be notified as soon as possible if a participant does not begin protocol treatment as scheduled. For additional registration questions, please email **FCCC.MONITOR@fccc.edu**

The FCCC ISRU will notify the site by email once registration is confirmed and the sequence number has been assigned. Participants must be registered and have received a sequence number prior to the initiation of treatment.

**Exceptions to the current registration policies will not be permitted.**

## 5.3 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required.

The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the Investigator, the Sponsor, and the subject. Ganciclovir or valganciclovir should be preemptively initiated in patients with positive CMV PCR and symptoms consistent with CMV infection, patients presenting with fever and no clear source in whom quantitative CMV testing is unavailable, and asymptomatic patients with increasing viral load.

**Bactrim Prophylaxis:** Bactrim DS 1 tablet three times weekly, or 1 SS tablet daily, or equivalent (if sulfa allergic) for PJP prophylaxis will be administered to the patients.

### 5.3.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.
All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment must be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment must be recorded for SAEs and ECIs as defined in Sections 8.2 and 8.3. Growth factors and blood product transfusions are allowed at the investigator's discretion in order to maintain adequate blood counts in patients with documented bone marrow involvement.

### 5.3.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab or copanlisib
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology or acute medical reasons (e.g. asthma exacerbation), but not solely as an anti-tumor therapy. The use of physiologic doses of corticosteroids may be

approved after consultation with the Sponsor. Patients may be using topical or inhaled corticosteroids. The use of corticosteroids as antiemetics prior to copanlisib administration will not be allowed

- Strong inhibitors or inducers of CYP3A4/5 (see appendix 5)
- Substrates of CYP3A4/5 with narrow therapeutic index
- Medications that carry a strong risk for QT prolongation
- Herbal medications/preparations (except for vitamins)

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.
The Exclusion Criteria describes other medications which are prohibited in this trial.
There are no prohibited therapies during the Post-Treatment Follow-up Phase.

**5.4 Supportive Care and Management of Immune-related Adverse Events**

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

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 5.2.1.2 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

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

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

- All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

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

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

- **Hypophysitis**:

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

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

  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.

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

- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper
  - For **Grade 3-4** events, treat with intravenous corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids (prednisone 1-2 mg/kg or equivalent).
  - For **Grade 3-4** events, treat with systemic corticosteroids (prednisone 1-2 mg/kg or equivalent).
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- Myocarditis
  - Based on the severity of AE administer corticosteroids
  - Ensure adequate evaluation to confirm etiology and/or exclude other causes
- All other Immune-related AEs
  - Based on type of and severity of AE administer corticosteroids
  - Ensure adequate evaluation to confirm etiology and/or exclude other causes

**Management of Pembrolizumab Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 4 Infusion Reaction Treatment Guidelines

| NCI CTCAE Grade | Treatment | Premedication at subsequent dosing |
|---|---|---|
| Grade 1<br>Mild reaction; infusion interruption not indicated; intervention not indicated | Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. | None |
| Grade 2<br>Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); | **Stop Infusion and monitor symptoms.**<br>Additional appropriate medical therapy may include but is not limited to:<br>IV fluids<br>Antihistamines<br>NSAIDS | Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with:<br><br>Diphenhydramine 50 mg po (or equivalent dose of antihistamine). |

| NCI CTCAE Grade | Treatment | Premedication at subsequent dosing |
|---|---|---|
| prophylactic medications indicated for < =24 hrs | Acetaminophen<br>Narcotics<br>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.<br>If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.<br>**Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.** | Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic). |
| Grades 3 or 4<br>Grade 3:<br>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)<br>Grade 4:<br>Life-threatening; pressor or ventilatory support indicated | **Stop Infusion.**<br>Additional appropriate medical therapy may include but is not limited to:<br>IV fluids<br>Antihistamines<br>NSAIDS<br>Acetaminophen<br>Narcotics<br>Oxygen<br>Pressors<br>Corticosteroids<br>Epinephrine<br><br>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.<br>Hospitalization may be indicated.<br>**Subject is permanently discontinued from further trial treatment administration.** | No subsequent dosing |
| Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. | | |

- **Treatment of blood pressure increases associated with copanlisib**

It is important that patients with pre-existing arterial hypertension adhere to their regular medication schedule and take their usual doses on the days of study drug infusion.

The management of acute blood pressure increases following copanlisib will need to be individualized for each patient, but prior experience suggested the benefit of dihydropyridine calcium channel blockers (i.e. amlodipine, felodipine). Nitrates should also be considered. Verapamil and diltiazem (non-dihydropyridine calcium channel blockers and moderate inhibitors of CYP 3A4) should be used with caution due to a potential CYP 3A4 interaction. In general, it is advisable for sites to be prepared, so that antihypertensive medication is readily available in case of need.

In the event of the occurrence of arterial hypertension ≥ 150/90 mmHg during infusion of copanlisib at any cycle, antihypertensive treatment is suggested as indicated in section 5.2.1.3.5. In the event of the occurrence of CTCAE Grade 3 arterial hypertension (≥ 160/100 mmHg) during infusion of copanlisib, the infusion should be interrupted and antihypertensive treatment as suggested in section 5.2.1.3.5 should be administered. Infusion can be resumed when blood pressure has returned to <150/90 mmHg.

- **Management of infusion-related hyperglycemia**

Mild to moderate asymptomatic increases of blood glucose may occur with copanlisib infusion, and with larger increases potentially occurring post-prandially. Please refer to table below for dose modifications and management of hyperglycemia.

| | | |
|---|---|---|
| **Asymptomatic glucose increases ≤ 250mg/dL (13.9 mmol/L)** | Does not generally require treatment with glucose lowering medication. | Oral Hydration |
| **Asymptomatic glucose increase > 250 mg/dl (13.9 mmol/L)** | • Repeat glucose testing.<br>• If glucose value is decreasing, glucose level may be followed without glucose lowering medication treatment if hydration status is normal as clinically assessed<br>• Consultation with endocrinologist is recommended | • Oral and or IV Hydration as appropriate |
| **Symptomatic or persisting glucose increase > 250mg/dL (13.9 mmol/L)** | • Hydration status should be clinically assessed.<br>• If clinical assessment is consistent with dehydration, fluids should be given as clinically appropriate (orally or IV).<br>• Laboratory test confirming increase should be repeated. If the repeated glucose value is persistent and/or patient is symptomatic and/or the hydration status indicates the need for hydration, glucose lowering medication should be administered.<br>• Prompt input from an endocrinologist should be obtained. | • Keep well hydrated rapid/ short acting insulin may be given if glucose persisting at > 250 mg/dL (13.9 mmol/L), and the patient is symptomatic<br>• Rapid/short acting insulin according to the institution sliding scale coverage of glucose persisting at > 250 mg/dL (13.9 mmol/L) is recommended, with oral or IV hydration as clinically appropriate |
| **Asymptomatic Glucose increase > 500mg/dL** | • Will require dose reduction for subsequent treatment infusions.<br>• Repeat glucose testing.<br>• If glucose value is decreasing, glucose levels may be followed without glucose lowering medication treatment if hydration status is normal as clinically assessed<br>Consultation with endocrinologist is recommended | • Keep well hydrated rapid/ short acting insulin may be given if glucose persisting at > 250 mg/dL (13.9 mmol/L), and the patient is symptomatic<br>• For insulin naïve patients, monitor for signs of hypoglycemia 3 hours post insulin administration due to risk for hypoglycemic events. |

- **Management of persistent infusion-related hyperglycemia on subsequent days:**

| Criteria | Recommendation | Suggested Treatment |
|---|---|---|
| **Persistent glucose > 200 mg/dL (11.1 mmol/L)(non-fasting) or >160 mg/dL (8.9 mmol/L)** | • Oral Glucose Lowering Medication, and **consultation with endocrinologist recommended** | • The use of sulphonylurea/metaglinides, insulin secretagogues medications to manage increased glucose levels post drug infusions is not recommended |

| | | |
|---|---|---|
| **(fasting) post infusion** | | • Treatment with glucose lowering medication suggested according the local standards of practice |

## 5.5 Diet/Activity/Other Considerations

### 5.5.1 Diet

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

#### *5.5.1.1* Recommendations on meal timing on infusion days (copanlisib)

Because of its inhibitory effect on the PI3K α-isoform, which is implicated in insulin metabolism, copanlisib infusions could be associated with a temporary increase in blood glucose. Addition of a meal in close proximity to copanlisib infusion may exacerbate glucose increase. It is recommended that timing and content of caloric intake on infusion days is monitored by the investigators. Consultation with a diabetologist or endocrinologist is advised**.**

The investigator will review the glucose profile during and post the copanlisib infusions.

Timing and content of caloric intake on infusion days will be managed by the investigator. Consultation with treating physician or diabetes/endocrinology physician is advised.

The investigator may manage the timing of post infusion meals based on the glucose profile during prior infusion(s) to minimize glucose increases. This is in addition to glucose lowering medication.

Low glycemic index meals (see Appendix 4) should be provided for patients who are kept in clinic for continued observation.

A low glycemic index diet is recommended for the first 48 hours after study drug infusion. However, caloric restriction is not intended for the population under study.

All glucose measurements, oral glucose lowering medication and/or insulin administration, if applicable, and meal timing will be collected as part of the clinical source documentation.

**NOTE:** Caloric intake and timing recommendations for diabetic patients who require insulin treatment prior to the infusion at any cycle visit should be managed by the investigator based on consultation with treating physician or diabetes/endocrinologist physician.

### 5.5.2 Contraception

Pembrolizumab and copanlisib may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab and copanlisib have transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier

method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

### 5.5.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab and/or copanlisib, 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, Merck and Bayer without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor, Merck, Bayer and followed.

### 5.5.4 Use in Nursing Women

It is unknown whether pembrolizumab and copanlisib 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.

## 5.6 Participant Withdrawal/Discontinuation Criteria

Participants may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a participant may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4 – Other Procedures.

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Disease progression (for definition see Appendix 12.3 Measurement of Effects)
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment

- Investigator's decision to withdraw the subject
- The participant has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 36 cycles of treatment with pembrolizumab (Cohort 1)
  *Note: Subjects who stop pembrolizumab after 36 cycles may be eligible for up to 18 cycles of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 5.8.*
- Administrative reasons
- Completed 36 cycles with the combination of MK3475 and copanlisib

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (events of clinical interest will be collected for 90 days after the end of treatment as described in Section 5.4). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, end of study or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

### 5.7 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study drug

In the event of Merck or Bayer decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

### 5.8 Retreatment

Patients will be eligible for retreatment with pembrolizumab and/or copanlisib after completion of the trial treatment **IF** they achieved a complete response during the treatment phase **AND** remained in a complete remission until completion of the trial phase (36 cycles) **AND** experience a documented relapse within one year after completion of the trial phase. Retreatment will have to be discussed with the sponsor and will at most be for another 18 cycles. Prior to retreatment the patient will have to fulfill all the initial eligibility criteria as outlined in Section 5.1 Entry Criteria.

