SPONSOR: Diwakar Davar

TITLE: Phase II neoadjuvant study of PD-1 inhibitor pembrolizumab in PD-1 naive cutaneous squamous cell carcinoma (cSCC)

IND NUMBER: IND exempt

NCT NUMBER: NCT04808999

Principal Investigators:

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1.0 TRIAL SUMMARY

Abbreviated Title	Phase II neoadjuvant study of PD-1 inhibitor pembrolizumab in PD-1 naive cutaneous squamous cell carcinoma (cSCC) (Neo-SCC)
Trial Phase	Phase II
Clinical Indication	High-risk resectable cutaneous squamous cell carcinoma (cSCC)
Trial Type	Neoadjuvant
Type of control	Non-randomized
Route of administration	IV
Trial Blinding	N/A
Treatment Groups	Single
Number of trial participants	30
Estimated enrollment period	24 months
Estimated duration of trial	84 (24 months enrollment + 60 months followup) months
Duration of Participation	12 months
Estimated average length of treatment per patient	12 months

2.0 TRIAL DESIGN

2.1 Trial Design

This is a phase II single-arm two-stage neoadjuvant study of pembrolizumab in patients with PD-1 naïve high-risk resectable cutaneous squamous cell carcinoma (cSCC). Each patient will be treated over a 52-week period. Patients with high-risk resectable cSCC who have yet to undergo definitive surgery are eligible to enroll. Patients with nodal and/or in-transit relapse including those who have received prior adjuvant RT are eligible to enroll. However, patients who have received either nivolumab or pembrolizumab or other anti-PD-(L)1 therapy are NOT eligible.

The study schema is outlined in the Figure below (see **Figure 2.2-1**). Suitable patients will be identified pre-operatively. Patients will undergo a 28-day screening evaluation consisting of systemic staging scans, tumor biopsy, and blood studies to confirm suitability. Once enrolled, patients will receive pembrolizumab peri-operatively for 6 weeks (200mg Q3W; 2 cycles) prior to definitive surgery (**Neoadjuvant Phase**). Following peri-operative therapy, patients will undergo restaging scans and surgical evaluation followed by definitive surgical resection (**Surgical Phase**).

Post-operatively, patients will receive 15 further cycles of pembrolizumab over a 45-week period (200mg Q3W) (**Adjuvant Phase**). In the post-operative period, if patients are deemed eligible for RT, this will be administered concurrently with pembrolizumab. The total duration of pembrolizumab therapy is 1 year (52 weeks).

2.2 Trial Schema

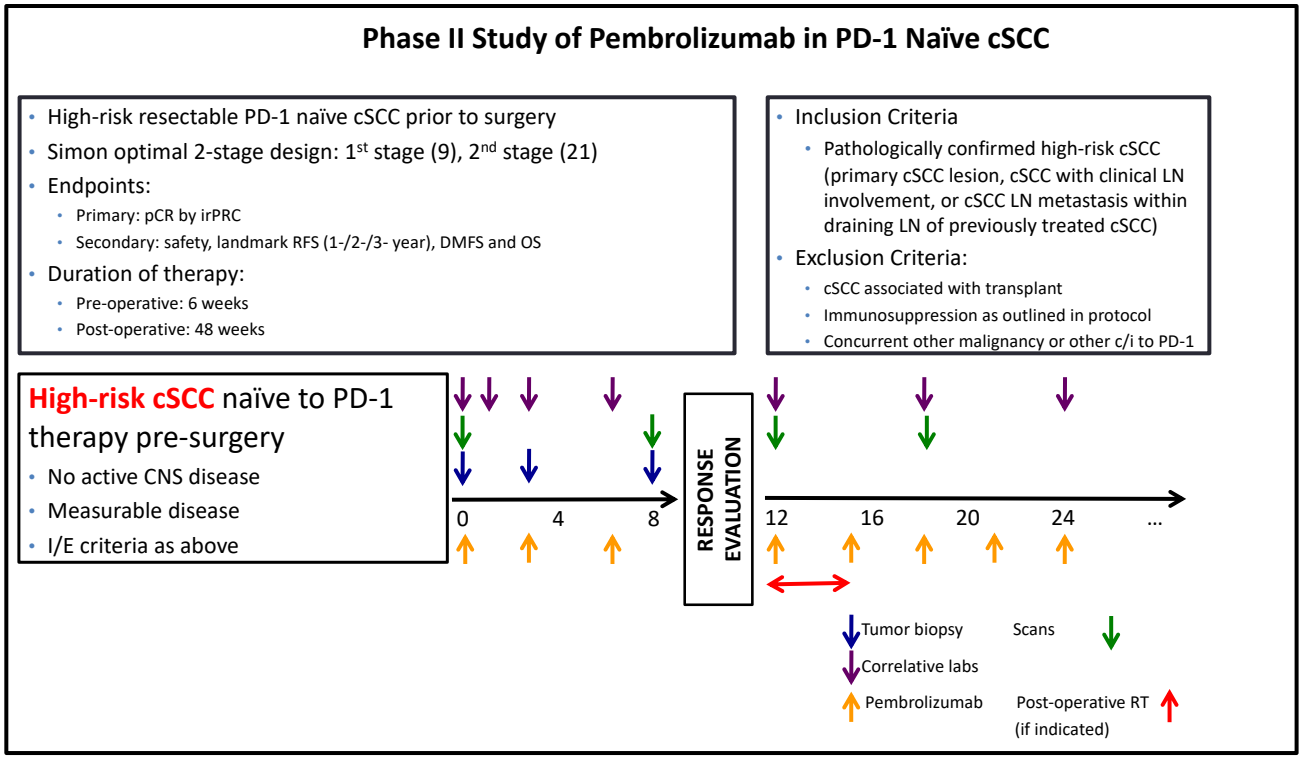


Figure 2.2-1: Trial Schema

2.1 Trial Flow Chart

Trial Period		**Neoadjuvant Phase[B]**		**Surgical Phase[C]**		**Adjuvant Phase[D]**					**Post-Treatment[F]**	
Treatment Cycle/Title:	**Screening Phase[A]**	**1**	**2**	**Surgical Re-assessment**	**Definitive Surgery**	**1**	**2**	**3**	**4+**	**End of Treatment[E]**	**30-day Safety Follow-up**	**Post-Treatment Surveillance**
Scheduling Window (Days):	-28 to -1	± 3	± 3	± 7	± 7	± 3				± 7	± 7	± 7-14
Administrative Procedures												
Informed Consent	X											
Inclusion/Exclusion Criteria	X											
Demographics and Medical History	X											
Prior and Concomitant Medication Review	X	X	X			X	X	X	X	X	X	X
Pembrolizumab Administration[G]		X	X			X	X	X	X			
Adjuvant radiotherapy[H]						X	X					
Clinical Procedures/Assessments												
Surgical Assessment[I]	X			X								

Radiation Oncology Assessment[H]				X								
Full Physical Examination[J]	X	X	X	X		X	X	X	X	X	X	X
Laboratory Procedures and Assessments												
Pregnancy Test – Urine or Serum β-HCG[K]	X											
Clinical laboratory tests[L]	X	X	X			X	X	X	X	X		X
Imaging Assessments[M]	X			X			X			X (q9)		X
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood												
Pre-treatment tumor biopsy[N]	X											
Surgical specimen[N]					X							
Correlative labs[O]	X	X	X	X		X		X	X (q6)	X		
Stool sampling[P]		X		X		X			X (q12)			
DHQ-3[Q]		X										
Post-progression biopsy[R]										X		
Adverse Event Monitoring												
AE monitoring	Assessed continually from ICF through + 30-day Safety Follow-up											
Concomitant medications		Assessed continually from C1D1 pembrolizumab through + 30-day Safety Follow-up										

Study Calendar Notes:

[A]Screening Phase
- Commences upon signing of ICF and lasts 28 days. During this period, patients must undergo all study-specific assessments as delineated above including staging scans, biopsy, assessments by Medical Oncology, Surgical Oncology and Radiation Oncology.

[B]Neoadjuvant Phase
- Commences following **Screening Phase** and lasts 6 weeks. During this Phase, patients receive 2 cycles of pembrolizumab.

[C]Surgical Phase
- Commences following **Neoadjuvant Phase** and lasts 2-4 weeks. During this period, patients undergo restaging scans, and other study-specific assessments as delineated above including definitive surgical resection.

[D]Adjuvant Phase
- Commences following **Neoadjuvant Phase** and lasts 48 weeks.
- During this period, patients undergo RT (if applicable) and receive further pembrolizumab to complete 45 weeks of therapy. Patients also undergo restaging scans, and other study-specific assessments as delineated above including definitive surgical resection.

[E]End-of-treatment (EOT) assessments.
- EOT will be performed within 7 days following removal of subject from treatment.
- Removal of a subject from treatment is defined as the time in which the Investigator decides to discontinue pembrolizumab treatment for a subject for reasons including unacceptable toxicity and/or disease progression.
- Management of patients who develop unacceptable toxicity is defined in **Section 5.2.2. and Table 5.2.2-1.**
- Patients who progress during this period should undergo a Post-progression biopsy.

[F]Post-Treatment follow up including **30-day Safety Follow-up** and **Post-Treatment Surveillance**.
- **30-day Safety Follow-up** begins +30 days following completion of Cycle 15 **Adjuvant Phase**.
    - Procedures to be followed during this phase are outlined in **Section 6.1.5.3.1** and will include a visit, labs (CBC, CMP, LDH, TSH, free T4) and any other studies deemed necessary at the discretion of the treating physicians and according to established Standard of Care.
- **Post-Treatment Surveillance** begins upon completion of **30-day Safety Follow-up.**
    - Procedures to be followed during this phase are outlined in **Section 6.1.5.3.2** and will include imaging (contrast enhanced CT or MRI), labs (CBC, CMP, LDH, TSH, free T4) and any other studied deemed necessary at the discretion of the treating physicians and according to established Standard of Care.

[G]Pembrolizumab is dosed 200mg Q3W during Neoadjuvant and Adjuvant Phases.
- During the **Neoadjuvant** and **Adjuvant Phases** of this study, patients will receive 200mg Q3W on D1 of each cycle for a total of 2 cycles (Neoadjuvant Phase) and 15 cycles (**Adjuvant Phase**).
- There is a window of +/- 3 days for drug administration.
- Missed cycles during the **Neoadjuvant Phase** will not be made up. Missed cycles in the **Adjuvant Phase** will be made up.

[H]Radiation therapy guidelines
- Radiation Oncology assessment should be made during Surgical Re-assessment.
- Radiation therapy will commence post-surgery following wound healing per the direction of the treating Radiation Oncologist. Every effort should be made to begin RT within 4 weeks of completion of surgery.
- Radiation therapy will follow guidelines as elaborated upon in **Section 5.6**.
- Radiation therapy may be omitted in patients who attain a pathologic complete response as delineated in n **Section 5.6** at the discretion of the treating Investigator, Surgical Oncologist, Radiation Oncologist and Principal Investigator.

[I]Surgical Assessment
- Assessment of planned resectability must be made during **Screening**.

- Planned surgery after **Neoadjuvant Phase** must be with treating surgeon (Surgical Oncologist; ENT Surgeon; Orthopedic Oncologist; Mohs Surgeon) who initially made determination of planned resectability and will follow guidelines as elaborated upon in **Sections 5.5.1** to **5.5.3**.

[J]Full physical exam

- Full physical exams will be conducted at **Screening**, each treatment visit, EOT, and during Post-Treatment Surveillance.
- Full physical exams should include assessment of ECOG performance status and weight.
- Height will be recorded at **Screening** only.