## 6.0 TRIAL FLOW CHART

| **Trial Period:** | **Screening Phase** | | **Induction Phase (Day -21 to -1)** | | | **Treatment Cycles [A]** | | | | | | | | | | **End of Treatment** | **Post-Treatment** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Cycle/Title: | Pre-screening | Main Study Screening | | | | 1 | | 2 | | 3 | | 4 | | To be repeated after Cycle 8 5-8 | | At time of Discon | Safety Follow-up | Follow Up Visits [B] | Survival Follow-Up |
| Scheduling Window (Days): | | -50 to -22 | Day -21 | Day -14 | Day -7 | D1 ± 3 | D8[o] ± 3 | D1 ± 3 | D8 ± 3 | D1 ± 3 | D8 ± 3 | D1 ± 3 | D8 ± 3 | D1 ± 3 | D8 ± 3 | | 30 days post discon | Every 12 weeks post discon | |
| **Administrative Procedures** | | | | | | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion Criteria | | X | | | | | | | | | | | | | | | | | |
| Demographics and Medical History | | X | | | | | | | | | | | | | | | | | |
| Prior and Concomitant Medication Review | | X | | | | X | | X | | X | | X | | X | | X | | | |
| Pembrolizumab Administration[Q] | | | | | | X | | X | | X | | X | | X | | | | | |
| Copanlisib Administration[M, Q] | | | X[N] | X | | X | X | X | X | X | X | X | X | X | X | | | | |
| Post-study anticancer therapy status | | | | | | | | | | | | | | | | | | X | X |
| Survival Status | | | | | | | | | | | | | | | | | | | X |
| **Clinical Procedures/Assessments** | | | | | | | | | | | | | | | | | | | |
| Review Adverse Events | | X | | | | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Full Physical Examination | | X | | | | X | | X | | X | | X | | X | | X | X | X | |
| Vital Signs [I] and Weight | | X | | | | X | X | X | X | X | X | X | X | X | | X | X | X | |

| **Trial Period:** | **Screening Phase** | | **Induction Phase (Day -21 to -1)** | | | **Treatment Cycles [A]** | | | | | | | | | | **End of Treatment** | **Post-Treatment** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Cycle/Title: | Pre-screening | Main Study Screening | | | | 1 | | 2 | | 3 | | 4 | | To be repeated after Cycle 8<br>5-8 | | At time of Discon | Safety Follow-up | Follow Up Visits [B] | Survival Follow-Up |
| Scheduling Window (Days): | | -50 to -22 | Day -21 | Day -14 | Day -7 | D1 ± 3 | D8[o] ± 3 | D1 ± 3 | D8 ± 3 | D1 ± 3 | D8 ± 3 | D1 ± 3 | D8 ± 3 | D1 ± 3 | D8 ± 3 | | 30 days post discon | Every 12 weeks post discon | |
| Height | | X | | | | | | | | | | | | | | | | | |
| ECOG Performance Status | | X | | | | X | | X | | X | | X | | X | | X | X | X | |
| **Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory** | | | | | | | | | | | | | | | | | | | |
| Pregnancy Test – Urine or Serum B-HCG | | X [H] | | | | | | | | | | | | | | | | | |
| PT/INR and aPTT | | X [G] | | | | | | | | | | | | | | | | | |
| CBC with Differential | | X [G] | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Comprehensive Serum Chemistry Panel [J] | | X [G] | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| LDH | | X [G] | | | | X | | X | | X | | X | | X | | X | X | X | |
| Uric Acid | | X [G] | | | | X | | X | | X | | | | | | | | | |
| Phophorus | | X [G] | | | | X | | X | | X | | | | | | | | | |
| Magnesium | | X [G] | | | | | | | | | | | | | | | | | |
| Urinalysis | | X [G] | | | | | | | | | | | | | | | | | |
| Lipase and amylase | | X[G] | | | | X | | X | | X | | X | | X | | | | | |
| T3, FT4 and TSH [C] | | X [G] | | | | X | | X | | X | | X | | X[C] | | X | X | | |
| CMV monitoring [P] | | X[G] | | | | X | | X | | X | | X | | X | | | | | |
| **Efficacy Measurements** | | | | | | | | | | | | | | | | | | | |
| Tumor Imaging [D,L] | | X | | | | | | | | | | | | X[D] | | X | | X [E] | |

| **Trial Period:** | **Screening Phase** | | **Induction Phase (Day -21 to -1)** | | | **Treatment Cycles [A]** | | | | | | | | | | **End of Treatment** | **Post-Treatment** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Cycle/Title: | Pre-screening | Main Study Screening | | | | 1 | | 2 | | 3 | | 4 | | To be repeated after Cycle 8<br>5-8 | | At time of Discon | Safety Follow-up | Follow Up Visits [B] | Survival Follow-Up |
| Scheduling Window (Days): | | -50 to -22 | Day -21 | Day -14 | Day -7 | D1 ± 3 | D8[o] ± 3 | D1 ± 3 | D8 ± 3 | D1 ± 3 | D8 ± 3 | D1 ± 3 | D8 ± 3 | D1 ± 3 | D8 ± 3 | | 30 days post discon | Every 12 weeks post discon | |
| **Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood** | | | | | | | | | | | | | | | | | | | |
| Archival or Newly Obtained Tissue Collection | | X | | | | | | | | | | | | | | | | | |
| Correlative Studies Blood Collection [F, K] | | | X [F, K] | | X[F] | | | X[F] | | X[F] | | | | X[K] | | X [F, K] | | X [K] | |

**A** Total of 36 treatment cycles

**B** Patients should be assessed every 12 weeks (84 ± 7 days) for the first 2 years (or until disease progression) clinically for disease status - see section 7.1.5.4. Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy they move into survival follow-up

**C** Check during treatment phase once every cycle.

**D** Preferably FDG PET/CT at baseline, but if unavailable a contrast-enhanced CT scan is allowed. If PET CT is performed, the CT component must be of diagnostic quality. Subsequent imaging should be of the same modality as the imaging at baseline – see Sections 7.1.2.6 and 12.3. Once a patient achieved at PET-negative CR after completion of treatment, subsequent imaging can be a contrast-enhanced CT scan only. The first imaging during the treatment phase will be within 1 week prior to or on the day of starting treatment cycle 5; subsequent imaging will be every 12 weeks (± 3days) thereafter during the treatment phase (i.e. within 1 week prior to or on the day of starting treatment C9D1, C13D1, C17D1,…etc). Scan at the end of treatment should be performed within 14 days of the visit.

**E** Radiologic imaging to monitor disease status will be performed every 12 weeks (84 ± 7 days) for the first 24 months (year 1&2 of follow-up), then every 26 weeks (182 ± 14 days) for the next year after completing therapy (year 3 of follow-up). After 3 years, patient will be followed clinically every 3-6 months with diagnostic imaging only as clinically indicated.

**F** Peripheral blood samples will be collected immediately prior to the induction phase on day -21 (time 1); induction on day -7 (time 2); cycle 2 day 1, immediately prior to dose 2 (time 3); prior to dose 3, cycle 3 day 1 (time 4); prior to dose 5, cycle 5 day 1 (time 5); prior to dose 9, cycle 9 day 1 (time 6); and at time of progression (time 7) or end of treatment due to toxicity. Blood for correlative studies must be collected from Mon-Thurs so that it can be processed immediately at Fox Chase Cancer Center. Also, blood for correlative must not be collected a day before a holiday. Blood must reach Fox Chase Cancer Center on a working day.

**G** Within 10 days of treatment initiation

**H** Within 72 hours of treatment initiation if participant is a woman of child bearing potential. After that as per institutional practice.

**I** Vital signs consist of temperature, pulse, respiration, and blood pressure and will be monitored every 15 minutes during the pembrolizumab infusion and for 60 minutes after completion of each infusion. Copanlisib administration will have blood pressure measured through observation period.

**J** A direct bilirubin must be performed if the total bilirubin is above the upper limit of normal. Serum chemistry includes test for albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, sodium, total protein, SGOT [AST], SGPT [ALT].

| **Trial Period:** | **Screening Phase** | | **Induction Phase (Day -21 to -1)** | | | **Treatment Cycles** [A] | | | | | | | | | | **End of Treatment** | **Post-Treatment** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Cycle/Title: | Pre-screening | Main Study Screening | | | | 1 | | 2 | | 3 | | 4 | | To be repeated after Cycle 8<br>5-8 | | At time of Discon | Safety Follow-up | Follow Up Visits [B] | Survival Follow-Up |
| Scheduling Window (Days): | | -50 to -22 | Day -21 | Day -14 | Day -7 | D1 ± 3 | D8[o] ± 3 | D1 ± 3 | D8 ± 3 | D1 ± 3 | D8 ± 3 | D1 ± 3 | D8 ± 3 | D1 ± 3 | D8 ± 3 | | 30 days post discon | Every 12 weeks post discon | |

**K** Cell free DNA/ImmunoSeq TCR at baseline and every 12 weeks for 2 yrs then every 6 months for 1 yr and at time of progression or end of treatment due to toxicity

**L** For patients undergoing PET/CT, response will also be assessed using the 5-point scale (Deauville criteria).[2] Refer to section 13 for measurements of effect.

**M** Blood glucose levels and Blood pressure measurement (not more than 4 per visit) must be done before copanlisib administration on day -21 and day -14 and conditions as described in section 5.2.2.2 must be met for drug administration during the induction phase alone. During copanlisib administration, blood pressure should be measured at 30 min (during infusion), and 60 min (end of infusion) from start of the infusion, 1 hr and 2 hr (after the infusion).

**N.** Patients in cohort 2 who will receive copanlisib must be fasting for at least 8 hours before the drug administration on Day -21 of the induction phase. Blood glucose level should be monitored and copanlisib may not be given if blood glucose level is higher than 160 mg/dl. Follow guidelines as described in section 5.2.2.2 for copanlisib administration.

**O.** Day 8 treatment of each cycle with copanlisib may not take place (see section 4.2.3.1) if RP2D is dose level -1. If Day 8 treatment does not take place all visit related activities on day 8 will also not happen.

P. Before starting copanlisib, all patients should have CMV status assessed. For seropositive patients, CMV quantitative polymerase chain reaction (PCR) testing with every cycle. Interrupt Copanlisib in patients with evidence of active CMV infection of any grade or viremia until the viremia has resolved. Ganciclovir or valganciclovir should be preemptively initiated in patients with positive CMV PCR and symptoms consistent with CMV infection, patients presenting with fever and no clear source in whom quantitative CMV testing is unavailable, and asymptomatic patients with increasing viral load. Patients can continue with pembrolizumab while copanlisib is being held.

Q In cohort 2, on the days when patients receive both the drugs, sequence of administration must be copanlisib, followed by pembrolizumab.

## 7.0 TRIAL PROCEDURES

### 7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.
Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or Merck, Bayer for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

#### 7.1.1 Administrative Procedures

##### 7.1.1.1 Informed Consent

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

###### 7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.
A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.
Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB requirements, applicable laws and regulations and Sponsor requirements.

##### 7.1.1.2 Inclusion/Exclusion Criteria

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

#### 7.1.1.3 Medical History

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

#### 7.1.1.4 Prior and Concomitant Medications Review

##### 7.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

##### 7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 8.0.

#### 7.1.1.5 Disease Details and Treatments

##### 7.1.1.5.1 Disease Details

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

##### 7.1.1.5.2 Prior Treatment Details

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

##### 7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

### 7.1.2 Clinical Procedures/Assessments

#### 7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0 (see Section 14.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.
All AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (irAE). See Section

5.4 regarding the identification, evaluation and management of AEs of a potential immunological etiology.

Please refer to section 8.0 for detailed information regarding the assessment and recording of AEs.

#### 7.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam will also be performed every 3 cycles during the treatment phase, 30 days post treatment, and every 3 months during follow-up.

#### 7.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

#### 7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

#### 7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 14.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart. After Cycle 8 assessment of ECOG status will be performed every other cycle in conjunction with the directed or full physical exam.

#### 7.1.2.6 Tumor Imaging and Assessment of Disease

Scans will be performed at baseline, and thereafter every 12 weeks (± 3 days) while on treatment. Imaging during follow up is outlined in section 7.1.5.4. It is critical that all FDG PET/CT or CT scans be performed in an identical way to the baseline scan with the same scan direction and consistent arm pointing. The interval between FDG injection and initiation of emission scanning should be the same or similar to the baseline scan. If tumor flare is suspected, the patient must undergo a second scan within a month of the first scan and the case must be discussed with the principle investigator. If progression is documented at that time, patient must come off study. A scan should be performed within 14 days of the end of treatment visit.

#### 7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

For details in regards to tumor tissue collection please see Section 7.1.3.1.2 Tumor tissue collection for central pathology review and correlative studies and the trial lab manual.

Peripheral blood samples will be collected immediately prior to the first dose of pembrolizumab (time 1), at cycle 2 (immediately prior to dose 2; time 2) and cycle 3 (immediately prior to dose 3; time 3) and at time of progression (time 4) for correlative studies as outlined in Section 6.0 Trial Flow Chart.

In evaluating the effect of the treatment on altering immunity, quantity of main interest is the change in the percentage of activated T cells and Natural Killer cells from Time 1 to Time 2, and from Time 2 or Time 3 to Time 4.

The results of these studies are for the purposes of the trial only and will not be returned to the site or reported to the patient.

Processing of blood samples will occur at FCCC as outlined in the Lab Manual. Blood samples will be shipped to Protocol Support Laboratory (PSL) at Fox Chase. Samples will be distributed from the PSL at Fox Chase to Kerry Campbell's lab. Remaining cells will be stored in the PSL.

### 7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

#### 7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5.

Laboratory tests for screening should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

#### 7.1.3.1 Biomarker Evaluations

##### 7.1.3.1.1 Blood Collection for correlative studies/biomarkers

Sample collection, processing, storage, and shipment instructions for samples will be provided in the trial Lab Manual.
The time points for blood sampling for correlative studies are described in Section 6.0 – Trial Flow Chart.

Table 5 Laboratory Tests

| Hematology | Chemistry | Urinalysis | Other |
|---|---|---|---|
| Hematocrit | Albumin | Blood | Serum β-human chorionic gonadotropin† |
| Hemoglobin | Alkaline phosphatase | Glucose | (β-hCG)† |
| Platelet count | Alanine aminotransferase (ALT) | Protein | PT (INR) |
| WBC (total and differential) | Aspartate aminotransferase (AST) | Specific gravity | aPTT |
| Red Blood Cell Count | Lactate dehydrogenase (LDH) | Microscopic exam *(If abnormal)* | Total thriiodothyronine (T3) |
| Absolute Neutrophil Count | Carbon Dioxide | results are noted | Free tyroxine (T4) |

| Hematology | Chemistry | Urinalysis | Other |
|---|---|---|---|
| | *($CO_2$ or biocarbonate)* | Urine pregnancy test † | Thyroid stimulating hormone (TSH) |
| | Uric Acid | | |
| | Calcium | | |
| | Chloride | | Blood for correlative studies |
| | Glucose | | |
| | Phosphorus | | |
| | Potassium | | |
| | Sodium | | |
| | Magnesium | | |
| | Total Bilirubin | | |
| | Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)* | | |
| | Total protein | | |
| | Blood Urea Nitrogen | | |
| † Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. | | | |

#### 7.1.3.1.2 Tumor tissue collection for central pathology review and correlative studies

Pathology samples from the confirmatory relapse biopsies taken within 28 days of enrollment are to be submitted within one (1) month following registration or collection. Representative FFPE tumor tissue blocks from confirmatory relapse specimen (MANDATORY) are to be submitted to the Fox Chase Cancer Center PSL in addition to any available specimens and reports from the original tumor biopsy at diagnosis.

The following pathology material needs to be submitted:

- Paraffin embedded biopsy or cell block, and
- Any available pathology report related to that tumor sample, including flow cytometry, genetic and molecular reports.

**NOTE:** If a block is unavailable for submission, slides are to be submitted. All slides must be adequately labeled, with slides numbered sequentially in the order cut. Alternative submission requirement:

- One (1) H&E slide, and
- Fifteen (15) 4 µm unstained air-dried on plus slides.

Original diagnostic material (from initial diagnostic material) will also be reviewed at Fox Chase if available. These include:

- Pathology reports of the initial **tumor biopsy at diagnosis**, including flow cytometry reports, cytogenetic and molecular reports, and
- Any available H&E and IHC slides of the initial tumor biopsy at diagnosis.

**NOTE:** Original material will be sent back to the referring institution.

Shipment of pathology samples is outlined in the lab manual for this trial.

### 7.1.4 Other Procedures

#### 7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events, which are present at the time of discontinuation/withdrawal, should be followed in accordance with the safety requirements outlined in Section 8.0 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 36 cycles of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 5.1. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

### 7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart.

#### 7.1.5.1 Screening

##### 7.1.5.1.1 Screening Period

Subjects will be screened within 28 prior to protocol treatment. Study procedures and information regarding the nature of the study will be reviewed with potential subjects and written informed consent will be obtained prior to any study related procedures. Screening procedures are described in Section 6.0 – Trial Flow Chart.

#### 7.1.5.2 Treatment Period

Subjects will be treated every 3 weeks of pembrolizumab for up to 36 cycles. During the treatment phase patients will be evaluated prior to any treatment dose of pembrolizumab for toxicities and every 3 months for disease progression as outlined in detail in Section 6.0 – Trial Flow Chart.

#### 7.1.5.3 Post-Treatment Visits

##### 7.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with a study drug attributable AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. Events of Clinical Interest that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

#### 7.1.5.4 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks (84 ± 7 days) for the first 2 years clinically for disease progression. Radiologic imaging (see Section 14.3 Measurement of Effect) to monitor disease status will be performed every 12 weeks (84 ± 7 days) for the first 24 months (year 1 & 2 of follow-up), then every 26 weeks (182 ± 14 days) for the next year after completing therapy (year 3 of follow-up). After 3 years patient will be followed clinically every 3-6 months with diagnostic imaging only as clinically indicated. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as detailed in Section 5.8. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

##### 7.1.5.4.1 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase. Survival follow-up will take place approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. This contact can be done by telephone, medical record search, office visit, etc. After 3 years of follow-up this contact can go to every 6 month.

## 8.0 Assessing and Recording Adverse Events

Adverse Events (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, treatment or procedure regardless of whether it is considered related to the medical treatment or procedure *(NCI CTEP Guidelines March 28, 2011)*

**Serious Adverse Event (SAE)** is an AE that results in the following outcomes-

- Death
- Life threatening adverse event
- Requires inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours),
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- Congenital anomaly/ birth defect.

A **"life-threatening**" adverse event places the patient at immediate risk of death in the judgment of the investigator or sponsor.

**NOTE:** Important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent any of the above outcomes.

### 8.1 Severity Rating

The investigator will evaluate the severity of each adverse event. NCI Common Terminology Criteria for Adverse Events (CTCAE v.5.0) or study specific toxicity tables provided in the protocol define severity. If not included in CTCAE v.5.0, severity is expressed in numerical grade using the following definitions:

- Grade 1: Mild-asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate-minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL.
- Grade 3: Severe-severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE

### 8.2 Attribution/Relationship to study drug

- Definite – clearly related
- Probable – likely related
- Possible – may be related
- Unlikely – doubtfully related
- Unrelated – clearly not related

### 8.3 Expectedness

**An Expected Adverse Event** is one where the specificity or severity is consistent with the current information available from the resources.

**An Unexpected Adverse Event** is one where the nature, severity, or frequency of the event is related to participation in the research is not consistent with either:

1. The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts: or

2. The expected natural progression of any underlying disease, disorder, or condition of the subject (s) experiencing the adverse event and the subjects(s) predisposing risk factor profile for the adverse event.
   (OHRP Guidance on reviewing unanticipated problems 2007)

## 9.0 RECORDING AND REPORTING RESPONSIBILITIES

### 9.1.1 Investigative Site Recording Responsibilities:

1. Upon identification of an AE or SAE, the site investigator will utilize the above definitions to properly classify attribution and expectedness of the event. These must be recorded for each event.

2. All AEs and SAEs will be recorded in the "AE case report forms" (CRF) and in progress reports with details about the grade and attribution of each episode, action taken with respect to the study drug, and the patient's outcome will be recorded in the CRF. All events will be recorded on case report forms for the duration of the study until they resolve.

3. All SAEs will be recorded on the FDA MedWatch form 3500a. The attribution and expectedness must be recorded on the MedWatch form. If this information is not available at the time of initial reporting, a final report must be documented with attribution and expectedness. It may be necessary to submit follow up reports to the Sponsor should the event require further investigation. All subsequent SAEs must be recorded for up to 30 days after the last treatment.