[K]Pregnancy test

- Pregnancy testing should be performed in women of childbearing potential and at **Screening** only.

[L]Clinical laboratory tests

- Laboratory tests to be obtained are delineated in **Table 6.1.3-1.**
- Thyroid function and urinalysis will only obtained at **Screening** and every 2nd treatment.
- Infectious serology will only be obtained at **Screening**.

[M]Imaging assessments to assess tumor status will be obtained at **Screening** (baseline value should be performed ≤4 weeks prior to first pembrolizumab dose).

- **Screening**:
  - Scans should be performed ≤4 weeks prior to first pembrolizumab dose.
- **Neoadjuvant Phase**:
  - Contrast-enhanced CT scans should be repeated prior to surgery at week 7 as delineated in **Section 6.1.2.5.1.**
- **Adjuvant Phase:**
  - During Adjuvant Phase, contrast-enhanced CT scans will be repeated every 9 weeks starting with Cycle 2 (or approximately 9 weeks after pre-surgical scan) as delineated in **Section 6.1.2.5.2.**
  - Frequency of imaging assessments in patients who complete therapy and transition to **Post-Treatment Surveillance** is delineated in **Section 6.1.5.3.2.**

[N]Tumor biopsy and surgical specimen handling

- Pre-treatment tumor biopsy:
  - Pre-treatment tumor biopsy is mandatory.
  - Tumor biopsy should be obtained via one of the following techniques: core biopsy (preferred; **minimum 6 cores**, **16G or 18G**), punch biopsy or surgical biopsy.
- Surgical specimen
  - Processing of surgical specimen is detailed in **Section 6.1.2.5. and Appendix 7**.

[O]Correlative blood samples are to be collected at the following times:

- During **Screening,** prior to administration of C1D1 and C2D1 doses (**Neoadjuvant Phase**); Surgical re-assessment (**Surgical Phase**); and every 6 weeks starting with C1D1 (**Adjuvant Phase**) and **EOT.**
- K_2 EDTA sample to be obtained at **Screening** only.

[P]Stool sampling will be performed at C1D1 (**Neoadjuvant Phase**); Surgical re-assessment (**Surgical Phase**); and every 12 weeks starting with C1D1 (**Adjuvant Phase**).

[Q]Dietary history questionnaire will be performed concordantly with stool sampling at C1D1 only.

- Dietary questionnaire is detailed in **Appendix 6**.

[R]Post-progression biopsy

- This is optional but preferred in patients in whom progression is confirmed at EOT. Tumor biopsy should be obtained via one of the following techniques: core biopsy (preferred; **minimum 6 cores**, **16G or 18G**), punch biopsy or surgical biopsy.

3.0 OBJECTIVE(S), HYPOTHESIS(ES), AND ENDPOINT(S)

3.1 Primary Objective(s), Hypothesis(es), and Endpoint(s)

(1) **Objective:** To establish the proportion of patients with pathologic complete response [(pCR, 0% residual viable tumor (RVT)] of neoadjuvant pembrolizumab in high-risk resectable cSCC.

Hypothesis: That neoadjuvant pembrolizumab produces pCR in high-risk resectable cSCC.

Primary Endpoint: pCR proportion as assessed using immune related response criteria.[1-3]

3.2 Secondary Objective(s), Hypothesis(es), and Endpoint(s)

(1) **Objective:** To describe spectrum of pathologic response in high-risk resectable cSCC treated with neoadjuvant pembrolizumab.

Hypothesis: That neoadjuvant pembrolizumab produces a spectrum of pathologic response in high-risk resectable cSCC.

Key Secondary Endpoint: Pathologic responses (major pathologic response – <0 to ≤10% RVT; partial pathologic response – <10 to ≤50% RVT) as assessed using immune related response criteria.[1-3]

(2) **Objective:** To evaluate landmark 1-year recurrence-free survival (RFS) in cSCC patients receiving neoadjuvant and adjuvant pembrolizumab.

Hypothesis: That neoadjuvant and adjuvant pembrolizumab improves landmark 1-year RFS in cSCC patients receiving neoadjuvant and adjuvant pembrolizumab.

Key Secondary Endpoint: Landmark 1-year RFS.

(3) **Objective:** To evaluate median RFS, DMFS and OS; landmark 6-month, 2-year and 3-year RFS and landmark 1-year and 2-year OS in cSCC patients receiving neoadjuvant and adjuvant pembrolizumab.

Hypothesis: That neoadjuvant and adjuvant pembrolizumab improves median RFS and OS; landmark 6-month, 2-year and 3-year RFS and landmark 1-year and 2-year OS in cSCC patients receiving neoadjuvant and adjuvant pembrolizumab.

Secondary Endpoint: Median RFS; median OS; landmark 6-month, 2-year and 3-year RFS; landmark 1-year and 2-year OS.

3.3 Exploratory Objective(s), Hypothesis(es), and Endpoint(s)

(1) **Objective:** To evaluate pre- and on- treatment increases in CD8 T cell density intra-tumorally.

Hypothesis: That cSCC patients responding to neoadjuvant pembrolizumab demonstrate on-treatment increases in CD8 T cell density.

Exploratory endpoint: CD8 TIL at post- vs. pre- treatment samples

(2) **Objective:** To evaluate immunophenotypic parameters in PBMC and TIL by multi-parameter flow cytometry.

Hypothesis: That cSCC patients responding to neoadjuvant pembrolizumab demonstrate evidence of immune activation in tumor tissue, blood, and plasma by multiparameter flow cytometry, transcriptomic, genomic and cytokine analyses.

Exploratory Endpoint: Immune activation in tumor tissue, blood, and plasma by multiparameter flow cytometry, transcriptomic, genomic and cytokine analyses.

(3) **Objective:** To evaluate the incidence of secondary cutaneous and non-cutaneous cancers in cSCC patients treated with neoadjuvant pembrolizumab.

Hypothesis: That cSCC patients treated with neoadjuvant pembrolizumab demonstrate reduced incidence of secondary cutaneous and non-cutaneous cancers.

Endpoint: Incidence of secondary cutaneous and non-cutaneous cancers.

4.0 BACKGROUND & RATIONALE

4.1 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T cell. For more details on specific indications refer to the Investigator brochure.

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades.[4] Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma.[5-7]

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 immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2).[8,9]

The structure of murine PD-1 has been resolved.[10] PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail 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, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade.[9,11-13] The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins.[14,15]

PD-1 binds to PD-L1 (B7-H1)[16,17] and PD-L2 (B7-DC).[18,19] PD-1 negatively regulates T cell functions through the engagement of PD-L1, which is expressed by a wide variety of tissues.[20,21] PD-L1 is also expressed by human tumors, including melanoma, either constitutively or after treatment with IFN-α. In mice, LCMV-specific CD8+ T-cells exhibit a diminished capability to produce cytokines, lyse infected cells and proliferate in a progressive and hierarchical fashion.[22] These "exhausted" T-cells up-regulate PD-1, and PD-1/PD-L1 blockade leads to increased cytokine production and proliferation, resulting in a significant reduction of the viral load.[22] We have previously shown that the large majority of tumor antigen-specific CD8+ T cells upregulate PD-1 expression, which appears to be associated with T cell exhaustion/dysfunction in animals and humans.[23,24] We observed that PD-1 upregulation on spontaneous tumor antigen-specific CD8+ T cells occurs along with T cell activation and is not directly associated with an inability to produce cytokines *ex vivo* upon stimulation with cognate antigen.[24] Blockade of the PD-1/ programmed death ligand 1 (PD-L1) pathway in combination with prolonged antigen stimulation with PD-L1+ antigen-presenting cells or melanoma cells augmented the frequencies of cytokine-producing, proliferating and total tumor antigen-specific NY-ESO-1 CD8+ T cells.[24]

PD-1/PD-L1 blockade is associated with improved response and survival rates in the setting of advanced cancer in multiple cutaneous malignancies including melanoma,[25-29] and cutaneous squamous cell carcinoma (cSCC).[30-33]

4.1.2 Preclinical and Clinical Trial Data

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

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Population

cSCC has several hallmarks of a tumor that is potentially sensitive to PD-1/PD-L1 blockade including: hallmarks of UV-mediated skin damage as characterized by presence of C>T transitions;[34] a very high mutation burden (30-60 per Mb; compared to 13 per Mb in melanoma); PD-L1 expression by primary and metastatic tumors;[35] and presence of CD8+ T cells in both pre-cancerous lesions and invasive cSCC.[36]

In patients with advanced unresectable or locally advanced (LA) cSCC, PD-1 blockade is efficacious with response rates of 44-50% with cemiplimab[31,37] and 34-42% with pembrolizumab.[32,33] Specifically, in the CARSKIN trial, an open-label, multicenter phase II study that evaluated pembrolizumab in immunocompetent unresectable cSCC, authors reported overall response rate (ORR) of 42% in 57 evaluable patients.[32] Separately, in KEYNOTE-629, an open-label phase II study of immunocompetent unresectable and locally advanced (LA) cSCC, authors reported overall response rate (ORR) of 34% in 70 evaluable patients.[33] In patients with unresectable LA cSCC, cemiplimab produces 44% objective responses with a moderate incidence of grade 3-5 adverse events (50%).[37]

These promising results have prompted adjuvant studies of these agents in patients with high-risk resected cSCC following definitive surgery and radiation therapy (cemiplimab - NCT03969004; pembrolizumab - NCT03833167/MK-3475-630/KEYNOTE-630). In both these studies, eligible

patients have locally advanced (LA) cSCC defined as ≥T2 tumors with at ≥1 high-risk clinical and/or histologic as defined using the Brigham and Women's Hospital (BWH) system (**Appendix 1B** and **Appendix 1C**).[38]

Separately, in the setting of high-risk resectable stage III/IV disease, peri-operative cemiplimab was well-tolerated and associated with a high rate of pathological response (70%) in a small single-institution study.[39] This study included 20 patients with either stage III disease (T_3N_0Mx; $T_{1-3}N_1$) or stage IV disease ($T_4N_0M_x$; $T_{1-3}N_2M_x$; $T_{1-4}N_3M_x$), and the reported data has prompted further evaluation of peri-operative anti-PD-1 in cSCC in various schedules as summarized below.

Study Reference	Anti-PD-1	Sample Size	Primary Endpoint	Duration of "Neoadjuvant Phase"	Duration of "Adjuvant Phase"	Eligibility Criteria
NCT04154943	Cemiplimab	76	Major pathologic response rate (criteria unspecified)	12 weeks	None	Stage II-IV (M1 excluded)
NCT04632433	Cemiplimab	25	Major pathologic response rate (criteria unspecified)	6 weeks	54 weeks (18 cycles)	Stage III
NCT04315701	Cemiplimab	34	Pathologic response rate (criteria unspecified)	9-12 weeks	None	Stage II-IV (M1 excluded)
NCT04428671	Cemiplimab	20	Pathologic response rate (criteria unspecified)	9 weeks	54 weeks (18 cycles)	Stage III-IV (M1 excluded)

Of note, these studies vary considerably in design and inclusion exclusion criteria with neoadjuvant phases ranging from 6-12 weeks; inconsistent inclusion of adjuvant anti-PD-1 in the post-operative phase; variable definition of "high-risk"; and pathologic evaluation criteria. In particular, neoadjuvant anti-PD-1 therapy has not been studied in cSCC patients defined as high-risk by BWH criteria.

This is an important consideration as while both AJCC and BWH criteria have similar monotonicity and homogeneity, the BWH staging system is more distinct than AJCC 8, with a higher specificity (93%) and positive predictive value (30%) for identifying cases at risk for metastasis and death particularly in AJCC T2 and T3 tumors.[40] While AJCC 8 T2 and T3 grades have similar risks of nodal metastases (10-year cumulative incidence rates of 12% and 14%, respectively); BWH T2a tumors have a significantly lower risk of nodal metastases than BWH T2b tumors (5% vs. 24% respectively).

Hence, there is a pressing need to evaluate the impact of neoadjuvant anti-PD-1 therapy upon pathologic complete response (pCR) using validated criteria[1-3] in a biologically "high-risk" cSCC

patient population, while evaluating the impact of this upon relapse-free survival given the observations from studies of neoadjuvant anti-PD-1 therapy in melanoma wherein pathological response was associated with improved relapse-free survival (RFS).[41-44]

We therefore propose, in this study, to formally evaluate whether both biologically and clinically high-risk disease benefit from neoadjuvant anti-PD-1 therapy. We also propose to evaluate whether response to neoadjuvant anti-PD-1 therapy is associated with improved RFS; while identifying pharmacodynamic biomarkers of response to neoadjuvant anti-PD-1 therapy in blood and tumor tissue.

4.2.2 Justification for Dose

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W.[45] Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.[46] Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides

similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose.[47]

Supported by these PK characteristics and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints:

- Primary endpoint: Pathologic response rate as assessed using immune related pathologic response criteria.[1-3]
- Key secondary endpoint: Landmark 1-year RFS.
- Other secondary endpoints: Median RFS; median OS; landmark 6-month, 2-year and 3-year RFS; landmark 1-year and 2-year OS.

4.2.3.2 Planned Exploratory Biomarker Research

- Pre-treatment tumor biopsy, post-treatment surgical sample and (if applicable) post-progression biopsies
    - Immunohistochemical analyses: CD8+ TIL density, PD-L1 expression and multiplex analyses
    - T cell functional studies to assess T cell apoptosis (Annexin V) and T cell proliferation (CFSE labelling)
    - Characterization of immune cells in tumor using multiparameter flow cytometry (MFC) evaluating immune cell subsets (CD4+ T cells, CD8+ T cells, Foxp3+ Tregs, CD56+ NK cells, CD141+ DC), expression of activation markers (Ki67, GZMA, GZMB), expression of inhibitory/activating receptors (PD-1, Tim-3, TIGIT, GITR, CD226, CD137, ICOS) and expression of ligands (PD-L1, phosphatidylserine, CD112, CD155, GITR-L)
    - Characterization of immune cells in tumor using single cell transcriptomics
    - Transcriptomics and genomic analyses
- Pre- and on- treatment PBMC
    - Characterization of immune cells in peripheral blood using multiparameter flow cytometry (MFC) evaluating immune cell subsets (CD4+ T cells, CD8+ T cells, Foxp3+ Tregs, CD56+ NK cells, CD141+ DC), expression of activation markers (Ki67, GZMA, GZMB), expression of inhibitory/activating receptors (PD-1, Tim-3, TIGIT, GITR,

CD226, CD137, ICOS) and expression of ligands (PD-L1, phosphatidylserine, CD112, CD155, GITR-L)

  - Single cell transcriptomics

- Pre- and on- treatment serum samples
  - Changes in cytokine profiles.
- Stool sampling pre- and on- treatment:
  - Microbiome analysis using metagenomic and metatranscriptomic sequencing

5.0 METHODOLOGY

5.1 Study Population

5.1.1 Participant Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Male/female participants who are at least 18 years of age on the day of signing informed consent with histologically confirmed diagnosis of **high-risk localized or locooregional cSCC as defined below** may be enrolled in this study.
    a. **NOTE:** Patients are eligible for this trial either at *initial presentation* for cSCC with locally advanced and/or concurrent regional nodal metastasis; or at the *time of recurrence* with locally advanced and/or concurrent regional nodal metastasis assuming following criteria are met per the cSCC-specific AJCC UICC 8th edition staging classification (see **Appendix 1B** and **Appendix 1C**).
        i. T_2 and N_x and M_0 (tumor >2 cm and ≤4 cm in greatest dimension) **OR**;
        ii. T_3 and N_x and M_0 (tumor >4 cm or minor bone erosion or perineural invasion or deep invasion) **OR**;
            1. Deep invasion is defined as invasion beyond the subcutaneous fat or >6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumor).
            2. Perineural invasion is defined as tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in caliber, or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression.
        iii. T_4 and Nx and M_0 (tumor with gross cortical bone/marrow, skull base invasion and/or skull base foramen invasion **if deemed surgically resectable**) **OR**;
        iv. T_x and N_{1-3} and M_0 (**if deemed surgically resectable**) **OR**;
    b. NOTE:
        i. If T_2, tumors must possess **≥2 NCCN/BWH clinical or pathologic risk factor(s)** as stated below.
        ii. NCCN/BWH clinical risk factors:
            1. Tumors ≥20 mm on trunk or extremities (excluding pretibia, hands, feet, nail units, and ankles).
            2. Tumors ≥10 mm on cheeks, forehead, scalp, neck, or pretibial areas.
        iii. NCCN/BWH pathologic risk factors:
            1. Poorly defined borders.
            2. Recurrent tumors.
            3. Neurologic symptoms to suggest perineural invasion.
            4. High-risk histologic subtypes including: poorly differentiated tumor, acantholytic (adenoid), adenosquamous, desmoplastic, or metaplastic (carcinosarcomatous) subtypes (as stated in the pathology report or written documentation by Mohs surgeon).
            5. Histopathologically documented perineural, lymphatic, or vascular involvement (as stated in the pathology report or written documentation by Mohs surgeon).

c. **NOTE:** Tumors of any size on the "mask areas" of the face [central face, eyelids, eyebrows, periorbital nose, lips (cutaneous and vermilion) are not eligible.
d. **NOTE:** Tumors of any size on genitalia, hands, and feet may be eligible at the discretion of the treating surgical oncologist.
e. **NOTE:** Patients with tumors that arise in the setting of chronic inflammation (Marjolin's ulcer) such as chronic wounds and/or scars are excluded.
f. **NOTE:** Determination of surgical resectability must be made before enrollment by the treating surgical oncologist (or ENT surgeon or equivalent).

2. Male participants:
A male participant must agree to use a contraception as detailed in **Appendix 3** of this protocol during the treatment period and for at least 120 days after the last dose of study treatment and refrain from donating sperm during this period.

3. Female participants:

A female participant is eligible to participate if she is not pregnant (see **Appendix 3**), not breastfeeding, and at least one of the following conditions applies:

a. Not a woman of childbearing potential (WOCBP) as defined in **Appendix 3**
OR
b. A WOCBP who agrees to follow the contraceptive guidance in **Appendix 3** during the treatment period and for at least 120 days after the last dose of study treatment.

4. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.

5. Have at least a single site of measurable disease based on RECIST 1.1. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

6. Willing to undergo pre-treatment biopsies.
   a. Prior archival tumor tissue sample are not permitted.
   b. Minimum tissue requirements: **core** (**16G or 18G, 6 cores; preferred**), punch or excisional biopsy of a tumor lesion that has not been previously irradiated.

7. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.

   a. ECOG evaluation should be performed at **Screening** and repeated on **Cycle 1 Day 1**.

8. Have adequate organ function as defined in the **Table 5.1.1-1** (see **Table 5.1.1-1**). Specimens must be collected within 10 days prior to the start of study treatment.

Table 5.1.1-1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

[b] Creatinine clearance (CrCl) should be calculated per institutional standard.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

5.1.2 Participant Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Diagnosis of immunodeficiency, immunosuppression and/or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
2. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).

3. Prior chemotherapy, targeted small molecule 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.
4. Has received prior radiotherapy within 2 weeks of start of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 2-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.
5. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study intervention.
6. A WOCBP who has a positive urine pregnancy test at **Screening** (see **Appendix 3**). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
7. Has received a live vaccine within 30 days prior to the first dose of study drug.
    a. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine.
    b. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
8. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 14 days prior to the first dose of study drug.
9. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs).

    a. Note: Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment and is allowed.

10. Concurrent non-hematologic malignancy other than cSCC within 1 year of data of first planned dose of therapy except for tumors with a negligible risk of metastasis and/or death as defined below:

    a. Adequately treated non-invasive malignancies including but not limited to melanoma in situ (MIS), BCC, CIS of cervix, or DCIS of breast may be enrolled.

        i. Patients with concurrent secondary malignancies may be enrolled at the discretion of the treating investigator if the secondary malignancy has been adequately treated and/or the management plan is active surveillance.

    b. Low-risk early-stage prostate adenocarcinoma (T1-T2a N0 M0 and Gleason score ≤6 and PSA ≤10 ng/mL) for which the management plan is active surveillance, or prostate adenocarcinoma with biochemical-only recurrence with documented PSA doubling time of > 12 months for which the management plan is active surveillance may be enrolled.

c. Indolent hematologic malignancies for which the management plan is active surveillance including but not limited to CLL/indolent lymphoma may be enrolled.

    i. Patients with high-risk hematologic malignancies (CML, ALL, AML, Hodgkin's or non-Hodgkin's lymphoma) are excluded even if the management plan is active surveillance.

11. Has known active CNS metastases and/or carcinomatous meningitis.

    a. Note: Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e. without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during **Screening**), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study intervention.

12. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

13. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

14. Has an active infection requiring systemic therapy.

15. Has a known history of Human Immunodeficiency Virus (HIV) infection.

16. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) and/or known active Hepatitis C virus (defined as anti-HCV reactive) infection.

    a. Patients with treated Hepatitis B/C with no evidence of active infection may be enrolled.

17. Has a known history of active TB (Bacillus Tuberculosis).

18. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

19. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

20. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the **Screening** visit through 120 days after the last dose of trial treatment.

21. Has had an allogenic tissue/solid organ transplant.

5.1.3 Lifestyle Considerations

5.1.3.1 Meals and Dietary Restrictions

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

5.1.3.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Refer to **Appendix 3** for approved methods of contraception.

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

5.1.4 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study intervention(s). The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck within 2 working days if the outcome is a serious adverse experience (e.g. death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to Merck and followed as described in Section 6.2.

5.1.5 Use in Nursing Women

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

5.2 Trial Intervention(s)

The intervention(s) to be used in this trial is outlined below in **Table**

Table 5.2-1 Trial Intervention

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	**Neoadjuvant Phase:** Day 1 of each 3-week cycle, 2 cycles	Experimental
Pembrolizumab	200 mg	Q3W	IV infusion	**Adjuvant Phase:** Day 1 of each 3-week cycle, 15 cycles	Experimental

Trial intervention should begin within 28 days of enrollment.

5.2.1 Timing of Dose Administration

Trial interventions 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 interventions may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial interventions will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30-minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The **Pharmacy Manual** contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

5.2.2 Dose modification and toxicity management <u>for immune-related AEs associated with pembrolizumab</u>

AEs associated with pembrolizumab exposure may represent an immunologic aetiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in **Table 5.2.2-1** (see **Table 5.2.2-1**).

Table 5.2.2-1 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:

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

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold		• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus)

	Grade 4 or recurrent Grade 3	Permanently discontinue	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	• Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 - 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold		• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)

	Grade 3 or 4	Withhold or permanently discontinue [d]	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3, or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 – 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Intolerable/persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue		

		based on the event [e].		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

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

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

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

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM)

[e] Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis.

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

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in **Table 5.2.2.-2**.

Table 5.2.2.-2 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug intervention**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of _____ with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion);	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs	No subsequent dosing

recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug intervention.**	
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Principal Investigator. The reason for interruption should be documented in the patient's study record.

5.3 Randomization or Treatment Allocation

Not applicable.

5.4 Stratification

Not applicable.