4. All patient data must be recorded in eCRFs by the investigative site within 7 days of the patient's visit. eCRFs will be available through Oncore electronic data capture system.

### 9.1.2 Investigative Site Reporting Responsibilities:

1. The investigator/ site is responsible to report all SAEs that occur on or after the first day of study treatment to the sponsor within 24 hours of becoming aware of the event. It may be necessary to submit a final SAE report if the initial report did not have the complete information. All subsequent SAEs must be recorded for up to 30 days after the last treatment.

   Each investigator is responsible to report all AEs/SAEs to their local IRB following guidelines set by that IRB. The FCCC OCR reserves the right to request an event be reported to the IRB at their discretion. Copies of events reviewed by the IRB must be sent by email to **SAE.FCCC@fccc.edu.**

2. If the investigator or IRB feels the event warrants a revision to the informed consent that was not already initiated by the ISRU, draft revisions will be made in track changes and submitted to the ISRU for consideration. Any consent revisions must receive ISRU approval **prior** to submission to the IRB.

3. Any investigator who is in doubt of whether a particular AE needs to be reported is directed to call the Study Monitor for confirmation with the Sponsor-Investigator

4. If the results of an investigator or ISRU investigation show an adverse event not initially determined to be reportable is so reportable (to IRB or FDA), the investigator

will report the event following the above guidelines based on the date the determination is made.

5. Investigative site should report Reportable New Information (RNI) to their local IRB according to the local IRB guidelines. This information should also be sent to ISRU. At minimum serious unexpected events that are associated with the treatment are considered to be reportable. Expected AEs that are experienced at a higher frequency or severity than expected in the patient population according to the investigator brochure are considered to be reportable.

6. Copies of all related correspondence and reporting documents must be submitted to the ISRU and will be maintained in the trial master file.

**Participating sites should report events to:**

Investigator-Sponsored Research Unit
Office of Clinical Research
Fox Chase Cancer Center
SAE.FCCC@fccc.edu

### 9.1.3 Sponsor Reporting Responsibilities:

- Adverse events which meet **all of the following criteria** must be reported to all participating institutions for IRB submission within 2 weeks of notification of the event.
    - Unexpected (in terms of nature, severity, or frequency) given
        i. (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and
        ii. (b) the characteristics of the subject population being studied;
    - Possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
    - Serious (refer to above definition) or otherwise one that suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.
- If the adverse event requires modification of the study protocol and informed consent, these changes will be provided to all participating institutions in the form of an amendment from the ISRU for each site's IRB of record along with the report of the adverse event.
- All participating sites must be notified of all amendments approved by FCCC IRB; or if the study is suspended such that the participating sites cannot accrue patients in the study until further notification.
- All participating sites must be notified when the study is closed by IRB.

- Copies of all related correspondence and reporting documents will be maintained in a centralized regulatory file for this study at ISRU.
- SAEs that are fatal or life threatening are reportable through the Food and Drug Administration (FDA) MedWatch program by telephone or fax no later than 7 calendar days after initial receipt of the information. Further information on the timing of submissions are as directed by FDA guidelines can be found in the following link: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm362555.htm.

  SAEs that are serious, unexpected and at least possibly related to the study drug (**unexpected suspected adverse events**) or events that suggest significant clinical risk will be submitted to FDA within 15 calendar days after initial receipt of this information. The 15 day report has to be submitted by in paper format (or electronic submission if that is available) to the IND as described in the "safe to proceed" letter.

  **The FAX number for reporting SAE to FDA (7-day reporting) can be found in the FDA "Study may proceed" letter.**

  **The SAE report can also be submitted by email to the Regulatory Project Manager and/or the Chief, Project Management Staff described in the "Study May Proceed" letter.**

- Reportable New Information (RNI) to IRB according to the IRB guidelines. This information should also be sent to all participating sites if associated with safety concern. At minimum serious unexpected events that are associated with the treatment are considered to be reportable. Expected AEs that are experienced at a higher frequency or severity than expected in the patient population according to the investigator brochure are considered to be reportable.
- All SAEs and reports of overdose with and without an adverse event will be reported to Merck Global Safety within 2 working days of receipt. (Attn: Worldwide Product Safety; FAX 215 993-1220)
- A copy of all Annual Progress Reports submitted as required by FDA and non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs.
- As soon as there is reasonable suspicion of the following AE, the investigator should immediately notify Bayer (within 24 hours) regardless of whether the event is assessed as causally related/not related to the study drug, or as serious/non-serious. The AESI should be entered on a Medwatch form and if the event is assessed as non-serious, the non-serious assessment should be noted in the form.
  - Non-infectious pneumonitis (NIP)
- The following should be reported within 24 hours after the initial receipt of information to BAYER by fax and/or e-mail: (973) 709-2185; DrugSafety.GPV.US@bayer.com

- All Serious Adverse Events occurring after start of administration of BAYER product, independent of their causal relationship to the STUDY DRUG
- Any other relevant safety information including but not limited to:
    i. reports of drug exposure via mother / father with and without adverse events (exposure during conception, pregnancy, childbirth and breastfeeding) including their outcome;
    ii. if linked to a serious adverse event, reports of misuse, abuse, overdose, medication error and other uses outside what is foreseen in the protocol, drug dependency, occupational exposure suspected transmission of an infectious agent, withdrawal syndrome, drug interactions with respect to the STUDY DRUG;

    and
- Any communication concerning safety related information to regulatory authorities or ethics committees including but not limited to:
- Development Safety Update Reports / relevant parts of IND reports for the STUDY;
- Any other safety related reports, issues and queries that are either raised by or communicated to regulatory authorities or ethics committees (e.g., reportable non-serious cases);

### 9.2 Definition of an Overdose

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab by 20% over the prescribed dose. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

### 9.3 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor, who will report this information 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 9.2, 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.
3. In the event a subject develops any of the following AEs, a detailed narrative of the event should be reported as an ECI to the Sponsor within 24 hours, who will report this information within 2 working days to Merck Global Safety:

a. Grade ≥ 3 diarrhea
b. Grade ≥ 3 colitis
c. Grade ≥ 2 pneumonitis
d. Grade ≥ 3 hypo- or hyperthyroidism

A comprehensive list of ECI is also provided in the appendix (Appendix 13.4 - Events of Clinical Interest (ECI) guidance). This appendix provides guidance regarding identification, evaluation and management of ECIs and irAEs. Additional ECIs are identified in this guidance document and also need to be reported to the Sponsor within 24 hours, who will report this information within 2 working days to Merck Global Safety.
Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

ECIs that occur in any subject from the date of first dose through 90 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the Merck's product, must be reported within 24 hours to the Sponsor, who will report this information within 2 working days to Merck Global Safety.

### 9.4 Reporting of Pregnancy and Lactation to the Sponsor-Investigator and to Merck and Bayer

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

## 10.0STATISTICAL ANALYSIS PLAN

### 10.1 Statistical Analysis Plan (cohort 1)

The primary endpoint is based on the median progression free survival (PFS). Estimates are based on historical controls from published data.[31,33,34,78] We will test the null hypothesis that median PFS is at most 3 months versus the alternative that it is at least 6 months. We will use a two-stage design with early stopping rules[79] and enroll an initial cohort of 13 patients. We will terminate the study for futility unless more than 6 patients are progression-free (as defined alive and achieving SD, PR or CR as per revised Cheson response criteria) at 3 months. Otherwise we will recruit an additional 11 patients and evaluate these 11 plus all eligible patients from the initial cohort (n=13) who were progression-free at 3 months at 6 months. If at least 10 out of 24 patients have not progressed at 6 months we will reject the null hypothesis. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.) Patients who are not evaluable for response will be replaced. However, all patients who received at least 1 dose of the study drug will be included in the safety analysis. The study has 80% power and 4.7% type I error. The chance of early stopping, after 13 patients, is 50% under the null and 5.5% in error.

Early stopping rules for safety/adverse events:
Adverse events will be assessed continuously throughout the study. If ever during evaluation of the first cohort of 13 eligible patients, 3 patients have to discontinue study treatment due to treatment related adverse events the study will be interrupted for consideration of dose reduction or termination. If ever 4 of the 24 eligible patients have to discontinue study treatment due to treatment related adverse events the study will be suspended and early termination for excess toxicity will be considered after careful investigation of the causes of the higher than expected toxicities. Once the root of the higher than anticipated toxicities has been determined, the study team will confer with the FCCC DSMC and IRB to make a determination whether accrual can be resumed or the study will be terminated early. The chance of early termination with a true toxicity of 25% is 67%. The chance of early termination when true toxicity is 5% is 2.5%. The overall chance of study termination under the null of 5% true toxicity is 4.2% and is 89% if true toxicity is 25%.

Correlative studies: Due to this limited sample size, all exploratory analyses of associations of biomarkers with outcomes and changes in marker levels pre- and during treatment will be largely descriptive in nature. Multiple imputation will be used to account for missing data in order to provide an unbiased estimate.

### 10.2 Statistical Analyses Plan (cohort 2)

There will be a phase 1 part (cohort 2a), during which the recommended phase 2 dose (RPTD) of the combination of pembrolizumab and copanlisib will be determined, followed by a phase 2 portion (cohort 2b), which will explore safety and efficacy of the combination. The phase 1 portion will follow a standard '3+3' escalation/de-escalation design as outlined above. A minimum of 4 and a maximum of 12 patients will be included in the phase 1 portion. For the phase 2 portion, an optimal Simon's two-stage design will be used. The null hypothesis that the true response rate is 30% will be tested against the alternative

hypothesis of a true response rate ≥60%. Response is defined as either a partial or complete response by Revised Cheson criteria (see 13.3) by 4 cycles of treatment. All eligible and evaluable patients who received at least 1 dose of the combination regimen will be included in this response analysis. Patients who come off study prior to second clinic visit for reasons other than progressive disease will be replaced. Patients who are lost to follow-up after re-evaluation will be counted as failures and will not be replaced. For the first stage, 8 patients will be treated at the RPTD of the combination. If at least 4 patients achieve a response, we will accrue 16 more for a total of 24 patients treated at the RPTD (including those patients treated during the phase 1 portion at the RPTD). If of the first 8 patients, 3 or less respond, the trial will be stopped. The null hypothesis will be rejected if 11 or more responses are observed in 24 patients and the combination deemed worthy of further consideration. This design yields a power of 80% with a type I error of 5% when the true response rate is ≥60% ORR. The probability of early stopping under the null hypothesis is 80%.