5.5 Surgical Considerations

The members of the treatment team will make every effort to comply with the surgical procedures within the time windows allowed in this study protocol. However, under certain circumstances and as discussed between the sub-investigator(s) and the principal investigator, an alteration in the surgical schedule/timing is allowed. These include (but are not limited to) the following:

- A 4-week window between the baseline biopsy and the first dose of pembrolizumab is allowed.
- The definitive surgery should follow the guidelines in **Sections 5.5.1** to **5.5.3** as clinically indicated. The definitive surgery may be divided into more than one surgical procedure, scheduled at different time points as clinically/surgically indicated. Under certain circumstances, the definitive surgery may be done earlier if pembrolizumab was discontinued due to adverse events or other reasons. Tissue from any of these surgical procedures may be banked under this protocol following the same protocol procedures for tissue handling and banking. The tissue for banking

may be digested, frozen or handled in another alternative method as discussed with the investigator.

- If for some reason, the baseline biopsy or definitive surgery could not be completed due to unanticipated factors such as patient refusal, this will be documented.

- NOTE:

    - The surgical guidelines are general and may be followed or modified at the discretion of the expert surgical oncologist on the case as clinically indicated and depending on the specifics of the individual surgical case.

    - For the baseline biopsy required on this study, patients will undergo a core needle, punch biopsy, or other technique at the discretion of the sub-investigator/investigator. The choice of biopsy technique will be at the discretion of the surgeon or medical oncologist.

5.5.1 Primary excision for locally advanced cSCC

All patients with initial presentation of ≥2 T2 cSCC will be treated by wide excision of the primary. Definitive surgery will include wide excision of the primary +/- sentinel lymph node assessment (latter if deemed necessary). For patients with known primary cSCC and no history of wide local excision (or Mohs surgery) of that primary lesion, an adequate wide excision of the primary lesion (minimum margin 1 cm) is recommended. The wide local excision will be done at the time of sentinel lymph node assessment or complete lymphadenectomy (latter if deemed necessary).

The specimen shall be excised to include skin and all subcutaneous tissue down to the muscular fascia. Fascia may be included at the discretion of the operating surgeon. Closure of the defect may be via primary closure, split thickness skin graft, or rotation-flap at the discretion of the surgeon. At the time of the definitive lymphadenectomy, the biopsy site will be included in the operative specimen.

5.5.2 Regional lymphadenectomy

Note: For patients undergoing sentinel node mapping and lymphoscintigraphic and dye lymphographic identification of regional nodal drainage, the minimum number of nodes may be less than the mandatory minimum numbers of: 5/groin, 10/axilla, and 15/cervical node dissection.

All patients should undergo one of the following staging lymphadenectomies, as found surgically applicable by the treating surgical oncologist. At the time of the definitive lymphadenectomy, the biopsy site will be included in the operative specimen.

Head and neck lesions:

Face, ear and anterior scalp: Modified radical neck or radical neck dissection. Parotidectomy to be included if lymphoscintogram indicates flow to the area.

Submandibular and anterior neck: Modified radical or radical neck dissection. Posterior scalp, posterior neck and uppermost trunk (areas that drain to posterior cervical triangle): Modified posterior triangle neck dissection with suboccipital nodes.

Upper extremity lesions:

Axillary node dissection to include at least 10 nodes taken from levels I and II. Level III nodes should be dissected if they are clinically involved. The pectoralis minor muscle may be divided or sacrificed at the surgeon's discretion.

Lower extremity lesions:

Superficial inguinal node dissection or deep inguinal node dissection will be performed at the discretion of the surgeon. Inguinal node dissection to include at least 5 nodes.

5.5.3 Lymphadenectomy for local recurrence

Regional node recurrences will be treated using the appropriate lymphadenectomy procedure for the anatomical site as delineated above. Whenever possible, diagnosis of regional node recurrence will be made using core biopsy technique. At the time of the definitive lymphadenectomy, the biopsy site will be included in the operative specimen.

5.6 Radiation Therapy Considerations

Since patients on study have documented high risk features for loco-regional recurrence, ***radiation therapy is recommended for all patients except for patients with pathological complete response to neoadjuvant therapy***. The necessity of postoperative radiation to the primary site and draining lymph node basin should be considered separately. Regimens, treatment fields, and dose constraints should follow NCCN and AAPM guidelines and/or institutional standard of care. Radiation therapy is recommended to commence **within 6 weeks** after surgical resection, however delays to ensure wound healing prior to RT is allowed. RT will be administered concurrently with anti-PD-1 therapy. Acceptable toxicity has been reported in multiple phase I studies of concurrent radiation administered with anti-PD-1 therapy.[48-52] Radiation therapy may be delivered either as external beam photon or electron plans or via high dose rate brachytherapy targeted to the skin surface.

Post-surgery, adjuvant RT is recommended for patients with the following tumors as assessed based on pre-operative staging using cSCC-specific AJCC UICC 8th edition staging classification:

- T2 and Nx and M0 (tumor >2 cm and ≤4 cm in greatest dimension);
- T3 and Nx and M0 (tumor >4 cm or minor bone erosion or perineural invasion or deep invasion);
- T4 and Nx and M0 (tumor with gross cortical bone/marrow, skull base invasion and/or skull base foramen invasion if deemed surgically resectable);
- Tx and N1-3 and M0 (if deemed surgically resectable);

Primary site

Recommendations for primary tumors as stated above.

In patients who achieve pCR, adjuvant RT is not recommended.

Draining nodal basin

Adjuvant RT to nodal basin is recommended in patients with node positive disease or if the draining lymph node region has not been adequately addressed by LND. For positive cervical or cervical nodes, ipsilateral at risk elective nodal irradiation should be considered. Dose painting or simultaneous integrated boost techniques could be utilized for positive margins or gross residual disease.

In patients who achieve pCR, adjuvant RT is not recommended.

Pretreatment Evaluations

If the radiation fields include head and neck cervical nodes or the parotid gland, a dental evaluation and routine prophylaxis should be performed prior to initiation of adjuvant therapy.

Dose Specifications

The prescription volume will be specified with separate primary as well as draining lymph node basin volumes, as PTVp and PTVn. Dose will be specified in Gy. Bolus should be utilized to achieve adequate skin dose and dose under bolus confirmed at least once during the first 3 fractions of treatment.

Treatment Planning/Target Volumes

Pretreatment scans should be fused with treatment planning CT as needed to delineate target volumes.

5.6.1 RT to the primary site

The recommended total prescription dose to the primary site should be 24-36 Gy in 5 fractions (5-7.0 Gy per fraction) to the planning target volume (PTVp). A minimum of 95% of the planning target volume (PTVp) should receive prescription dose. Fractions should be a minimum of 40 hrs apart for any fraction size of 5 Gy or greater. Radiation to the primary site may be delivered via photons, electrons, or HDR brachytherapy. BED equivalent BID fractionation may be utilized for HDR regimens.

While the above short course hypofractionated regimens is strongly recommended, conventionally fractionated or moderately hypofractionated RT regimens from 46-66 Gy in 20-33 fractions (2-2.5 Gy per fraction) may be administered if deemed necessary to adequately spare normal tissues.

5.6.2 RT to the draining nodal basin

The recommended total prescription dose to the nodal basin site should be 24-36 Gy in 5 fractions (5-7.0 Gy per fraction) to the planning target volume (PTVn). A minimum of 95% of the planning target volume

(PTVp) should receive prescription dose. Radiation to the primary site may be delivered via photons or electrons.

While the above short course hypofractionated regimens is strongly recommended, conventionally fractionated or moderately hypofractionated RT regimens from 46-66 Gy in 20-33 fractions (2-2.5 Gy per fraction) may be administered if deemed necessary to adequately spare normal tissues.

5.6.3 Treatment planning and target volumes

Treatment Planning/Target Volumes

Pretreatment scans should be fused with treatment planning CT as needed to delineate target volumes.

Post-neoadjuvant preoperative therapy Gross Tumor Volume (postneo-GTV) will delineated from pre-operative tumor extent, by use of pre-operative imaging, operative and pathologic reports, and/or sentinel lymph node lymphoscintigraphy, when available.

Primary Site Clinical Target Volume (CTVp)

The CTVp is defined as the postneo-GTVp and/or surgical scar with a 0.5-2.5 cm margin depending on site of primary disease as well as a 1.0-4.0cm expansion deep to the surgical bed to encompass microscopic disease. When possible, it is recommended that the margin along the skin surface be delineated with radiopaque wire at the time of simulation. The CTVp expansion needs to be trimmed away from the edges of anatomic boundaries of microscopic disease spread, including vertebral bodies, osseous structures, and organs at risk. The depth should extend to the depth of the subcutaneous fat or 1cm deeper than the distal edge of the tumor and be at least 1cm. These constraints would have to be limited anatomically for disease surrounding the eyes. The CTVp in certain instances may encompass the immediately adjacent nodal regions.

Draining Nodal Basin Clinical Target Volume (CTVn)

Head and Neck Nodal Regions

Radiation treatment field is recommended to include ipsilateral neck nodes down to the clavicle for patients at risk of spread. CTVn is to include ipsilateral parotid node for lesions of frontal, preauricular, temporal areas, auricle and cheek. CTVn is to include suboccipital nodes for primary lesions located behind the mastoid. Elective uninvolved cervical neck levels can be treated at a lower dose than involved nodal levels.

Axillary Nodal Regions

The target volume includes the full axillary, lateral subpectoral, supraclavicular and low jugular nodes, and all the incision and drain sites. All clips marking the dissected region will be included in the treatment volume. For primary lesions distal to the epitrochlear region, if SLN or LND demonstrates positive node in that region, recommended CTVn should also include the epitrochlear nodal basin with a 2-3cm distal and proximal expansion along vessels with 1-2cm radial expansion around vessels.

Inguinal/Femoral Nodal Regions

The target volume should include the inguinal nodes form the superior extent of the pubic ramus to 2 cm caudad of the inguino-femoral junction. No more than one-half of the limb volume or two-thirds of the limb circumference should be irradiated. For primary lesions distal to the popliteal region, if SLN or LND demonstrates positive node in that region, recommended CTVn should also include the popliteal nodal echelon with a 2-3cm distal and proximal expansion along vessels with 1-2cm radial expansion around vessels. For primary lesions near the ano-genital regions, CTVn may also include the external iliac region.

Planning Target Volume (PTV)

Additional margin shall be added to the CTVp and CTVn for set up error and movement. This expansion should be 0.3 to 1.0 cm and does not need to be uniform in all dimensions.

Critical Structures

Organs at risk to be contoured depends on site of primary and nodal disease. Dose constraints to uninvolved normal tissues should follow AAPM/Quantec guidelines using standard dose constraints for conventionally fractionated or 5 fraction constraints.

5.7 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 final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

5.7.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant'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 prior to the first dose of trial intervention and up to 30 days after the last dose of trial intervention should be recorded. Concomitant medications administered after 30 days after the last dose of trial intervention should be recorded for SAEs and ECIs as defined in **Section 7.2 (Safety Monitoring)**.

5.7.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. All treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

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

5.7.3 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in **Section 5.2.2** (**Table 5.2.2-1**).

Where appropriate, these guidelines include the use of oral or IV 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.

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

5.8 Participant Discontinuation Criteria

Discontinuation of study intervention does not represent withdrawal from the study.

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment.
- Confirmed radiographic disease progression outlined in **Section 7.1.2.6.**
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Unacceptable adverse experiences as described in **Section 5.2.2.**
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test.
- Noncompliance with study treatment or procedure requirements.
- Recurrent Grade 2 pneumonitis.
- The participant is lost to follow-up.
- Completion of 17 treatments with pembrolizumab.
- Administrative reasons.

5.9 Participant withdrawal From Study

A participant must be withdrawn from the study if the participant or the participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specified details regarding procedures to be performed at the time of withdrawal from the study as well as specific details regarding withdrawal from future biomedical research are outlined in **Sections 7.1.4.1** and **7.1.4.2.**

5.10 Participant Replacement Strategy

Subjects who receive at least 1 dose of pembrolizumab in the Neoadjuvant Phase are evaluable for safety. Patients who complete Neoadjuvant Phase and receive surgery will be evaluable for pathologic response rate and other efficacy endpoints. Patients who did not undergo surgery for reasons of disease progression precluding surgery (rapid disease progression) will be deemed pathologic non-responders.

If in the opinion of the treating investigator and treating surgical oncologist in consultation with Principal Investigator, subject's disease is rapidly progressing to the point that window to intervene surgically is narrowing, treatment may be discontinued to permit surgery. These patients are evaluable for pathological response rate and other efficacy endpoints. These patients are eligible to receive adjuvant RT and adjuvant pembrolizumab during Adjuvant Phase.

5.11 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 participants
4. Plans to modify or discontinue the development of the study drug.

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

6.0 TRIAL ASSESSMENTS AND PROCEDURES

6.1 Trial Procedures

- Study procedures and their timing are detailed in **Section 6.1.2. (Clinical Procedures/Assessments)** and summarized in **Section 2.1 (Trial Flow Chart)**.

- Adherence to the study design requirements, including those specified in the **Trial Flow Chart** (**Section 2.1**) is essential and required for study conduct.

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria.

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

6.1.1 Administrative and General Procedures

6.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical trial. If there are changes to a participant's status during the study (e.g. health requirements) the investigator must ensure appropriate consent is in place.

6.1.1.2 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant'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 participant before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the participant must receive the IRB/ERC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant'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 participant's dated signature or by the participant'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/ERC requirements, applicable laws and regulations and Sponsor requirements.

6.1.1.3 Inclusion/Exclusion Criteria

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

6.1.1.4 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 participant has enrolled in this study will be recorded separately and not listed as medical history.

6.1.1.5 Prior and Concomitant Medications Review

6.1.1.5.1 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 participant within 28 days before starting the trial. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

6.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the trial. In addition, new medication started during the Second Course should be recorded. All medications related to reportable SAEs and ECIs should be recorded as defined in **Section 7.2 ()**.

6.1.1.6 Disease Details and Treatments

6.1.1.6.1 Disease Details

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

6.1.1.6.2 Prior Treatment Details

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

6.1.1.6.3 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 participant 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 participant will move into survival follow-up.

6.1.1.7 Assignment of Screening Number

This will be done upon completion of ICF and patient registration in Hillman Cancer Center's Clinical Trials Management Application (CTMA).

6.1.1.8 Assignment of Randomization Number

Not applicable.

6.1.1.9 Trial Compliance (Medication/Diet/Activity/Other)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial.

6.1.2 Clinical Procedures/Assessments

6.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each participant 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 **Appendix 2**). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to **Section 7.2** for detailed information regarding the assessment and recording of AEs.

6.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during **Screening**. Clinically significant abnormal findings should be recorded as medical history.

6.1.2.3 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 2.1**). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at **Screening** only.

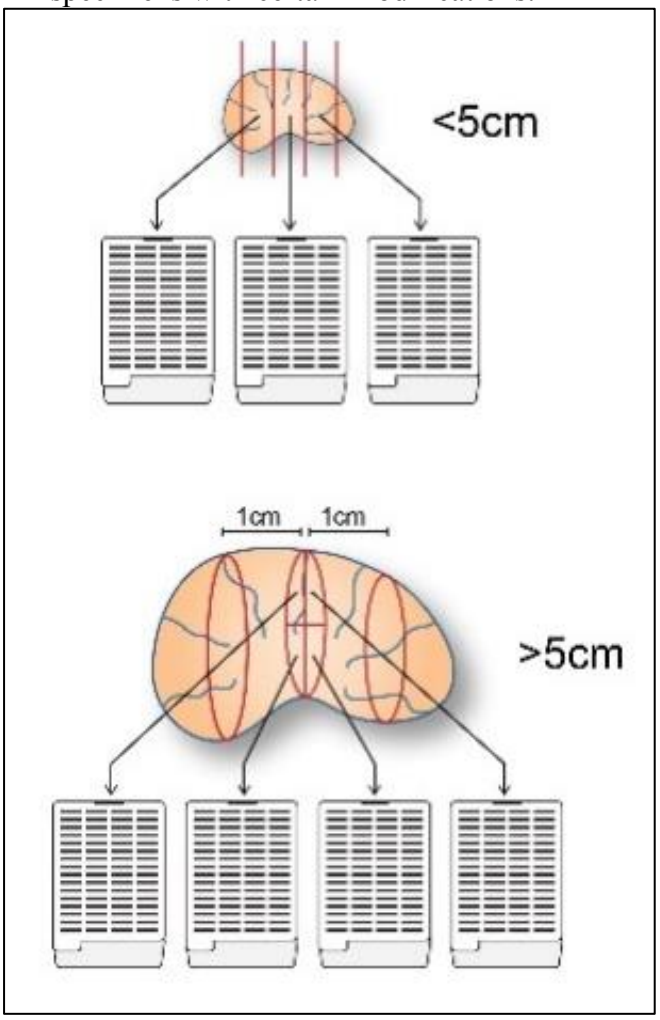
6.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see **Appendix 1A**) at **Screening**, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the **Trial Flow Chart (Section 2.1)**.

6.1.2.5 Pathology Sampling and Neoadjuvant Assessment

Pathology sampling

In order to achieve accurate and reproducible pathologic assessment in neoadjuvant treated specimens, grossing assessment and tissue submission following neoadjuvant treatment should be standardized. These recommendations will largely adhere to recommendations made by the International Neoadjuvant Melanoma Consortium (see figure below) for the evaluation of melanoma specimens as applied to cSCC specimens with certain modifications.



For LN specimens:

- If the largest grossly positive lymph node measures ≤ 5 cm in greatest dimension, then the entire lymph node should be entirely submitted at 2 mm serially sectioned intervals.
- For any grossly positive lymph node measuring > 5 cm in greatest dimension, representative sections of the largest lymph nodes may be utilized to avoid oversampling as indicated below.
- Following serial sectioning of each lymph node, for those grossly positive nodes > 5 cm, sections representing a complete cross section of the entire surface area should be submitted per 1 cm of each grossly positive lymph node.

- All lymph nodes < 5cm in specimens where the largest node(s) exceeds 5 cm should be submitted entirely.

For primary tumor specimens:

- If the largest primary tumor specimen measures ≤ 5 cm in greatest dimension, then the entire primary tumor specimen should be entirely submitted at 2 mm serially sectioned intervals.
- For any grossly positive primary tumor specimen measuring > 5 cm in greatest dimension, representative sections of the primary tumor specimen may be utilized to avoid oversampling as indicated below.
- Following serial sectioning of each lymph node, for those grossly positive nodes > 5 cm, sections representing a complete cross section of the entire surface area should be submitted per 1 cm of each grossly positive lymph node.
- All lymph nodes < 5cm in specimens where the largest node(s) exceeds 5 cm should be submitted entirely.

Neoadjuvant assessment
This will follow the guidelines laid out in **Appendix 7** (**Pathology Sampling and Response Assessment Criteria**).

The primary assessment will be the proportion of RVT as defined in **Section 7.4** and delineated in **Appendix 7.**

6.1.2.6 Tumor Imaging and Disease Assessment

6.1.2.6.1 Initial Tumor Imaging

Initial tumor imaging at **Screening** must be performed within 28 days prior to the date of allocation. The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1.

The screening images must be submitted to the central imaging vendor for retrospective review.

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within 28 days prior to the date of allocation and can be assessed by the central imaging vendor.

Brain imaging is required to rule out radiographically detectable brain metastases at the time of enrollment. Magnetic resonance imaging is preferred; however, CT imaging will be acceptable, if MRI is medically contraindicated or CT is mandated by local practice.

Other imaging (MRI neck with contrast etc.) may be obtained in addition (but not in lieu) of definitive staging scans if needed either at initial staging and/or following Neoadjuvant Phase to assess resectability at the direction of the treating investigator.

6.1.2.6.2 Tumor Imaging During the Study

Following Neoadjuvant Phase, first on-study imaging assessment should be performed at 7 weeks (42 days ± 7 days) from the date of allocation.

Post-surgery, during the Adjuvant Phase, first on-study imaging assessment should be performed at Cycle 2 or approximately 9 weeks (63 days ± 7 days) after pre-surgical scan. Subsequently, all on-study imaging assessments should be performed every 9 weeks (63 days ±7 days) starting at week 12. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the Investigator.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging every [X] weeks, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per iRECIST (**Section 6.1.2.6.6**), disease progression should be confirmed 4-8 weeks after first radiologic evidence of PD in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the investigator until progression is confirmed by the site provided they have met the conditions detailed in **Section 6.1.2.6.6.**

Participants who receive confirmatory imaging and are found not to have PD per iRECIST do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable. Participants who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue study treatment. Exceptions are detailed in **Section 7**.

6.1.2.6.3 End of Treatment and Follow-up Tumor Imaging

In participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. In participants who discontinue study treatment due to documented disease progression and the investigator elects not to implement iRECIST, this is the final required tumor imaging.

For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment as delineated in Section 6.1.5.3.2 and below. This will be done to monitor disease status until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

The first restaging scan during Post-Treatment Surveillance begins 9 weeks (63 ± 7 days) following last imaging study during Adjuvant Phase. Subsequent restaging scans will be obtained at the following frequency: every 3 months (±2 weeks) if patient is < 2 years from study entry, every 6 months (±4

weeks) if patient is 2-5 years from study entry, and every 12 months (±4 weeks) if patient is > 5 years from study entry for up to 5 years.

6.1.2.6.4 Second Course (Retreatment) Tumor Imaging

Not applicable.

6.1.2.6.5 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study treatment). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, the Sponsor allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden. The first half of the flowchart in Figure 1 illustrates the imaging flow involving verification of PD for clinically stable participants.

6.1.2.6.6 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1 but adapted to account for the unique tumor response seen with immunotherapeutic drugs. When clinically stable, participants should not be discontinued until progression is confirmed by the Investigator, working with local radiology, according to the rules below. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response.

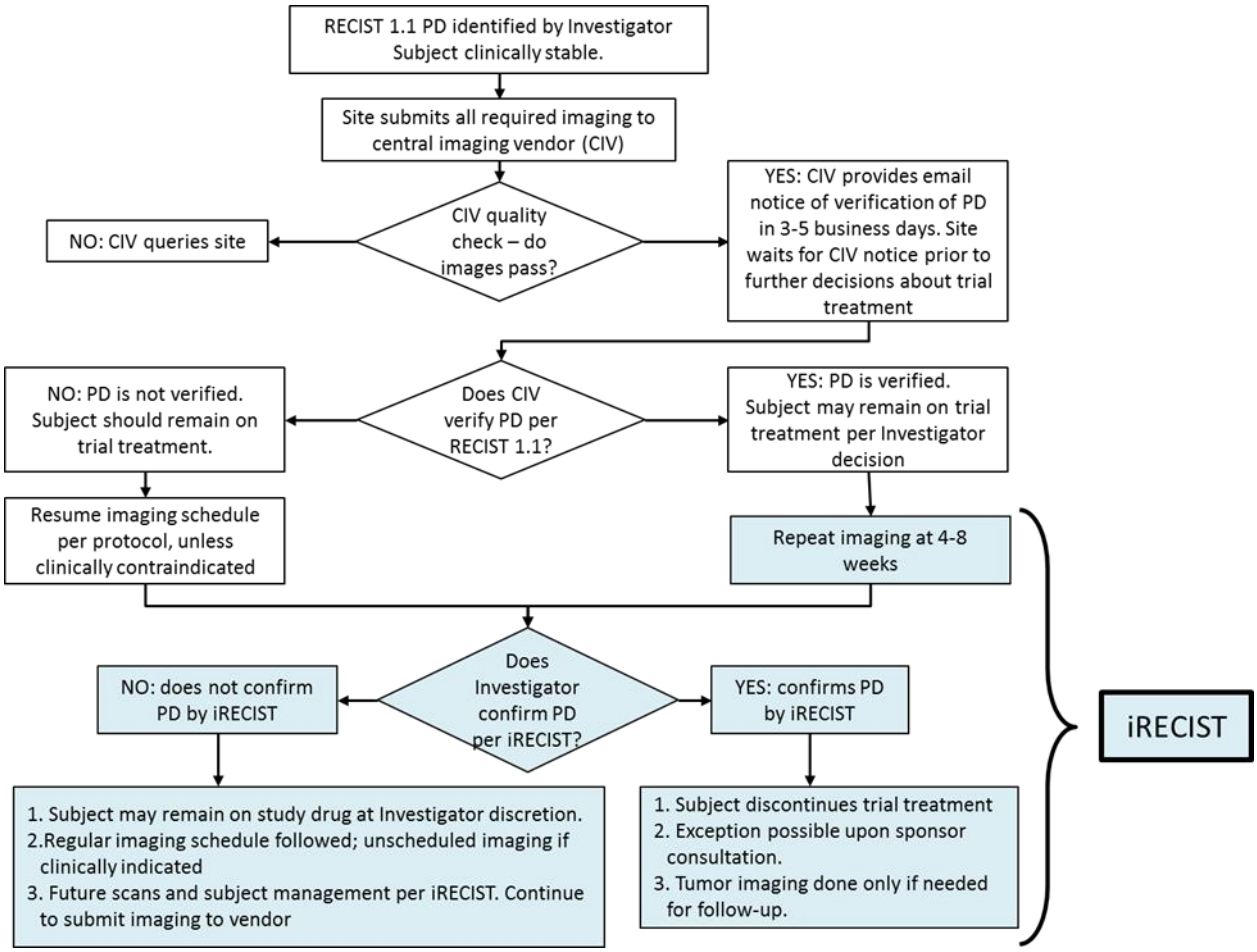
A description of the adaptations and iRECIST process is provided in **Appendix 4**, with additional detail in the iRECIST publication.[53] iRECIST will be used by the Investigator to assess tumor response and progression, and make treatment decisions as delineated in **Table 6.1.2.5.6-1** below (see **Table 6.1.2.5.6-1**).

Table 6.1.2.5.6-1 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per Investigator assessment	No additional imaging required	Discontinue treatment (exception is possible upon consultation with Sponsor)	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per Investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit	Continue study treatment at the Investigator's discretion	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per Investigator assessment.	Continue regularly scheduled imaging assessments	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.

iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1..

Figure 1: Imaging and Treatment for Clinically Stable Participants after First Radiologic Evidence of PD Assessed by the Investigator



6.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

Planned correlative analyses will include but are not limited to flow cytometric analyses of tumor samples, TIL and peripheral blood mononuclear cells (PBMC), IHC analyses of pre-/post- treatment tumor samples, tumor whole exome/RNA sequencing. Single-cell RNA sequencing will be performed on a subset of treated patients. Studies will be performed under the direction of the Principal Investigator along with co-Investigator Hassane Zarour in Dr. Zarour's lab.

Tumor tissue

Patients must undergo biopsy (e.g. punch or open biopsy) within 28 days of entry to the study (baseline biopsy). Definitive surgery will be performed after 2 cycles of pembrolizumab, and any clinically indicated variation from this schedule should be discussed between the investigator, treating sub-investigator and surgical oncologist. Tumor tissue will be processed as described in the lab manual:

Primary cSCC (if available)
FFPE tissue block(s) or 10 unstained slides (air dried; 4μm thickness) from all prior resections of primary cSCC will be requested as well.

Blood biospecimens
Blood biospecimens will be collected at baseline, and per the schedule outlined in **Trial Flow Chart** (**Section 2.1**).

At **EACH time point** please submit the following:

- Six (6) 10mL GREEN top sodium heparin tubes
- Two (2) 5mL YELLOW top SST tube
- One (1) 8.5mL Streck cf DNA tube
- One (1) 4mL K2 EDTA tube (**Screening** only)

Each tube must be clearly labeled to include:

- Protocol number: HCC 20-300
- Patient sequence number
- Patient initials
- Originating institution/investigator name
- Date and time drawn
- Collection time point

Stool specimens
Stool biospecimens will be collected at baseline, and per the schedule in **Trial Flow Chart** (**Section 2.1**).

Dietary questionnaire
DHQ-3 questionnaire may be administered electronically or on paper. Electronic administration is preferred. Data will be entered into DHQ-3 online per instructions as outlined in **Appendix 6**.

6.1.3 Laboratory Procedures/Assessments

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

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in **Table 6.1.3** (see **Table 6.1.3-1**).

Table 6.1.3-1 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Urine (or serum) β-human chorionic gonadotropin (β-hCG)†
Hemoglobin	Alkaline phosphatase	Glucose	
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)
Absolute Lymphocyte Count	Uric Acid	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Calcium		
	Chloride		
	Glucose		[$]Infectious serology: hepatitis B (HepBsAg and HepBsAb); hepatitis C (HIV RNA; and if positive, quantitative DNA test); and HIV (HIV 1/2 ELISA)
	Phosphorus		
	Potassium		Blood for correlative studies
	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.

‡ If considered standard of care in your region.

[$] Only at **Screening**.

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.

6.1.4 Other Procedures

6.1.4.1 Discontinuation and withdrawal

When a participant discontinues 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 should be followed in accordance with the safety requirements outlined in **Section 7.2. - Assessing and Recording Adverse Events**. Participants who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in **Section 5.2.3**. After discontinuing treatment following assessment of CR, these participants 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 7.1.5.3.2**).

Participants who withdraw prior to completion of the trial should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2.

6.1.4.2 Withdrawal from Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the investigator. The investigator will inform the Sponsor. It is the responsibility of the investigator to subsequently inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request for withdrawal being received will continue to be used as part of the overall research study data and results. No new analyses should be generated after the request is received.

In the event that the specimens have been completely anonymized, there will be no link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

6.1.4.3 Blinding/Unblinding

6.1.5 Visit Requirements

Visit requirements and their timing are detailed in **Section 6.1.2 Clinical Procedures/Assessments** and summarized in **Trial Flow Chart** (**Section 2.1**).

6.1.5.1 Screening

Informed 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 prior to enrollment.

During initial enrollment visit, study investigator (or designee) must discuss the following with patients:

- Inclusion and exclusion criteria
- Medical history – pertinently any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator.
- Prior and concomitant medications. All medications related to reportable SAEs and ECIs should be recorded as defined in **Section 6.2**.
- Disease details and treatments.

6.1.5.2 Treatment Periods

6.1.5.2.1 Neoadjuvant Phase

Commences following **Screening** (Weeks 1-6).

During this phase, patients receive:

- Pembrolizumab: 200mg I.V. infusion every 3 weeks for 2 cycles.

6.1.5.2.2 Surgical Phase

Commences following Neoadjuvant Phase (>6 weeks).

During this phase, patients undergo restaging scans, surgical and radiation oncology assessment followed by definitive surgery.

6.1.5.2.3 Adjuvant Phase

Begins following recovering from surgery (Weeks 9 onwards).

During this phase, patients receive:

- Adjuvant RT if applicable as delineated in **Section 5.6 (Radiation Therapy Considerations**)
- Pembrolizumab: 200mg I.V. infusion every 3 weeks for 15 cycles.

6.1.5.3 Post-Treatment Follow-up

6.1.5.3.1 30-day Safety Follow-up

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of study 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. Participants with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first. SAEs 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.

6.1.5.3.2 Post-Treatment Surveillance

Participants who complete study therapy or discontinue study treatment for a reason other than disease progression will move into the **Follow-Up Phase**. These patients are evaluated per the standard follow-up schedule including imaging (CT vs. CT/PET vs. PET at the discretion of the treating physician) at the intervals directed below.

The first restaging scan during **Post-Treatment Surveillance** begins 9 weeks (63 ± 7 days) following last imaging study during **Adjuvant Phase**. Subsequent restaging scans will be obtained at the following frequency: every 3 months (±2 weeks) if patient is < 2 years from study entry, every 6 months (±4 weeks) if patient is 2-5 years from study entry, and every 12 months (±4 weeks) if patient is > 5 years from study entry for up to 15 years. From a study perspective, relapse and survival information will be collected for up to 5 years.

Patients who develop recurrent cSCC will be followed for information on survival and for information on salvage patterns. During this period, given the field effect that underlies cSCC development in this patient population, every effort will be made to distinguish recurrence of the original lesion from a new primary lesion. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of the study as detailed in **Section 5.2.3**.

Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

6.1.5.3.3 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. This will be done every 3 months.

6.2 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in **Appendix 5 (Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting)**.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

6.2.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before intervention allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention allocation/randomization through 30 days following cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation/randomization through 90 days following cessation of study intervention or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of intervention allocation/randomization through 120 days following cessation of study intervention, or 30 days following cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to Merck if the event is considered drug-related.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify Merck.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to Sponsor-Investigator and Merck within the time frames as indicated in **Table 6.2.1-1**.

Table 6.2.1-1 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Merck:**
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 2 business days but no longer than 3 calendar days of learning of event
Pregnancy/Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 2 business days but no longer than 3 calendar days of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 2 business days but no longer than 3 calendar days of learning of event

6.2.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

6.2.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up.. In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in **Appendix 5 (Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).**

6.2.4 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable country specific regulatory requirements, global laws and regulations.

6.2.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to Merck.

All reported pregnancies 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.

6.2.6 Events of Clinical Interest (ECIs)

Selected nonserious and SAEs are also known as ECIs and must be reported to Merck.

Events of clinical interest for this study include:

1. An overdose of pembrolizumab that is not associated with clinical symptoms or abnormal laboratory results. For purposes of this study, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

7.0 STATISTICAL ANALYSIS PLAN

7.1 Study Design

This is a single-arm phase II study of neoadjuvant pembrolizumab using Simon optimal two-stage design. Pembrolizumab (I.V.) will be administered for 6 weeks pre-operatively (weeks 1-6) followed by planned surgical resection at week 7-10. Following recovery from surgery, pembrolizumab (I.V.) will commence and continue for 45 weeks.

7.2 Safety Monitoring

Anti-PD-1 therapy including pembrolizumab has been tested in PD-1 naïve cSCC in multiple studies. The safety profile observed thus far suggests that the risk of toxicities is unlikely to be significantly increased in the neoadjuvant setting.

However, in the context of this neoadjuvant trial, we will monitor dose limiting toxicities (DLTs) for 4 weeks for the 1st 3 patients accrued. At the end of this period, the PI and the study team will review the data to assess the safety of the treatment.

DLT is defined as any adverse event(s) (AEs) considered possibly, probably, or definitely related to pembrolizumab, which occur during the first 28 days of therapy in the Neoadjuvant Phase only. During DLT monitoring period, no further accrual will be permitted. Any patient who has started the studied treatment will be evaluable for safety.

The following AEs will be considered DLTs if deemed related to study therapy:

- Hematologic
    - Grade 4 neutropenia
    - Febrile neutropenia, defined as absolute neutrophil count (ANC) ≤1000/mm3 with a temperature of ≥ 38.3 degrees °C
    - Grade ≥ 3 neutropenic infection
    - Grade ≥ 3 thrombocytopenia with bleeding
    - Grade 4 thrombocytopenia
- Non-hematologic
    - Grade ≥ 3 toxicities (non-laboratory)
    - Grade ≥ 3 nausea, vomiting or diarrhea despite maximal medical intervention
    - Grade 4 aspartate aminotransferase (AST) and alanine aminotransferase (ALT)
- Other (non-AST/ALT) non-hematologic Grade ≥ 3 laboratory value if the abnormality leads to overnight hospitalization

An AE believed to be caused by tumor flare or pseudoprogression does not necessarily need to be considered a DLT. Any such cases that would otherwise meet DLT criteria must be discussed immediately with the Principal Investigator. If the Principal Investigator agrees that tumor flare is a likely explanation for the AE, treatment with pembrolizumab may continue so long as the subject is closely monitored by the Principal Investigator or study staff while on study.

7.3 Statistical Analysis Plan

We hypothesize that the pre-operative administration of neoadjuvant pembrolizumab in high-risk PD-1 naive potentially resectable cSCC patients will be associated with anti-tumor effect as determined by pathologic response at the time of surgical resection. We also hypothesize that neoadjuvant pembrolizumab will be associated with increased $CD8^+$ TIL in responders at surgery and circulating $PD\text{-}1^+Ki67^+$ $CD8^+$ T cells in responders on treatment compared to baseline.

Although the efficacy of neoadjuvant PD-1 blockade is known in melanoma and MCC, neoadjuvant PD-1 blockade has only been minimally studied in high-risk cSCC as stated in **Section 4.2.1 (Rationale for the Trial and Selected Population)**. While there are 4 planned/ongoing studies, only a single study has publically reported data.[39] In a small single-institution phase II study in patients with either stage III ($T_3N_0M_x$; $T_{1\text{-}3}N_1$) or stage IV ($T_4N_0M_x$; $T_{1\text{-}3}N_2M_x$; $T_{1\text{-}4}N_3M_x$) cSCC, neoadjuvant cemiplimab was well-tolerated and associated with a high rate of pathological response (70%) in a small single-institution study.[39] In this study, 11 patients (55%) had pathologic complete responses.[39]

Further, the impact upon RFS in cSCC patients who experience pathological response with peri-operative anti-PD-1 therapy is unclear. As such, the pathologic response rate of neoadjuvant PD-1 blockade in high risk cSCC as defined herein is unknown at this time. In the interests of maximizing safety while minimizing exposure to potentially ineffective therapy, we have designed a **two-stage phase II** study using **Simon's optimal design**.

The null hypothesis that the **true pathologic complete response (pCR) rate is 5%** will be tested versus a one-sided **alternative of 25% or higher**. In the **1st stage**, **9 patients** will be accrued. If there are 0 pCR, the study will be stopped. If **≥1 pCR** are observed in **1st stage**, **21 additional patients** will be enrolled in the **2nd stage**. Neoadjuvant pembrolizumab will be considered futile if **≤3 pCR** are observed across **both stages**; while neoadjuvant pembrolizumab will be regarded as worthy of further study if **>4 pCR** are observed across **both stages**.

This design using **Simon's optimal design**, and a sample size of 30 patients across both stages, yields a type I error rate of 0.05 with power of 0.90 when the true response rate is 0.25. The probability of early stopping when the true pathologic response rate is 5% is 0.63.

7.4 Efficacy Analysis

Definition of evaluable patient

See **Section 5.10.**

Briefly, subjects who receive at least 1 dose of pembrolizumab in the Neoadjuvant Phase are evaluable for safety. Patients who complete Neoadjuvant Phase and receive surgery will be evaluable for pathologic response rate and other efficacy endpoints. The primary endpoint of pathological response will be assessed using immune related pathologic response criteria.[1-3]

Determination of residual volume of tumor (RVT)

In the context of melanoma, early neoadjuvant studies in melanoma reported pCR utilizing criteria to define the residual volume of tumor (RVT) derived from neoadjuvant studies of chemotherapy in select tumors including lung cancer.[54]

Neoadjuvant anti-PD-1 immunotherapy results in distinct histopathologic features compared to neoadjuvant chemotherapy. Specifically, neoadjuvant PD-1 therapy produces unusual features beyond CD8+ T cell infiltrate previously associated with response including features in areas adjacent to the actual tumor – a location termed "the regression bed".[55] Histopathologic features associated with response herein include neovascularization; proliferative fibrosis; presence of cholesterol clefts; development of tertiary lymphoid structures; presence of plasma cells, giant cells, foamy macrophages and granulomas.[1,3]

This observations have led investigators to propose new criteria – immune related pathologic response criteria (irPRC) – wherein immune related RVT (% irRVT) is defined as the total surface area of RVT divided by the total tumor bed area (comprising regression bed area + RVT area + areas of necrosis).[1,3] Compared to standard methods, the use of irPRC in neoadjuvant melanoma trials had lower inter-observer variability and better correlated with imaging assessments.

Multiple studies are evaluable the role of neoadjuvant anti-PD-1 in high-risk resectable cSCC as summarized in **Section 4.2.1 (Rationale for the Trial and Selected Population)**, all of which are ongoing with no reported data at this time. At this time, a small single-institution study of neoadjuvant cemiplimab for 6 weeks in high-risk resectable stage III/IV disease has reported data.[39] In 20 high-risk resectable cSCC defined as either stage III disease (T3N0Mx; T1-3N1) or stage IV disease (T4N0Mx; T1-3N2Mx; T1-4N3Mx), peri-operative cemiplimab administered over 6 weeks was well-tolerated and was produced 70% pathologic response.[39] Pathologic response in this study was assessed using the same criteria as previously reported for melanoma.[1,3] As such, in this study, the primary endpoint of this study is proportion of patients who achieve pCR as defined as 0% residual volume of tumor (RVT) in post-therapy specimen using irPRC criteria.[1-3]

Residual tumor will be determined in each resection specimen as outlined in **Appendix 7**. All tumors will be macroscopically localized after correlation with radiologic findings. Specimens were sectioned in 5 mm-thick slices. In patients with multiple metastases, each lesion will be extensively sampled from the center to the periphery to include multiple sections of tumor and non-neoplastic parenchyma. Sampling of the tumor nodules in the pathology suite will be directed at the most viable section of the tumor nodule. More than one section per centimeter will be reviewed from each tumor nodule. The number of hematoxylin-eosin slides reviewed per tumor nodule will be at least four (range, 1 to 14 slides). Hematoxylin-eosin stained sections will be reviewed by two melanoma pathologists blinded with respect to clinical information and treatment regimen.

<u>Definition of pathologic complete response (pCR)</u>

pCR is defined as 0% RVT remaining in post-therapy specimen using irPRC criteria.[1-3] Other categories of response based on %RVT are given below:

- Major pathologic response (MPR): >0 but ≤10% RVT
- Partial pathologic response: >10% but ≤50% RVT

- Pathologic non-response: >50% RVT

pCR rate will be calculated by the proportion of patients with a pCR, along with its exact 95% confidence interval. Other response rates will be analyzed similarly.

Definition of other endpoints (RFS, OS, DMFS and landmark survival)

In the setting of neoadjuvant breast cancer, RFS has typically been calculated from the date of surgery to the first evidence of recurrence (any site)[56,57]. In neoadjuvant studies in melanoma, RFS has variably been calculated from *either* date of surgery *or* date of treatment initiation *to* first evidence of recurrence. Given the relative novelty of neoadjuvant anti-PD-1 therapy in cSCC, we will endeavor to capture both of these as follows.

RFS_1 is defined as the time from initiation of treatment till cSCC relapse or death; while RFS_2 is defined as the time from date of surgery till cSCC relapse or death. cSCC relapse will be defined as local relapse, locoregional relapse and/or distant relapse. Both RFS_1 and RFS_2 will be captured, and reported at the time of final reporting. In this context, patients who are alive and recurrence-free will be censored at the last follow-up. Landmark RFS at 6-month, 1-year, 2-year and 3-year timepoints will be collected and reported. Given the field effect associated with cSCC carcinogenesis and the expectation that patients may develop new *primary* cSCCs that do not represent l local, locoregional and/or distant relapse, the development of **new low-grade cSCC lesions** (cSCCis, well-differentiated cSCC) or **new pre-cancerous lesions** (keratoacanthomas, actinic keratoses) will not be treated as RFS-defining events, similar to the Guidance provided by the FDA in the context of bladder cancer adjuvant therapy.[58]

Distant metastasis-free survival (DMFS) is defined as the time interval between the date of surgery in the study and the date of the occurrence of distant metastases or death (all causes), whichever occurs first. In this context, patients who are alive and event-free will be censored at the last follow-up.

Overall survival (OS) is defined as initiation of treatment till death from cSCC. Given that cSCC patients are typically older, the treating Investigator or Principal Investigator will endeavor to confirm etiology of death prior to assuming that death occurred as a result of disease progression. In this context, patients who are alive will be censored at the last follow-up. Landmark OS at1-year, and 2-year timepoints will be collected and reported.

All suspected relapse should be biopsied to confirm relapse as stated in **Section 2.1** (**Study Flow Chart**). In the event where this is difficult and/or dangerous, imaging may be used as a surrogate. Kaplan-Meier estimates of all survival endpoints will be provided. The corresponding median survival time (with 95% confidence intervals) will be determined, along with survival estimates at selected time points (e.g. 6 months, 1 years, and 2 years).

7.5 Safety Analysis

As per NCI CTCAE Version 5.0, the term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns.

As pembrolizumab has previously been studied in cSCC, no "dose-escalation" or a formal continuous monitoring rule will be used in this study. However, to accurately capture toxicities for the use of this agent in this space, we will be monitoring toxicities closely. The detailed data and safety monitoring plan is in **Section 7.7 (Data Safety and Monitoring Plan).**

7.6 Biomarker Analysis

To search for potential prognostic biomarkers (and toxicity marker) for the regimen, logistic regression will be used to assess the association between each marker and pathological response.

The Cox proportional hazards model will be used to assess the association of each marker and survival endpoints (i.e. RFS and OS).

7.7 Data Safety and Monitoring Plan

All enrolled patients will be reviewed weekly to discuss AEs, in particular during DLT period.

Principal Investigator/Sub-investigators, regulatory, CRS management, clinical research coordinators, clinical research associates, data managers, and clinic staff meet monthly in disease center Data Safety Monitoring Boards (DSMB) to review and discuss study data to include, but not limited to, the following:

- Serious adverse events
- Subject safety issues
- Recruitment issues
- Accrual
- Protocol deviations
- Unanticipated problems
- Breaches of confidentiality

All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria version 4.0. All study treatment associated adverse events that are serious, at least possibly related and unexpected will be reported to the IRB. Any modifications necessary to ensure subject safety and decisions to continue, or close the trial to accrual are also discussed during these meetings. If any literature becomes available which changes the risk/benefit ratio or suggests that conducting the trial is no longer ethical, the IRB will be notified in the form of an Unanticipated Problem submission and the study may be terminated.

All study data reviewed and discussed during these meetings will be kept confidential. Any breach in subject confidentiality will be reported to the IRB in the form of an Unanticipated Problem submission. The summaries of these meetings are forwarded to the UPCI DSMC which also meets monthly following a designated format.

For all research protocols, there will be a commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to subjects or others (including adverse events). DSMC progress reports, to include a summary of all serious adverse events and modifications, and approval will be submitted to the IRB at the time of renewal.

Protocols with subjects in long-term (survival) follow-up or protocols in data analysis only, will be reviewed twice a year rather than monthly by the disease center DSMB.

Both the UPCI DSMC as well as the individual disease center DSMB have the authority to suspend accrual or further investigate treatment on any trial based on information discussed at these meetings.

All records related to this research study will be stored in a double locked environment. Only the researchers affiliated with the research study and their staff will have access to the research records.

8.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

8.1 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 as summarized in **Table 8.1-1**.

Table 8.1-1 Product Descriptions

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

8.2 Packaging and Labeling Information

Supplies will be labeled in accordance with regulatory requirements.

8.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the participant, 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.

8.4 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.

8.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the participants 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.

9.0 ADMINISTRATIVE AND REGULATORY DETAILS

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11.0 APPENDICES

Appendix 1A: 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.

Appendix 1B: AJCC UICC 8th Edition Staging for cSCC

Cutaneous squamous cell carcinoma of the head and neck TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumor smaller than or equal to 2 cm in greatest dimension
T2	Tumor larger than 2 cm, but smaller than or equal to 4 cm in greatest dimension
T3	Tumor larger than 4 cm in maximum dimension or minor bone erosion or perineural invasion or deep invasion*
T4	Tumor with gross cortical bone/marrow, skull base invasion and/or skull base foramen invasion
T4a	Tumor with gross cortical bone/marrow invasion
T4b	Tumor with skull base invasion and/or skull base foramen involvement
* Deep invasion is defined as invasion beyond the subcutaneous fat or >6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumor); perineural invasion for T3 classification is defined as tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in caliber, or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression.	
Regional lymph nodes (N)	
Clinical N (cN)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(–)
N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–); **or** Metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–); **or** In bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)
N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(–)
N2c	Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(–); **or** Metastasis in any node(s) and clinically overt ENE [ENE(+)]
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(–)
N3b	Metastasis in any node(s) and ENE(+)
NOTE: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(–) or ENE(+).	
Pathological N (pN)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(–)
N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); **or** Larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–); **or** Metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–); **or** In bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension, ENE(–)
N2a	Metastasis in a single ipsilateral lymph node 3 cm or smaller in greatest dimension and ENE(+); **or** A single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(–)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(–)
N2c	Metastases in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(–)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(–); **or** In a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); **or** Multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+); **or** A single contralateral node of any size and ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(–)
N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); **or** Multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+); **or** A single contralateral node of any size and ENE(+)
NOTE: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(–) or ENE(+).	

Appendix 1C: Brigham and Womens Hospital (BWH) Risk Factors for cSCC

BWH Staging High-Risk Features
• Clinical tumor diameter ≥2 cm • Tumor invasion beyond the subcutaneous fat • Poorly differentiated histology • Perineural invasion of nerve(s) ≥0.1 mm in caliber

Appendix 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)

Appendix 3: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

- A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
    - Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in **Section 5.2**.

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 9 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
    - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in **Table A3-1** during the protocol-defined time frame in **Section 5.2**.

Table A3-1 Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception [b, c] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b, c] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b, c] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly). b) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

Appendix 4: Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

In participants who show evidence of radiological PD by RECIST 1.1 the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management (see **Section 6.1.2.5.6** and **Table 6.1.2.6.1-1**). This decision by the Investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed clinically unstable should be discontinued from study treatment at site-assessed first radiologic evidence of PD and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥ 20% and ≥ 5 mm from nadir
    - Please note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
    - For target lesions, worsening is a further increase in the sum of diameters of ≥ 5 mm, compared to any prior iUPD time point
    - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
    - For new lesions, worsening is any of these:
        - An increase in the new lesion sum of diameters by ≥ 5 mm from a prior iUPD time point
        - Visible growth of new non-target lesions
        - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the scan on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation scan proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 6.

Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (ie, achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the PD threshold (≥ 20% and ≥ 5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions
  - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
  - If non-target lesions had shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear

- Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
- Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, except in one respect. If new lesions occurred at a prior instance of iUPD, and at the confirmatory scan the burden of new lesions has increased from its smallest value (for new target lesions, their sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication.[53]

Appendix 5: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

11.1.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- NOTE: For purposes of AE definition, study intervention (also referred to as Merck product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by Merck for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology “accidental or intentional overdose without adverse effect.”

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.

11.1.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the participant's medical history.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

11.1.3 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to Merck in the same time frame as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.

- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose of pembrolizumab

11.1.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- There may be instances when copies of medical records for certain cases are requested by the Merck. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Merck.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

1. The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology for Adverse Events (CTCAE), version 5. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
    - 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 activities of daily living (ADL).
    - Grade 3: 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.

Assessment of causality

1. Did Merck product cause the AE?

2. The determination of the likelihood that Merck product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

3. The following components are to be used to assess the relationship between Merck's product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the AE:

    - **Exposure:** Is there evidence that the participant was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

    - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

- **Dechallenge:** Was Merck product discontinued or dose/exposure/frequency reduced?

- If yes, did the AE resolve or improve?

- If yes, this is a positive dechallenge.

- If no, this is a negative dechallenge.

- (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck product; (3) the study is a single-dose drug study; or (4) Merck product(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to Merck product in this study?

- If yes, did the AE recur or worsen?

- If yes, this is a positive rechallenge.

- If no, this is a negative rechallenge.

(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) Merck product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY MERCK PRODUCT, OR IF RE-EXPOSURE TO MERCK'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INIRB/IEC.

4. **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?

5. The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

6. Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).

    - Yes, there is a reasonable possibility of Merck product relationship:

- There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.

- No, there is not a reasonable possibility of Merck product relationship:

- Participant did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a participant with overdose without an associated AE.)

7. For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

8. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Merck. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Merck.

9. The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

10. The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

11. For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to Merck within 2 business days but no longer than 3 calendar days of receipt of the information.

11.1.5 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Merck

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

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215-661-6229) at the time of submission to FDA.

Appendix 6: Dietary History Questionnaire (DHQ-3) for Microbiome Sampling

Dietary history questionnaire will be administered either on paper or electronically and data entered and stored securely electronically. Instrument will be administered by PI or designee. Detailed information for study staff:

- Please obtain patient's username and password from study PI.
- Please provide instructions (see below) to patients.
- Patients are to be instructed to provide detailed dietary information either during visit (preferred) or at home.
- The instrument that will be utilized is the DHQ-3 "past month with portion size" obtained from https://epi.grants.cancer.gov/dhq3/

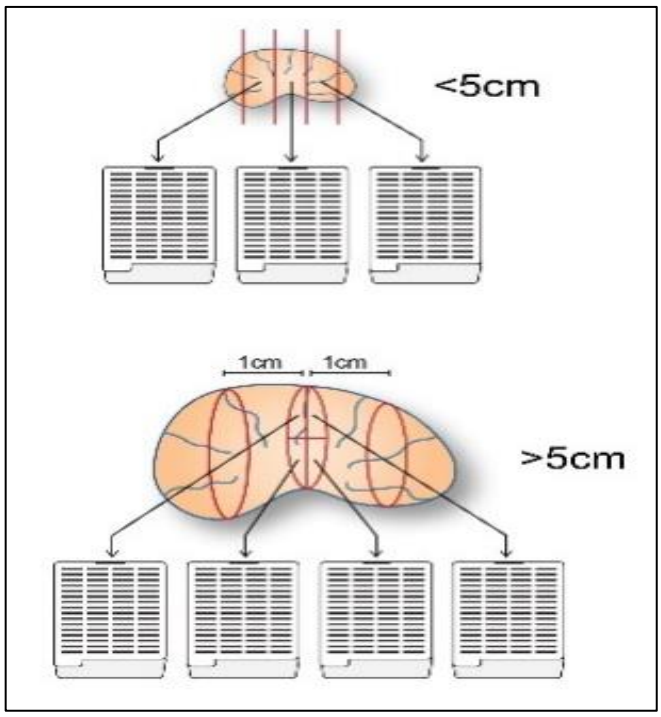
Detailed information for patients:

- Thank you for participating in this study. We are interested in evaluating your dietary history. To do this we are using a validated questionnaire termed the "Diet History Questionnaire (DHQ-3)".
- This questionnaire takes approximately 30 minutes to complete. You can do this either while receiving your therapy or at home.
- After completing the questionnaire, you will receive a Respondent Nutrition Report. This report shows estimated daily nutrient and food group intakes based on questionnaire responses. Recommended values are only available for some nutrients and food groups.
- Please feel free to discuss this with your study doctor.

Dietary study login URL: https://epi.grants.cancer.gov/dhq3/
Your username (case sensitive): _____
Your study password (case sensitive): _____

Appendix 7: Pathology Sampling and Response Assessment Criteria

In order to achieve accurate and reproducible pathologic assessment in neoadjuvant treated specimens, grossing assessment and tissue submission following neoadjuvant treatment should be standardized. These recommendations will largely adhere to recommendations made by the International Neoadjuvant Melanoma Consortium (see figure below) for the evaluation of melanoma specimens as applied to cSCC specimens with certain modifications.



For LN specimens:

- If the largest grossly positive lymph node measures ≤ 5 cm in greatest dimension, then the entire lymph node should be entirely submitted at 2 mm serially sectioned intervals.
- For any grossly positive lymph node measuring > 5 cm in greatest dimension, representative sections of the largest lymph nodes may be utilized to avoid oversampling as indicated below.
- Following serial sectioning of each lymph node, for those grossly positive nodes > 5 cm, sections representing a complete cross section of the entire surface area should be submitted per 1 cm of each grossly positive lymph node.
- All lymph nodes < 5cm in specimens where the largest node(s) exceeds 5 cm should be submitted entirely.

For primary tumor specimens:

- If the largest primary tumor specimen measures ≤ 5 cm in greatest dimension, then the entire primary tumor specimen should be entirely submitted at 2 mm serially sectioned intervals.
- For any grossly positive primary tumor specimen measuring > 5 cm in greatest dimension, representative sections of the primary tumor specimen may be utilized to avoid oversampling as indicated below.

- Following serial sectioning of each lymph node, for those grossly positive nodes > 5 cm, sections representing a complete cross section of the entire surface area should be submitted per 1 cm of each grossly positive lymph node.
- All lymph nodes < 5cm in specimens where the largest node(s) exceeds 5 cm should be submitted entirely.

Synoptic

Background and Demographic Information:
- Sex/Age:

Pre-Treatment Pathology
- Location of tumor
- Nature of tumor:
- Date of initial diagnosis:
- Pre-treatment biopsy:
  - Date:
  - Nature of biopsy:
  - Location/anatomic site:
  - Tumor present/absence:

Post-Treatment Imaging
- Date:
- Post-treatment imaging findings:

Surgical Resection:
- Date:
- Type of surgery:
- Location/anatomic site:

Post-Treatment Pathological Response Assessment
- Tissue banked
  - Yes ☐
  - No ☐
- Nature of lesion
  - Lymph node ☐
  - Cutaneous lesion ☐
  - Both (LN + skin) ☐
- Largest positive LN/nodule size (in mm^2):
- Sizes of other lymph nodes/nodules (in mm^2):
- Blocks number of positive LN/nodules:
- Treatment response evaluation metrics:
  - Size of tumor bed:
  - Gross/microscopy:
    - Percentage of viable tumor:

        - Percentage of stromal fibrosis:
        - Percentage of necrosis:
    - For lymph nodes:
        - Extra-capsular extension
            - Y/N ☐
            - Viable/regressed ☐

- Response assessment (based on %RVT):
    - Pathologic CR (pCR; %RVT=0%) ☐
    - Other
        - State %RVT ☐ _____