Early stopping rules for safety/adverse events: A discontinuation rate for toxicities related to study treatment of ≤30% will be deemed acceptable, while a ≥50% discontinuation rate for toxicities related to study treatment will be considered unacceptable. An interim analysis will be conducted when 8 patients have accrued to determine safety by the Principal Investigator and the statistician. If ≥4 of the initial 8 treated patients at the RPTD discontinue due to study related toxicities, the study will be stopped for safety. If after 24 patients have been enrolled, or at any time point during the study with treatment at the RPTD, 11 or more patients discontinue due to study related toxicities, the study will also be stopped for safety. With this design, the probability of stopping early with a ≥50% true toxicity rate is 64%, and 19% if the true toxicity is ≤30%. The probability of stopping at any point due to a ≥50% true toxicity rate is 82%, while it is ≤22% if the true toxicity is 30%.

Accrual: The expected monthly accrual rate is 1-2 patients. Thus, accrual is anticipated to take approximately 2.5 years.

## 11.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

### 11.1 Investigational Product

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

Pembrolizumab will be provided by Merck and copanlisib will be provided by Bayer as summarized in Table 6.

Table 6 Product Descriptions

| Product Name & Potency | Dosage Form |
|---|---|
| Pembrolizumab 100 mg/ 4 mL | Solution for Injection |
| Copanlisib 60 mg/vial | Solution for Injection |

### 11.2 Packaging and Labeling Information

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

### 11.3 Clinical Supplies Disclosure

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

### 11.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

### 11.5 Returns and Reconciliation

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

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

## 12.0 Administrative, Regulatory, Data Monitoring and Safety Details

### 12.1 Monitoring Plan

FCCC ISRU will monitor the medical and study records of each participant accrued throughout the course of the study. In addition, the ISRU will collect and report data to the study Sponsor Investigator who will review these data on a regular basis at a rate dependent on subject accrual. All serious adverse events (SAEs) will be reviewed on a real time basis first by the study site PI and subsequently by the ISRU and Sponsor Investigator as applicable.

### 12.2 Data Safety Monitoring Committee

Interim analysis of toxicity, outcome and ongoing scientific investigations will be performed at least every 3 months by the Fox Chase Cancer Center Data Safety Monitoring Committee (FCCCDSMC). In this capacity the FCCCDSMC will serve as an advisory committee to the OCR. The FCCCDSMC will review those aspects of this trial that are outlined in the responsibilities section of the Data and Safety Monitoring Plan (DSMP). If the committee decides that changes should be made to this trial, it will make recommendations in writing to the Study Principal Investigator, the Associate Director of Clinical

Research, and the Protocol Management Executive Committee, which, in turn, have the authority to approve or disapprove these recommendations. These changes will be discussed with the Study Principal Investigator before they are implemented. These changes may include early termination of accrual. Other changes might include altering the accrual goals or changing the eligibility criteria for the trial.

### 12.3 Compliance with Law, Audit and Debarment

This study will be conducted in accordance will local, state and Federal regulations and according to accepted good clinical practice guidelines.

### 12.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

### 12.5 Retention of Records

Time points for the retention of records are described in detail in the contract between the grantor and the CTO and passed on to the participating site. Please refer to the study specific terms for specific time points. In all cases the QA Specialist / Study Monitor must be notified of any plans to move records to an offsite location prior to doing so.

### 12.6 Study Agents

Any study agent supplied through the CTO from the manufacturer or a third party distributor may not be used for any purpose outside the scope of this protocol. The agent may not be transferred to any party not participating in the clinical trial.

### 12.7 Informed Consent

The IRB approved informed consent documents must be signed by the patient, or the patient's legally authorized representative, before his or her participation in the study. The case history for each patient shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent documents must be provided to the patient or the patient's legally authorized representative. If applicable, they will be provided in a certified translation of the local language.

Original signed consent forms must be filed in each patient's study file or medical record with a copy in the study file.

### 12.8 Data Reporting

The FCCC Study Monitor will request case report forms to be completed within 2 weeks of the protocol visit. Participating sites are responsible to respond to queries prior to the next scheduled monitoring visit.

The ISRU staff is responsible for compiling and submitting data to the Sponsor Investigator and statistician on an ongoing basis for monitoring as described in the data safety monitoring plan and reporting to the Data and Safety Monitoring Committee.

All patient information will be stored in an EDC system accessible only to the study team members for the purpose of entering, reviewing and analyzing data. Any paper records, such as case report files, produced will be stored in a secure location.

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## 14.0 APPENDICES

### 14.1 ECOG Performance Status

| Grade | Description |
|---|---|
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work). |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 5 | Dead. |
| * As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair. | |

### 14.2 Common Terminology Criteria for Adverse Events V5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

### 14.3 Measurement of Effect

**Revised Cheson Lymphoma Response Criteria**

**NOTE:** These criteria are based upon the criteria from the Revised Response Criteria for Malignant Lymphoma, (Cheson et al.), Journal of Clinical Oncology, 2007, Vol. 25:579-586.

The criteria use the following categories of response: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Relapse and Progression (PD). In the case of stable disease, follow-up assessments must have met the SD criteria at least once after study entry at a minimum interval of six weeks.
The following guidelines are to be used for establishing tumor measurements at baseline and for subsequent comparison:

- The six largest dominant nodes or extranodal masses must be identified at baseline.
- If there are 6 or fewer nodes and extranodal masses, all must be listed as dominant
- If there are more than 6 involved nodes or extranodal masses, the 6 largest dominant nodes or extranodal masses should be selected according to the following features: a) they should be clearly measurable in at least two perpendicular measurements; b) they should be from as disparate regions of the body as possible; and c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
- Measurements for all dominant nodes and extranodal masses will be reported at baseline. Measurements on non-dominant nodes are not required.
- The lymph nodes or extranodal masses selected for measurement should be measured in two perpendicular diameters, one of which is the longest perpendicular diameter. The lymph nodes should be measured in centimeters to the nearest one tenth of a centimeter (e.g.,2.0 cm, 2.1cm, 2.2 cm, etc.)
- The two measured diameters of each lymph node site or extranodal mass should be multiplied giving a product for each nodal site or extranodal mass. The product of each nodal site should be added, yielding the sum of products of the diameters (SPD). The SPD will be used in determining the definition of response for those who have less than a complete response.
- Patients should be assessed with PET/CTs. Where PET is not available, response should be assessed as above, but only using CT scans. However, residual masses should not be assigned CRu status, but should be considered partial responses.
- For patients undergoing PET/CT, tumor assessment at all timepoints should also include the 5-point scale (Deauville criteria) as an adjunct to the Cheson criteria.[2] Scoring guidelines for the 5-point scale are below. A score of 1, 2, or 3 indicates a complete metabolic response. Refer to section 14.3.1 for further definition of complete response.

| | |
|---|---|
| 1 | No uptake |
| 2 | ≤ Mediastinal blood pool |
| 3 | > Mediastinum and ≤ liver |
| 4 | Moderately > liver at any site |
| 5 | Markedly increased uptake above liver and/or new sites of disease |
| X | New areas of uptake unlikely to be related to lymphoma |

### 14.3.1 Complete Response

Complete disappearance of all detectable clinical evidence of disease, and disease-related symptoms if present prior to therapy.

In patients with a typically FDG-avid lymphoma with no pre-treatment PET scan, or for lymphomas for which the PET scan was positive prior to therapy: a post-treatment residual mass of any size is permitted as long as it is PET-negative.

For variably FDG-avid lymphomas without a pretreatment PET scan, or if a pretreatment PET scan was negative: all lymph nodes and extranodal masses must have regressed on CT to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm prior to therapy). Previously involved nodes that were 1.1-1.5 cm in their long axis and > 1.0 cm in their short axis prior to treatment must have decreased to ≤ 1 cm in their short axis after treatment

The spleen and/or liver, if considered enlarged prior to therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination, and nodules related to lymphoma should disappear. However, no normal size can be specified because of the difficulties in accurately evaluating splenic and hepatic size and involvement. For instance, a spleen considered normal size may contain lymphoma, whereas an enlarged spleen may not necessarily reflect the presence of lymphoma, but variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes.

**NOTE:** Complete Remission/unconfirmed (CRu): Using the above definition for CR and that below for PR eliminates the category of CRu.

### 14.3.2 Partial Response (PR)

The designation of PR requires all of the following: A ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or extranodal masses.

No increase in the size of other nodes, liver or spleen.

No new sites of disease.

For a typically FDG-avid lymphoma with no pretreatment PET scan or one that was PET-positive prior to therapy, the post-treatment PET should be positive at any previously involved sites.

For variably FDG-avid lymphomas/FDG-avidity unknown, without a pre-treatment PET scan, or if a pretreatment PET scan was negative, CT scan criteria should be used.

Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders.

When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.

### 14.3.3 Stable Disease (SD)

Failing to attain the criteria needed for a PR or CR, but not fulfilling those for progressive disease (see below).

Typically FGD-avid lymphomas: The PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.

For variably FDG-avid lymphomas/FDG-avidity unknown: For patients without a pretreatment PET scan or if the pre-treatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

### 14.3.4 Progression (PD) and Relapse

For determination of relapsed and progressive disease, lymph nodes should be considered abnormal if the long axis is more than 1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if the short axis is more than 1 cm. Lymph nodes ≤ 1 x ≤ 1 cm will not be considered as abnormal for relapse or progressive disease.

Treatment decisions in patients with presumed refractory, relapsed or progressive disease should not be made solely on the basis of a single PET scan without histologic confirmation.

Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size.

Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

At least a 50% increase from nadir in the SPD of any previously involved nodes or extranodal masses, or in a single involved node or extranodal mass, or the size of other lesions (e.g. splenic or hepatic nodules). To be considered progressive disease, a lymph node or extranodal mass with a diameter of the short axis of less than 1.0 cm must increase by ≥ 50% and to a size of 1.5 cm x 1.5 cm or more than 1.5 cm in the long axis.

At least a 50% increase in the longest diameter of any single previously identified node or extranodal mass more than 1 cm in its short axis.

Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these response criteria, the spleen is considered nodal disease. Disease that is only assessable (e.g.,

pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

### 14.3.5 Response Endpoints

All tumor assessments will be made using Revised Response (Cheson) criteria.

Pembrolizumab is expected to trigger immune-mediated responses, which require activation of the immune system prior to the observation of clinical responses. Such immune activation may take weeks to months to be evident. Some patients may experience tumor flare with objective volume increase of tumor lesions or other disease parameters (based on study indication, ie, hematologic malignancies) within 12 weeks following the start of pembrolizumab dosing. Such patients may not have had sufficient time to develop the required immune activation or, in some patients, tumor volume or other disease parameter increases may represent infiltration of lymphocytes into the original tumor or blood. In conventional studies, such tumor volume or relevant laboratory parameter increases during the first 12 weeks of the study would constitute PD and lead to discontinuation of imaging to detect response, thus disregarding the potential for subsequent immune-mediated clinical response. Therefore if at the first imaging time point (12 weeks after initiating treatment) patients demonstrate up to 2 new lesions, with sum of all lesions < 70% greater than baseline by SPD, or decreasing in size, and stable without evidence of rapid clinical deterioration, patients may be continue to be treated with pembrolizumab and clinically observed with imaging repeated after 1 month. If, at that time, there is Progression of Disease (POD) by standard Revised Response Criteria patients will be removed from study. For patients in whom investigators consider that tumor flare may be playing a role in the response seen on initial imaging, this must be documented at time of scan, and discussed with Study Chair. This may improve the overall assessment of the clinical activity of pembrolizumab and more likely capture its true potential to induce clinical responses. In regards to PFS analysis, the date of progression for patients who were initially considered to have tumor flare, but had further progression of disease (POD) on the repeat image after 1 month, will be the time of first imaging in which new lesions were originally detected.

### 14.3.6 Duration of Response

This is measured from the documented beginning of response (CR or PR) to the time of relapse. This is measured in responders.

### 14.3.7 Overall Survival

Overall survival is defined as the date of study entry to the date of death.

### 14.3.8 Progression-free Survival

Progression-free Survival (PFS) is defined as the time from entry onto study until lymphoma progression or death from any cause. PFS is often considered the preferable endpoint in lymphoma clinical trials. PFS reflects tumor growth and, therefore, occurs prior to the endpoint of overall survival. In addition, PFS is not confounded by the administration of subsequent therapy. Whether a prolongation of PFS represents direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the

risk-benefit ratio of the therapy under investigation. Unlike survival, the precise date of progression is generally unknown. It may be defined as the first date of documentation of a new lesion or enlargement of a previous lesion, or the date of the scheduled clinic visit immediately after radiologic assessment has been completed. Where there is missing information, censoring of the data may be defined as the last date at which progression status was adequately assessed or the first date of unscheduled new anti-lymphoma treatment.

### 14.4 Events of Clinical Interest (ECI) guidance

This appendix offers specific guidance for investigators for the management of ECI based on the "PEMBROLIZUMAB PROGRAM (MK-3475) EVENT OF CLINICAL INTEREST GUIDANCE DOCUMENT Version 5.0".

These recommendations should be seen as guidelines and the treating physician should exercise individual clinical judgment based on the patient. For any question of dose modification or other treatment options, the specific language in the protocol should be followed.

The treatment guidance provides specific direction when to hold and/or discontinue pembrolizumab for each immune related adverse event. Of note, when the guidance states to "discontinue" pembrolizumab this is the permanent discontinuation of treatment with pembrolizumab. "Hold" means to stop treating with pembrolizumab but resumption of treatment may be considered assuming the patient meets the criteria for resumption of treatment.

### 14.4.1 List of ECI

| | | |
|---|---|---|
| **Pneumonitis (reported as ECI if ≥ Grade 2)** | | |
| Acute interstitial pneumonitis | Interstitial lung disease | Pneumonitis |
| **Colitis (reported as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)** | | |
| Intestinal Obstruction | Colitis | Colitis microscopic |
| Enterocolitis | Enterocolitis hemorrhagic | Gastrointestinal perforation |
| Necrotizing colitis | Diarrhea | |
| **Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)** | | |
| Adrenal Insufficiency | Hyperthyroidism | Hypophysitis |
| Hypopituitarism | Hypothyroidism | Thyroid disorder |
| Thyroiditis | Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA) | |
| **Endocrine (reported as ECI)** | | |
| Type 1 diabetes mellitus (if new onset) | | |
| **Hematologic (reported as ECI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)** | | |
| Autoimmune hemolytic anemia | Aplastic anemia | Thrombotic Thrombocytopenic Purpura (TTP) |
| Idiopathic (or immune) Thrombocytopenia Purpura (ITP) | Disseminated Intravascular Coagulation (DIC) | Haemolytic Uraemic Syndrome (HUS) |
| Any Grade 4 anemia regardless of underlying mechanism | | |
| **Hepatic (reported as ECI if ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE)** | | |
| Hepatitis | Autoimmune hepatitis | Transaminase elevations (ALT and/or AST) |
| **Infusion Reactions (reported as ECI for any grade)** | | |
| Allergic reaction | Anaphylaxis | Cytokine release syndrome |
| Serum sickness | Infusion reactions | Infusion-like reactions |
| **Neurologic (reported as ECI for any grade)** | | |
| Autoimmune neuropathy | Guillain-Barre syndrome | Demyelinating polyneuropathy |
| Myasthenic syndrome | | |
| **Ocular (report as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)** | | |
| Uveitis | Iritis | |
| **Renal (reported as ECI if ≥ Grade 2)** | | |
| Nephritis | Nephritis autoimmune | Renal Failure |
| Renal failure acute | Creatinine elevations (report as ECI if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE) | |
| **Skin (reported as ECI for any grade)** | | |
| Dermatitis exfoliative | Erythema multiforme | Stevens-Johnson syndrome |
| Toxic epidermal necrolysis | | |
| **Skin (reported as ECI if ≥ Grade 3)** | | |
| Pruritus | Rash | Rash generalized |
| Rash maculo-papular | | |
| Any rash considered clinically significant in the physician's judgment | | |
| **Other (reported as ECI for any grade)** | | |
| Myocarditis | Pancreatitis | Pericarditis |
| Any other Grade 3 event which is considered immune-related by the physician | | |

### 14.4.2 Pneumonitis

The following AE terms, if considered ≥ Grade 2, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

– Pneumonitis

– Interstitial lung disease

– Acute interstitial pneumonitis

If symptoms indicate possible new or worsening cardiac abnormalities additional testing and/or a cardiology consultation should be considered. All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection. It is important that patients with a suspected diagnosis of pneumonitis be managed as per the guidance below until treatment-related pneumonitis is excluded. Treatment of both a potential infectious etiology and pneumonitis in parallel may be warranted. Management of the treatment of suspected pneumonitis with steroid treatment should not be delayed for a therapeutic trial of antibiotics. If an alternative diagnosis is established, the patient does not require management as below; however, the AE should be reported regardless of etiology.

**Course of Action**

Grade 2 events:

– Report as ECI
– Hold pembrolizumab.
– Consider pulmonary consultation with bronchoscopy and biopsy/BAL.
– Consider ID consult
– Conduct an in person evaluation approximately twice per week
– Consider frequent Chest X-ray as part of monitoring
– Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
– Second episode of pneumonitis – discontinue pembrolizumab if upon re-challenge the patient develops a second episode of Grade 2 or higher pneumonitis.

Grade 3 and 4 events:

– Report as ECI
– Discontinue pembrolizumab.
– Hospitalize patient
– Bronchoscopy with biopsy and/or BAL is recommended.
– Immediately treat with intravenous steroids (methylprednisolone 125 mg IV). When symptoms improve to Grade 1 or less, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks.
– If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, treat with additional anti-inflammatory measures. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures, as needed
– Add prophylactic antibiotics for opportunistic infections.

### 14.4.3 Colitis

The following AE terms, if considered ≥ Grade 2 or resulting in dose modification or use of systemic steroids to treat the AE, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

– Colitis
– Colitis microscopic
– Enterocolitis
– Enterocolitis hemorrhagic
– Gastrointestinal perforation
– Intestinal obstruction
– Necrotizing colitis
– Diarrhea

All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, a Clostridium difficile titer and endoscopy. However the AE should be reported regardless of etiology.

**Course of Action**

Grade 2 Diarrhea/Colitis (4-6 stools/day over baseline, dehydration requiring IV fluids < 24 hours, abdominal pain, mucus or blood in stool):

– Report as ECI
– Hold pembrolizumab.
– Symptomatic Treatment
– For Grade 2 diarrhea that persists for greater than 3 days, and for diarrhea with blood and/or mucus,
o Consider GI consultation and endoscopy to confirm or rule out colitis
o Administer oral corticosteroids (prednisone 1-2 mg/kg QD or equivalent)
– When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
– If symptoms worsen or persist > 3 days treat as Grade 3

Grade 3 Diarrhea/Colitis (or Grade 2 diarrhea that persists for > 1 week):

– Report as ECI
– Hold pembrolizumab.
– Rule out bowel perforation. Imaging with plain films or CT can be useful.
– Recommend consultation with Gastroenterologist and confirmation biopsy with endoscopy.
– Treat with intravenous steroids (methylprednisolone 125 mg) followed by high dose oral steroids
(prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
Taper over 6 to 8 weeks in patients with diffuse and severe ulceration and/or bleeding.

– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
– If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider treatment with additional anti-inflammatory measures as described in the literature [5].
Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures as needed.

Grade 4 events:
– Report as ECI
– Permanently discontinue pembrolizumab.
– Manage as per Grade 3.

### 14.4.4 Endocrine

The following AE terms, if considered ≥Grade 3 or if ≥Grade 2 and require holding/discontinuation/modification of pembrolizumab dosing, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

– Adrenal insufficiency
– Hyperthyroidism
– Hypophysitis
– Hypopituitarism
– Hypothyroidism
– Thyroid disorder
– Thyroiditis

All attempts should be made to rule out other causes such as brain metastases, sepsis and/or infection. However, the AE should be reported regardless of etiology.

Hypophysitis or other symptomatic endocrinopathy other than hypo- or hyperthyroidism

Grade 2-4 events:
– Report as ECI if appropriate
– Hold pembrolizumab
– Rule out infection and sepsis with appropriate cultures and imaging.
– Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
– Pituitary gland imaging should be considered (MRIs with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis).
– Treat with prednisone 40 mg p.o. or equivalent per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
– Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis.
– Consultation with an endocrinologist may be considered.

### 14.4.5 Hyperthyroidism and Hypothyroidism

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

Grade 2 hyperthyroidism, Grade 2-4 hypothyroidism events:
– Report as ECI if appropriate (see Table 1)
– Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
– Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency.
– Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
– In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
– In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
– Consultation with an endocrinologist may be considered.

Grade 3 hyperthyroidism events:
– Report as ECI
– Hold pembrolizumab.
– Rule out infection and sepsis with appropriate cultures and imaging.
– Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 hyperthyroidism events:
– Report as ECI
– Discontinue pembrolizumab.
– Manage as per Grade 3

### 14.4.6 Type 1 diabetes mellitus (if new onset) and ≥ Grade 3 Hyperglycemia

The following AE terms are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

– Type I diabetes mellitus (T1DM), if new onset, including diabetic ketoacidosis (DKA)
– Grade 3 or higher hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA). Immune-mediated diabetes may present as new onset of Type 1 diabetes or an abrupt worsening of preexisting diabetes associated with laboratorial evidence of beta cell failure. All attempts should be made to rule out other causes such as type 2 diabetes mellitus (T2DM), T2DM decompensation, steroid-induced diabetes, physiologic stress-induced diabetes, or poorly controlled pre-existing diabetes (either T1DM or T2DM), but events meeting the above criteria should be reported as ECIs regardless of etiology. The patients may present with hyperglycemia (abrupt onset or abrupt decompensation) with clinical evidence of diabetic ketoacidosis or laboratory evidence of insulin deficiency, such as ketonuria, laboratory evidence of metabolic acidosis, or low or undetected c-peptide.

**Course of Action**
T1DM should be immediately treated with insulin.

T1DM or Grade 3-4 Hyperglycemia events:
- Report as ECI if appropriate (see Table 1)
- Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure, and resume pembrolizumab when patients are clinically and metabolically stable.
- Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
- Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- Consultation with an Endocrinologist is recommended.
- Consider local testing for islet cell antibodies and antibodies to GAD, IA-2, ZnT8, and insulin may be obtained.

### 14.4.7 Hematologic

The following AE term, if considered Grade ≥3 or requiring dose modification or use of systemic steroids to treat the AE, are considered an ECI and should be reported to the Sponsor within 24 hours of the event:

– Autoimmune hemolytic anemia
– Aplastic anemia
– Disseminated Intravascular Coagulation (DIC)
– Haemolytic Uraemic Syndrome (HUS)
– Idiopathic (or immune) Thrombocytopenia Purpura (ITP)
– Thrombotic Thrombocytopenic Purpura (TTP)
– Any Grade 4 anemia regardless of underlying mechanism

All attempts should be made to rule out other causes such as metastases, sepsis and/or infection. Relevant diagnostic studies such as peripheral blood smear, reticulocyte count, LDH, haptoglobin, bone marrow biopsy or Coomb's test, etc., should be considered to confirm the diagnosis. However the AE should be reported regardless of etiology.

**Course of Action**

Grade 2 events:

– Report as ECI
– Hold pembrolizumab
– Prednisone 1-2 mg/kg daily may be indicated
– Consider Hematology consultation.
Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3 events:

– Report as ECI
– Hematology consultation.
– Hold pembrolizumab Discontinuation should be considered as per specific protocol guidance.
– Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

– Report as ECI
– Hematology consultation
– Discontinue pembrolizumab for all solid tumor indications; refer to protocol for hematologic malignancies.
– Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate

### 14.4.8 Hepatic

The following AE terms, if considered ≥ Grade 2 or greater (or any grade with dose modification or use of systemic steroids to treat the AE), are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

– Autoimmune hepatitis
– Hepatitis
– Transaminase elevations

All attempts should be made to rule out other causes such as metastatic disease, infection or other hepatic diseases. However, the AE should be reported regardless of etiology.

-Drug Induced Liver Injury (DILI)

In addition, the event must be reported as a Drug Induced Liver Injury (DILI) ECI, if the patient meets the laboratory criteria for potential DILI defined as:

- An elevated alanine transaminase (ALT) or aspartate transaminase (AST) lab value that is greater than or equal to three times (3X) the upper limit of normal (ULN) and

- An elevated total bilirubin lab value that is greater than or equal to two times (2X) ULN and
- At the same time, an alkaline phosphatase (ALP) lab value that is less than 2X ULN,
- As a result of within-protocol-specific testing or unscheduled testing.
- Note that any hepatic immune ECI meeting DILI criteria should only be reported once as a DILI event.

**Course of Action**

Grade 2 events:

– Report as ECI

– Hold pembrolizumab when AST or ALT >3.0 to 5.0 times ULN and/or total bilirubin >1.5 to 3.0 times ULN.

– Monitor liver function tests more frequently until returned to baseline values (consider weekly).

o Treat with 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume pembrolizumab per protocol

– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or
equivalent per day within 12 weeks.

– Permanently discontinue pembrolizumab for patients with liver metastasis who begin treatment with Grade 2 elevation of AST or ALT, and AST or ALT increases ≥50% relative to baseline and lasts ≥1 week.

Grade 3 events:

– Report as ECI

– Discontinue pembrolizumab when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN.

– Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary

– Treat with high-dose intravenous glucocorticosteroids for 24 to 48 hours. When symptoms improve to Grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1 to 2 mg/kg should be started and continued over no less than 4 weeks.

– If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity.

– Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.

– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

– Report as ECI

– Permanently discontinue pembrolizumab

– Manage patient as per Grade 3 above

### 14.4.9 Neurologic

The following AE terms, regardless of grade, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

– Autoimmune neuropathy
– Demyelinating polyneuropathy
– Guillain-Barre syndrome
– Myasthenic syndrome

All attempts should be made to rule out other causes such as metastatic disease, other medications or infectious causes. However, the AE should be reported regardless of etiology.

**Course of Action**

Grade 2 events:

– Report as ECI
– Moderate (Grade 2) – consider withholding pembrolizumab.
– Consider treatment with prednisone 1-2 mg/kg p.o. daily as appropriate
– Consider Neurology consultation. Consider biopsy for confirmation of diagnosis.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3 and 4 events:

– Report as ECI
– Discontinue pembrolizumab
– Obtain neurology consultation. Consider biopsy for confirmation of diagnosis
– Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. If condition worsens, consider IVIG or other immunosuppressive therapies as per local guidelines. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

### 14.4.10 Ocular

The following AE terms, if considered Grade ≥2 or requiring dose modification or use of systemic steroids to treat the AE, is considered an ECI and should be reported to the Sponsor within 24 hours of the event:

– Uveitis
– Iritis

All attempts should be made to rule out other causes such as metastatic disease, infection or other ocular disease (e.g. glaucoma or cataracts). However, the AE should be reported regardless of etiology.

**Course of Action**

Grade 2 events:

– Evaluation by an ophthalmologist is strongly recommended.
– Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.
– Discontinue pembrolizumab as per protocol if symptoms persist despite treatment with

topical immunosuppressive therapy.

Grade 3 events:

– Evaluation by an ophthalmologist is strongly recommended

– Hold pembrolizumab and consider permanent discontinuation as per specific protocol guidance.

– Treat with systemic corticosteroids such as prednisone at a dose of 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

– Evaluation by an ophthalmologist is strongly recommended

– Permanently discontinue pembrolizumab.

– Treat with corticosteroids as per Grade 3 above

### 14.4.11 Renal

The following AEs if ≥ Grade 2 are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

– Nephritis

– Nephritis autoimmune

– Renal failure

– Renal failure acute

Creatinine elevations ≥ Grade 3 or any grade with dose modification or use of systemic steroids to treat the AE. All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury due to other chemotherapy agents. A renal consultation is recommended. However, the AE should be reported regardless of etiology.

**Course of Action**

Grade 2 events:

– Hold pembrolizumab

– Treatment with prednisone 1-2 mg/kg p.o. daily.

– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3-4 events:

– Discontinue pembrolizumab

– Renal consultation with consideration of ultrasound and/or biopsy as appropriate

– Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone IV or equivalent once per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Pembrolizumab Event of Clinical Interest Guidance Document

### 14.4.12 Skin

**Rash and Pruritus**

The following AEs should be considered as ECIs, if ≥ Grade 3 and should be reported to the Sponsor within 24 hours of the event:

– Pruritus
– Rash
– Rash generalized
– Rash maculo-papular
– In addition to CTCAE Grade 3 rash, any rash that is considered clinically significant, in the physician's judgment, should be treated as an ECI. Clinical significance is left to the physician to determine, and could possibly include rashes such as the following:
  - rash with a duration >2 weeks; OR
  - rash that is >10% body surface area; OR
  - rash that causes significant discomfort not relieved by topical medication or temporary cessation of study drug.

**Other Skin ECIs**

The following AEs should always be reported as ECIs, regardless of grade, and should be reported to the Sponsor within 24 hours of the event:

– Dermatitis exfoliative
– Erythema multiforme
– Steven’s Johnson syndrome
– Toxic epidermal necrolysis

Please note, the AE should be reported regardless of etiology.

**Course of Action**

Grade 2 events:

– Symptomatic treatment should be given such as topical glucocorticosteroids (e.g., betamethasone
0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral anti-pruritics (e.g., diphenhydramine HCl or hydroxyzine HCl).
– Treatment with oral steroids is at physician’s discretion for Grade 2 events.

Grade 3 events:

– Hold pembrolizumab.
– Consider Dermatology Consultation and biopsy for confirmation of diagnosis.
– Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

– Permanently discontinue pembrolizumab.
– Dermatology consultation and consideration of biopsy and clinical dermatology photograph.
– Initiate steroids at 1 to 2 mg/kg prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

#### 14.4.12.1 Immediate Evaluation for Potential Skin ECIs

A. Photographs:
Every attempt should be made to get a photograph of the actual ECI skin lesion or rash as soon as possible. Obtain appropriate consent for subject photographs if a consent form addendum is required by your IRB/ERC.

– Take digital photographs of:
o the head (to assess mucosal or eye involvement),
o the trunk and extremities, and
o a close-up of the skin lesion/rash.
– If possible, a ruler should be placed alongside the site of a skin occurrence as a fixed marker of distance.

– The time/date stamp should be set in the 'ON' position for documentation purposes.
– Photographs should be stored with the subject's study records.
– The Sponsor may request copies of photographs. The local study contact (e.g., CRA) will provide guidance to the site, if needed.

B. Past Medical History:
Collect past medical history relevant to the event, using the questions in Appendix 1 (Past Medical History Related to Dermatologic Event) as a guide. Any preexisting conditions not previously reported (e.g., drug allergy) should be entered into the Medical History eCRF.

C. Presentation of the Event:
Collect information on clinical presentation and potential contributing factors using the questions in Appendix 2 (Presentation of the Dermatologic Event) as a guide. This information should be summarized and entered in narrative format in the AE eCRF. Please use the available free-text fields, such as Signs and Symptoms. Note pertinent negatives where applicable to reflect that the information was collected. Any treatments administered should be entered on the Concomitant Medication eCRF.

D. Vitals Signs and Standard Laboratory Tests:
Measure vital signs (pulse, sitting BP, oral temperature, and respiratory rate) and record on the Vital Signs in eCRF. Perform standard laboratory tests (CBC with manual differential and serum chemistry panel, includingLFTs).

E. Focused Skin Examination:
Perform a focused skin examination using the questions in Appendix 3 (Focused Skin Examination) as a guide. Information should be summarized and entered on the Adverse Experience eCRF as part of the

narrative.

F. Dermatology Consult
Refer the subject to a dermatologist as soon as possible.
– For a "severe rash", the subject must be seen within 1-2 days of reporting the event.
– For clinically significant rash, the subject should be seen within 3-5 days.
The dermatologist should submit a biopsy sample to a certified dermatopathology laboratory or to a pathologist experienced in reviewing skin specimens. The site should provide the dermatologist with all relevant case history, including copies of clinical photographs and laboratory test results.

### 14.4.13 Other

The following AEs, regardless of grade, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

– Myocarditis
– Pericarditis
– Pancreatitis
– Any additional Grade 3 or higher event which the physician considers to be immune related
All attempts should be made to rule out other causes. Therapeutic specialists should be consulted as appropriate. However, the AE should be reported regardless of etiology.

**Course of Action**
Grade 2 events or Grade 1 events that do not improve with symptomatic treatment:

– Withhold pembrolizumab.
– Systemic corticosteroids may be indicated.
– Consider biopsy for confirmation of diagnosis.
– If pembrolizumab held and corticosteroid required, manage as per grade 3 below.

Grade 3 events:

– Hold pembrolizumab
– Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day.
– When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
– Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks. Otherwise, pembrolizumab treatment may be restarted and the dose modified as specified in the protocol

Grade 4 events:

– Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day.
– Discontinue pembrolizumab

### 14.4.14 Follow-up to Resolution

Subjects should be followed to resolution. The Adverse Experience eCRF should be updated with

information regarding duration and clinical course of the event. Information obtained from the consulting specialist, including diagnosis, should be recorded in the appropriate AE fields. Free-text fields should be used to record narrative information:

– Clinical course of the event
– Course of treatment
– Evidence supporting recovery
– Follow-up to the clinical course

Any treatments administered for the event should also be entered in the Concomitant Medication eCRF.

**14.4.15 ECI APPENDIX 1 – Past Medical History Related to Dermatologic Event**

**Past Medical History:**
Any preexisting conditions not previously reported (e.g., drug allergy) should be entered into the Medical History eCRF.

1. Does the subject have any allergies? □ Yes □ No

If yes, please obtain the following information:

a. Any allergy to drugs (including topical or ophthalmic drugs)? □ Yes □ No

List the drug name(s) and describe the type of allergic response (e.g. rash, anaphylaxis, etc):
_____
_____

b. Any allergy to external agents, such as laundry detergents, soaps, poison ivy, nickel, etc.? □ Yes □ No

Describe the agent and type of allergic response: _____
_____

c. Any allergy to food? □ Yes □ No

Describe the food and type of allergic response: _____
_____

d. Any allergy to animals, insects? □ Yes □ No

Describe the allergen and type of allergic response: _____
_____

e. Any other allergy? □ Yes □ No

Describe the allergen and type of allergic response: _____
_____

2. Does the subject have any other history of skin reactions, skin eruptions, or rashes? □ Yes □ No

If so what kind? _____

3. Has the subject ever been treated for a skin condition? □ Yes □ No

If so what kind? _____

4. Is the current finding similar to a past experience? □ Yes □ No

### 14.4.16 ECI APPENDIX 2 – Presentation of the Dermatologic Event

**Presentation of the event:**
Collect information on clinical presentation and potential contributing factors. Key information should be summarized and entered on the Adverse Experience eCRF. Any treatments administered should be entered on the Concomitant Medication eCRF.

1. What is the onset time of the skin reaction, skin eruption, or rash relative to dose of study drug?

_____

2. Has the subject contacted any known allergens? □ Yes □ No

If so what kind? _____

3. Has the subject contacted new, special, or unusual substances (e.g., new laundry detergents, soap, personal care product, poison ivy, etc.)? □ Yes □ No

If so what kind? _____

4. Has the subject taken any other medication (over the counter, prescription, vitamins, and supplement)? □ Yes □ No

If so what kind? _____

5. Has the subject consumed unaccustomed, special or unusual foods? □ Yes □ No

If so what kind? _____

6. Does the subject have or had in the last few days any illness? □ Yes □ No

If so what kind? _____

7. Has the subject come into contact with any family or house members who are ill? □ Yes □ No

If so who and what? _____

8. Has the subject recently been near children who have a skin reaction, skin eruption, or rash (e.g. *Molluscum Contagiosum*)? □ Yes □ No

9. Has the subject had recent sun exposure? □ Yes □ No

10. For the current rash, have there been any systemic clinical signs? □ Yes □ No

If so what kind? _____

i. Anaphylaxis? □ Yes □ No
ii. Signs of hypotension? □ Yes □ No
iii. Signs of dyspnea? □ Yes □ No
iv. Fever, night sweats, chills? □ Yes □ No

11. For the current rash, has the subject needed subcutaneous epinephrine or other systemic catecholamine therapy? □ Yes □ No

If so what kind? _____

12. For the current rash, has the subject used any other medication, such as inhaled bronchodilators, antihistaminic medication, topical corticosteroid, and/or systemic corticosteroid? □ Yes □ No

List medication(s) and dose(s): _____
_____

13. Is the rash pruritic (itchy)? □ Yes □ No

### 14.4.17 ECI APPENDIX 3 – Focused Skin Examination

**Focused Skin Examination:**
Key information should be summarized and entered on the Adverse Experience eCRF.

Primary Skin Lesions Description
Color: _____

General description:

_____
_____

Describe the distribution of skin reaction, skin eruption, or rash on the body:

_____
_____

Is skin reaction, skin eruption, or rash resolving or continuing to spread?

_____
_____

Any associated signs on physical examination?

_____

## 14.4.18 Appendix 4- Low Glycemic Meals

### The average Glycemic Index of common foods derived from multiple studies by different laboratories

Foods are categorized as having a low-glycemic index if the glucose reference index is ≤ 55. High-Glycemic Index foods have a glucose reference index >55. The summary table below contains glucose reference for common foods.

| High-carbohydrate foods | | Breakfast cereals | | Fruit and fruit products | | Vegetables | |
|---|---|---|---|---|---|---|---|
| White wheat bread* | 75 ± 2 | Cornflakes | 81 ± 6 | Apple, raw† | 36 ± 2 | Potato, boiled | 78 ± 4 |
| Whole wheat/whole meal bread | 74 ± 2 | Wheat flake biscuits | 69 ± 2 | Orange, raw† | 43 ± 3 | Potato, instant mash | 87 ± 3 |
| Specialty grain bread | 53 ± 2 | Porridge, rolled oats | 55 ± 2 | Banana, raw† | 51 ± 3 | Potato, french fries | 63 ± 5 |
| Unleavened wheat bread | 70 ± 5 | Instant oat porridge | 79 ± 3 | Pineapple, raw | 59 ± 8 | Carrots, boiled | 39 ± 4 |
| Wheat roti | 62 ± 3 | Rice porridge/congee | 78 ± 9 | Mango, raw† | 51 ± 5 | Sweet potato, boiled | 63 ± 6 |
| Chapatti | 52 ± 4 | Millet porridge | 67 ± 5 | Watermelon, raw | 76 ± 4 | Pumpkin, boiled | 64 ± 7 |
| Corn tortilla | 46 ± 4 | Muesli | 57 ± 2 | Dates, raw | 42 ± 4 | Plantain/green banana | 55 ± 6 |
| White rice, boiled* | 73 ± 4 | | | Peaches, canned† | 43 ± 5 | Taro, boiled | 53 ± 2 |
| Brown rice, boiled | 68 ± 4 | | | Strawberry jam/jelly | 49 ± 3 | Vegetable soup | 48 ± 5 |
| Barley | 28 ± 2 | | | Apple juice | 41 ± 2 | | |
| Sweet corn | 52 ± 5 | | | Orange juice | 50 ± 2 | | |
| Spaghetti, white | 49 ± 2 | | | | | | |
| Spaghetti, whole meal | 48 ± 5 | | | | | | |
| Rice noodles† | 53 ± 7 | | | | | | |
| Udon noodles | 55 ± 7 | | | | | | |
| Couscous† | 65 ± 4 | | | | | | |

| Dairy products and alternatives | | Legumes | | Snack products | | Sugars | |
|---|---|---|---|---|---|---|---|
| Milk, full fat | 39 ± 3 | Chickpeas | 28 ± 9 | Chocolate | 40 ± 3 | Fructose | 15 ± 4 |
| Milk, skim | 37 ± 4 | Kidney beans | 24 ± 4 | Popcorn | 65 ± 5 | Sucrose | 65 ± 4 |
| Ice cream | 51 ± 3 | Lentils | 32 ± 5 | Potato crisps | 56 ± 3 | Glucose | 103 ± 3 |
| Yogurt, fruit | 41 ± 2 | Soya beans | 16 ± 1 | Soft drink/soda | 59 ± 3 | Honey | 61 ± 3 |
| Soy milk | 34 ± 4 | | | Rice crackers/crisps | 87 ± 2 | | |
| Rice milk | 86 ± 7 | | | | | | |

Data are means ± SEM. *Low-GI varieties were also identified. †Average of all available data.

### 14.4.19 Appendix 5- prohibited medications

**Table: List of prohibited medications during the study**

| Category | Drug name |
|---|---|
| Strong CYP3A Inhibitors | Voriconazole, boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, eltegravir/ritonavir, grapefruit juice, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, |
| Moderate CYP3A Inhibitors | Grapefruit, grapefruit hybrids, pummelos, star-fruit, and Seville oranges (citrus paradisi fruit juice) |
| Strong CYP3A Inducers | Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum) |
| CYP3A Substrates with NTI | Alfentanil, apixaban (doses >2.5 mg only), aprepitant, astemizole, cisapride, cyclosporine, diergotamine, dihydroergotamine, ergotamine, fentanyl, lovastatin, nicardipine, nisoldipine, pimozide, quinidine, rivaroxaban, simvastatin, sirolimus, tacrolimus, terfenadine, thioridazine, |
| Other Investigational and Antineoplastic Therapies | Other investigational therapies must not be used while the patient is on the study. Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study treatments must not be given to patients while the patient is on the study medication. If such agents are required for a patient then the patient must be discontinued from the study. |
| Herbal Preparations/ Medications | Herbal preparations/medications are prohibited throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), ginkgo biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug |