An open-label, non-randomized, multi-arm, phase II trial to evaluate the efficacy of pembrolizumab combined with cetuximab in patients with recurrent/ metastatic head and neck squamous cell carcinoma (HNSCC)

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The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

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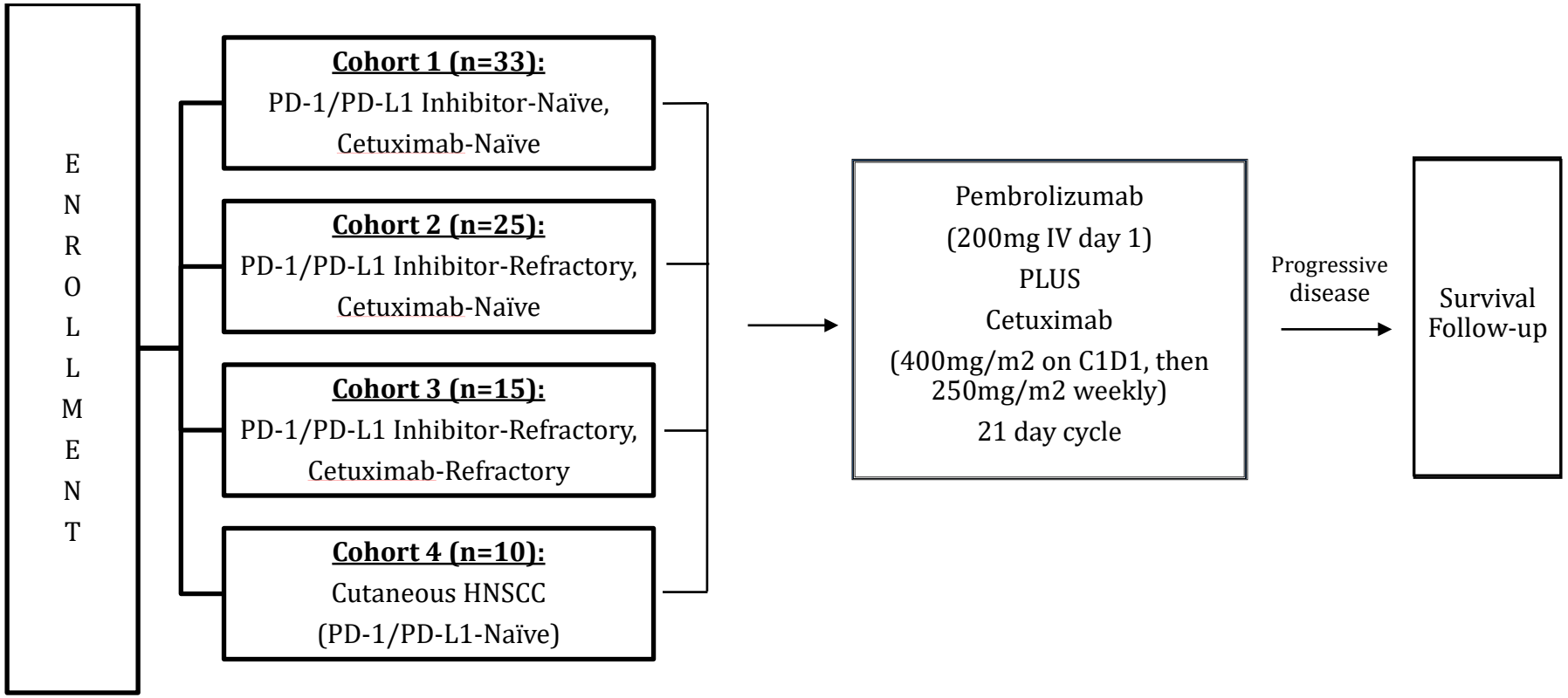
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LIST OF ABBREVIATIONS

ADCC	Antibody-dependent Cell-Mediated Cytotoxicity
AE	Adverse Event
AEOSI	Adverse Event of Special Interest
ALC	Absolute Lymphocyte Count
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CI	Confidence Interval
CMP	Comprehensive Metabolic Panel
CNS	Central Nervous System
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte-Associated Protein 4
DC	Dendritic Cell
DRSAE	Drug-Related Serious Adverse Event
DSMB	Data and Safety Monitoring Board
EBV	Epstein-Barr Virus
EGFR	Epidermal Growth Factor Receptor
ECOG	Eastern Cooperative Oncology Group
HIV	Human Immunodeficiency Virus
HNSCC	Head and Neck Squamous Cell Carcinoma
HRPP	Human Research Protections Program
IHC	Immunohistochemistry
irAE	Immune-related Adverse Event
IRB	Institutional Review Board
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Progressive Disease
PD-1	Programmed Death-1
PD-L1	Programmed Death Ligand-1
PD-L2	Programmed Death Ligand-2
PET	Positron Emission Tomography
PFS	Progression-free Survival
PMN	Polymorphonuclear
p.o.	per os/by mouth/orally

PR	Partial Response
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
TIL	Tumor Infiltrating Lymphocyte
TSH	Thyroid-Stimulating Hormone
UPR	Unanticipated Problems involving Risk to subjects or others
WBC	White Blood Cells

STUDY SCHEMA



Primary endpoint (all cohorts): Overall response rate

STUDY SUMMARY

Title	An open-label, non-randomized, multi-arm, phase II trial to evaluate the efficacy of pembrolizumab combined with cetuximab in patients with recurrent/ metastatic head and neck squamous cell carcinoma (HNSCC)
Short Title	Phase II trial of pembrolizumab combined with cetuximab for patients with recurrent/metastatic head and neck squamous cell carcinoma
Phase	2
Methodology	Open-label, non-randomized, multi-arm
Study Duration	3 years
Study Center(s)	University of California, San Diego; University of California, Los Angeles; University of Michigan, Ann Arbor; Washington University, Saint Louis;
Objectives	<u>Primary Objectives</u> To determine the clinical efficacy of pembrolizumab combined with cetuximab for patients with R/M HNSCC. **1.** Cohort 1 (PD-1/PD-L1 inhibitor-naïve, cetuximab-naïve): clinical efficacy defined as overall response rate. **2.** Cohort 2 (PD-1/PD-L1 inhibitor-refractory, cetuximab-naïve): clinical efficacy defined as overall response rate. **3.** Cohort 3 (PD-1/PD-L1 inhibitor-refractory, cetuximab-refractory): clinical efficacy defined as overall response rate. **4.** Cohort 4 (cutaneous HNSCC): clinical efficacy defined as overall response rate. <u>Secondary Objectives</u> 1. To determine 12 month progression-free survival probability. 2. To determine overall survival. 3. To determine duration of response. 4. To assess safety and tolerability of pembrolizumab combined with cetuximab. 5. To evaluate the correlation between molecular markers and disease outcome.
Number of Subjects	83 (Cohort 1, Simon two-stage design: 33; Cohort 2, Simon two-stage design: 25; Cohort 3, Simon two-stage design: 15; Cohort 4, single stage design: 10)
Diagnosis and Main Inclusion Criteria	Patients must meet all of the inclusion criteria to participate in this study. 1. Ability to understand and the willingness to sign a written informed consent. 2. Histologically or cytologically proven squamous cell carcinoma of the head and neck (lip, oral cavity, oropharynx, larynx, hypopharynx, non-EBV related nasopharynx, sinonasal, cutaneous), not amenable to curative intent therapy.

	3. Platinum-refractory disease, or ineligible/unfit for platinum-based therapy 4. Patients must have at least one measurable site of disease as defined by RECIST v.1.1, determined by investigator review 5. Age ≥ 18 years. 6. Eastern Cooperative Oncology Group (ECOG) Performance status 0 or 1. 7. Patient has adequate hematologic, hepatic and renal function 8. Female patient of childbearing potential has a negative serum or urine pregnancy within 72 hours prior to receiving the first dose of study medication. 9. Female patient of childbearing potential agrees to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. 10. Male patient with a partner of childbearing potential agrees to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy. <u>Additional Inclusion Criterion for Cohort 1 (PD-1/PD-L1 Inhibitor-naïve, Cetuximab-naïve) and Cohort 2 (PD-1/PD-L1 Inhibitor-refractory, Cetuximab-naïve):</u> 1. Cetuximab-naïve patients may not have received cetuximab therapy in the recurrent/metastatic setting (treatment in curative setting permitted) <u>Additional Inclusion Criterion for Cohorts 2 and 3 (PD-1/PD-L1 Inhibitor-refractory):</u> 1. PD-1/PD-L1 inhibitor-refractory patients must have documented disease progression after prior response to anti-PD-1/PD-L1 therapy (response defined as stable disease, partial or complete response) <u>Additional Inclusion Criterion for Cohort 4 (Cutaneous HNSCC):</u> 1. Cutaneous HNSCC must not be amenable to local treatment modalities, including surgery and/or radiation.
Study Product(s), Dose, Route, Regimen	Pembrolizumab 200mg IV flat dose every 3 weeks Cetuximab 400mg/m2 on Cycle 1, Day 1, then 250mg/mg weekly
Duration of administration	Cycles repeat every 21 days unless disease progression, unacceptable toxicity, investigator decision or patient withdrawal
Reference therapy	No
Statistical Methodology	<u>Primary Endpoint (all cohorts):</u> 1. Overall response rate by 6 months, defined as the proportion of patients with partial or complete response in tumor burden as defined by RECIST. <u>Secondary Endpoints:</u> 1. Progression-free survival probability from the time of study enrollment. 2. Overall survival, defined as time from study enrollment to death from any cause. 3. Duration of response, defined as time from documentation of tumor response to disease progression. 4. Safety and tolerability, defined as adverse events related to pembrolizumab and cetuximab (description, grade [CTCAE v4.03],

	seriousness). 5. Correlative analyses: a. Archival and/or newly obtained tumor specimens will be evaluated for biomarkers correlated with outcome to pembrolizumab or cetuximab, including PD-L1 expression, EGFR expression, p16 status, IDO expression, cyclin D1, bcl-xL and p53 status. b. Archival and/or newly obtained tumor specimens will be evaluated for immunophenotyping by flow cytometry: i. T cell subsets (CD3, CD4, CD8, CD25, FOXP3) ii. B cells (CD 19, CD20) iii. Macrophage I/II and myeloid-derived suppressor cells (MDSC) (CD16, CD68, CD206) iv. Natural killer cell activity (CD56, CD16) c. T cell receptor (TCR) sequencing from blood obtained at baseline, at time of first radiographic disease assessment on study, and at time of disease progression. d. Whole exome sequencing (for the purposes of neoantigen discovery) from newly obtained tumor specimen when feasible. <u>Study Populations</u> The <u>Safety population</u> will consist of all patients who have received at least one dose of pembrolizumab. The <u>Intention-to-Treat (ITT) population</u> will consist of all patients who have enrolled to the study.

SCHEDULE OF EVENTS

Procedure	**Screen/ Baseline** (≤ 21 days, *unless otherwise noted*)	**Treatment Cycles (3-week cycles)**															**End of Treatment** (28 (± 7) days after last dose)	**Follow-up** (q3 months)
		Cycle 1 (± 3 days)			**Cycle 2** (± 3 days)			**Cycle 3** (± 3 days)			**Cycle 4** (± 3 days)			**Each Additional Cycle** (± 3 days)				
		1	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**		
Informed Consent	*Within 28 days*																	
Eligibility	X																	
Medical History	X																	
Demographics	X																	
Concomitant Medications Assessment	X	X			X			X			X			X			X	
Adverse Event Assessment	X	X			X			X			X			X			X	
Physical Exam[1]	X	X			X			X			X			X			X	
Vital Signs & Height	X	X			X			X			X			X			X	
ECOG	X	X			X			X			X			X			X	
CBC with Diff[2]	*Within 7 days*	X			X			X			X			X			X	
CMP[3]	*Within 7 days*	X			X			X			X			X			X	
Magnesium[4]	*Within 7 days*	X			X			X			X			X			X	
TSH[5]	*Within 7 days*				X						X						X	
Pregnancy test[6]	*Within 72 hours*																	
Urinalysis[7] (dipstick)	X										X						X	
HIV (as clinically indicated)	X																	
HEP B & C (as clinically indicated)	X																	
Tumor tissue collection[8]	*Within 42 days*																	
Blood Collection for Correlative studies[9]	X										*Correlatives will also be obtained at time of first radiographic disease assessment (±7 days) and at time of disease progression (±7 days)*							

CT, MRI, or PET/CT[10]	*Within 28 days*										*Imaging will occur every 9 weeks (+/- 7 days)*								
Pembrolizumab administration		X			X			X			X			X					
Cetuximab administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Survival contact																			X

Cycles are 21 days in length.

1. Full physical exam at baseline; targeted physical exam at other time points.
2. CBC with Diff: Complete blood count with differential.
3. CMP: Comprehensive metabolic panel (bicarbonate, calcium, chloride, creatinine, glucose, potassium, sodium BUN, albumin, bilirubin total, alkaline phosphatase, total protein, ALT, AST).
4. Additional weekly magnesium monitoring (outside of pre-specified time points) may be completed at the investigator's discretion per institutional standard.
5. TSH monitoring will occur at baseline, cycle 2, cycle 4, then every 3 cycles thereafter (ie. Cycle 7, 10 etc.), and at the end of treatment.
6. Pregnancy test for females of child-bearing potential only.
7. Urinalysis (dipstick) will be performed at baseline, every 3 cycles following initiation of treatment (ie. Cycle 4, 7 and 10 etc.) and at the end of treatment. Urine microscopic examination should be performed if dipstick is abnormal.
8. Newly obtained tumor tissue collection should be performed when feasible: See Section 5.5 for specifications. Otherwise, an archived tumor specimen is adequate.
9. Blood for correlative studies should be collected at the same time blood is drawn for CBC and CMP if possible. 30 ml blood to be collected at baseline, time of first radiographic disease assessment (± 7 days) and at time of disease progression (± 7 days). See Section 5.5.
10. Imaging for radiographic disease assessment will be performed every 9 weeks following treatment initiation (± 7 days). The same imaging modality should be used throughout the study when feasible. For patients who are clinically stable, a repeat scan will be required 4 weeks (±7 days) after initial radiographic findings of disease progression as a confirmatory assessment. For CT or MRI, neck and chest should be evaluated; abdomen/pelvis as indicated. If a PET/CT is utilized, CT must be diagnostic quality.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Head and neck cancer is the sixth most common cancer worldwide, with the predominant histology involving squamous cell carcinoma (HNSCC). In the United States (US), HNSCC accounts for 3% of cancers diagnosed annually and 2% of cancer-related deaths. The 2014 estimates for number of new cases and anticipated deaths in the US are approximately 55,000 and 12,000, respectively.[1] The majority of patients with HNSCC initially present with advanced stage disease (stage III-IV), requiring site-specific multimodal therapy.[2-3] For patients who develop recurrent or metastatic (R/M) disease that is not amenable to curative intent treatment, cancer-related morbidity is high and survival is dismal. Historically, the most active standard cytotoxic regimens have been platinum-based and associated with response rates of up to 30%, with a median overall survival expectancy of 6-9 months. [4-5]

The epidermal growth factor receptor (EGFR) is overexpressed in more than 90% of HNSCC and plays a central role in the pathogenesis of HNSCC,[6-7] thus EGFR targeted agents have represented an attractive treatment approach in recent years. Cetuximab, an IgG1 chimeric (human-murine) monoclonal antibody that competitively binds to EGFR with high affinity, currently has two FDA-approved indications in the R/M setting: in combination with platinum-based therapy, and as monotherapy for patients who have progressed after platinum-based therapy. The phase III EXTREME trial confirmed the benefit of adding cetuximab to first-line platinum-based therapy with 5-fluorouracil (5-FU), with an improvement of median overall survival to 10.1 months from 7.4 months for patients treated with platinum/5-FU alone.[8] It is important to note, however, that prognosis still remains poor in this population, as such an active cytotoxic regimen still only resulted in observed response rates of 36% and median progression-free survival (PFS) of 5.6 months. For patients who are platinum-refractory or platinum-ineligible, cetuximab monotherapy demonstrates modest activity, with response rates on the order of 10-20% and median PFS averaging 2.4 months or less.[9-10] Therefore, novel therapeutic combinations which maximize clinical benefit while minimizing treatment-related toxicity are urgently needed.

In addition to mucosal HNSCC, cutaneous HNSCC has limited therapeutic options beyond curative intent therapy. SCC is the second most common cutaneous malignancy in the United States, with rapidly rising incidence rates and the most frequent implicated site involving the head and neck.[11-12] While most cases of cutaneous HNSCC can be treated with localized therapies, once these modalities are no longer feasible, survival is dismal. At present, there is a paucity of data related to systemic treatment options and there is no well-defined standard of care. Often, these patients are treated with platinum-based systemic therapies based on findings extrapolated from mucosal HNSCC, with little known regarding the efficacy of such an approach. More recently, EGFR targeted therapies have also emerged as a potential therapeutic option given EGFR over-expression in cutaneous HNSCC.[13-14] A number of case reports as well as one phase II study of cetuximab have demonstrated clinical activity in cutaneous SCC.[14] Intention-to-treat analysis of 36 patients (14% with HNSCC primaries) receiving cetuximab as first-line monotherapy for unresectable cutaneous SCC demonstrated disease control and overall response rates of 81% and 11%, respectively.[14] Thus, the combination of cetuximab with a novel therapeutic may also represent an attractive treatment strategy for cutaneous HNSCC.

1.2 PD-1 Receptor-Ligand Interactions

The importance of intact functions of immune surveillance in controlling outgrowth of neoplastic transformations has been known for decades.[15] 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 re-infused, inducing durable objective tumor responses in cancers such as melanoma.[16-17] 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).[18-19] The structure of murine PD-1 has been resolved.[20] PD-1 and 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 CD3ζ, PKCθ, and ZAP70, which are involved in the CD3 T-cell signaling cascade.[19, 21-23.]

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.[24-25] PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B cells, T regs, and natural killer cells.[26-27] Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells, as well as subsets of macrophages and dendritic cells.[28] The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types including nonhematopoietic tissues and in various tumors. [15, 25, 29-31] Both ligands are type 1 transmembrane receptors containing IgV-like and Ig constant–like (IgC-like) domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-L1 or PD-L2 to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various nonhematopoietic tissues, most notably on vascular endothelium; whereas PD-L2 is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues.[25] Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including renal cell carcinoma,[32] pancreatic carcinoma,[33] hepatocellular carcinoma,[34] and ovarian carcinoma.[35] Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma.[36]

The observed correlation of clinical prognosis with PD-L1 expression in multiple cancers suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Interestingly, evaluation of PD-L1 expression among 19 distinct histologies revealed that HNSCC had the highest frequency of PD-L1 expression, with 17 of 54 (31%) of HNSCC tumor samples expressing cell surface PD-L1.[37] Additional preclinical data evaluating PD-L1 expression with respect to HPV status demonstrated that 60-70% of HPV-positive HNSCC tumor samples had cell surface staining for PD-L1 by IHC or immunofluorescence and nearly 100% had PD-L1 staining at the interface between tumor and inflammatory stroma.[38-39] Approximately 30% of HPV-negative HNSCC stained for PD-L1 by IHC or immunofluorescence.[38-39] Greater than 75% of tumor infiltrating lymphocytes (TILs) from both HPV positive and HPV negative HNSCC expressed PD-1, even in cases where tumors stained negative for PD-L1 by IHC. TILs express PD-1 at higher levels than PBMC from matched patients, and blockade of PD-1/PD-L1 resulted in increased immune cell function, as determined by increased interferon-gamma secretion by fresh TILs isolated from patients with HNSCC.[38-39]

Early results from clinical trials evaluating PD-1 or PD-L1 blocking antibodies have shown promising results in melanoma and non-small cell lung cancer.[40-42] To date, while there are no published studies evaluating such therapies in HNSCC, early proof of concept studies are currently ongoing, with promising results. Interim results for the R/M HNSCC cohort of the phase Ib pembrolizumab trial (KEYNOTE-12) were presented at the European Society for Medical Oncology (ESMO) 2014 Congress.[43] The observed response rate of pembrolizumab monotherapy was approximately 20%, irrespective of HPV status, with median duration of response not reached at the date of analysis cut-off. Further, 6-month PFS rates were approximately 35% for the overall HNSCC cohort, with PFS and overall survival rates noted to be better in patients with HPV positive HNSCC. Interim results from 132 patients in the biomarker-unselected KEYNOTE-12 HNSCC expansion cohort were subsequently presented at the annual American Society of Clinical Oncology (ASCO) Meeting in 2015.[44] Overall response rate for the entire cohort was 24.8%, disease control rate was 49.6%, and 6-month PFS rate of approximately 30%. These preliminary findings suggest that pembrolizumab is a safe, well-tolerated therapy with promising anti-tumor activity in R/M HNSCC, irrespective of HPV status.

1.3 Pembrolizumab

Pembrolizumab (KEYTRUDA®; MK-3475) is a potent and highly selective humanized monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4)/kappa isotype designed to directly block the interaction between PD-1 and its ligands, programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection. On 04-Sep-2014, the United States (U.S.) Food and Drug Administration (FDA) granted accelerated approval to KEYTRUDA® for treatment of subjects with unresectable or metastatic melanoma and disease progression following treatment with ipilimumab (IPI) and, if BRAF V600 mutation positive, a BRAF inhibitor.

1.3.1 Clinical Pharmacology

The pharmacokinetic profile of pembrolizumab, with low clearance and limited volume of distribution, is typical for therapeutic antibodies. Exposure to pembrolizumab is approximately

linear in the dose range of clinical relevance (1 to 10 mg/kg). Furthermore, pembrolizumab has a low potential of eliciting the formation of anti-drug antibodies.

1.3.2 Clinical Safety

In the pembrolizumab monotherapy trials (P001/P002, P012, P013, and P028, plus the P011 monotherapy arm), the overall incidence of AEs ranged from 83.0% (73 of 88 subjects in P012) to 100% (10 of 10 subjects in P011). The most commonly reported AEs included fatigue, diarrhea, decreased appetite, nausea, dyspnea, and anemia. The incidence of drug –related AEs (DRAEs) ranged from 39.8% (35 of 88 subjects in P013) to 80.0% (8 of 10 subjects in P011). The most commonly reported DRAEs across all studies were nausea, fatigue, and diarrhea. The incidence of Grade 3-5 DRAEs across studies ranged from 6.8% (6 of 88 in P013) to 12.0% (187 of 1562 subjects) in P001/P002. The most commonly reported Grade 3-5 DRAEs were anemia, alanine aminotransferase increased, aspartate aminotransferase increased, and colitis. Most subjects who experienced an AE continued in the study, with the incidence of AEs leading to discontinuation ranging from 4.2% (18 of 430 subjects in P028) to 12.3% (192 of 1562 subjects in P001/P002). The majority of AEs leading to discontinuation were not considered drug related. Discontinuations due to a DRAE were infrequent and ranged from 0% (no subjects in P011) to 4.5% (4 of 88 subjects in P013). The most commonly reported DRAE leading to discontinuation was pneumonitis.

In general, the incidence of drug-related serious adverse events (DRSAEs) was low. Many of the events occurred in 1 subject each and/or <1.0% each.

In the pembrolizumab monotherapy trials, the most commonly reported DRSAEs (those that occurred in 3 or more subjects overall in at least 1 study) were pneumonitis (range of 0.7% to 1.3% of subjects); colitis (range of 0.3% to 1.1% of subjects), pyrexia (range of 0.3% to 0.5% of subjects); diarrhea (range of 0.2% to 0.4%); hepatitis (0.7% of subjects); nausea, adrenal insufficiency, hyponatremia, hyperthyroidism, hypophysitis, vomiting, and dyspnea (0.3% of subjects each); and dehydration, generalized edema, hypothyroidism, renal failure acute, and pericardial effusion (0.2% of subjects each). The remaining DRSAEs occurred in 1 or 2 subjects each per study.

Infusion reactions have been reported with pembrolizumab at a rate of 2.5%; these were generally Grade 1 and 2 and the majority were considered related by the Investigator. One event of Grade 4 anaphylaxis has been reported. Patients should be closely monitored for potential AEs during antibody infusion and potential AEs throughout the study.

Pembrolizumab has the same mechanism of action as other anti-PD-1 monoclonal antibodies. Accordingly, the AEs observed with other anti-PD-1 antibodies may serve as an indicator for the AEs to expect in cancer subjects. Furthermore, AEs from other immunotherapies for cancer were considered in the *Pembrolizumab Program (MK-3475) Event of Clinical Interest and Immune-Related Guidance Document.*

An immune-related adverse event (irAE) is defined as a clinically significant AE of any organ that is associated with study drug exposure, is of unknown etiology, and is consistent with an immune-related mechanism. Adverse events of special interest (AEOSI) data for melanoma and lung subjects demonstrates that irAEs were reported in 16.1% of subjects (251 of 1562) overall; AEOSI were considered by the Investigators to be drug related in 14.3% of subjects (223 of 1562). The majority of AEOSI were Grade 1 or 2 in severity. Serious AEOSI were identified in 3.9% of subjects, and serious AEOSI that were considered by Investigators to be

drug-related were identified in 3.3% of subjects overall. Grade 3-5 AEOSI were identified in 4.0% of subjects. There was 1 fatal AEOSI (pneumonitis) in the 10mg/kg Q3W arm. Forty subjects (2.6%) discontinued drug due to a drug-related AEOSI.

The most commonly reported immune-related adverse events across the dose schedules are hypothyroidism (7.2%), pneumonitis (2.9%), hyperthyroidism (2.2%), colitis (1.3%) and skin AEOSI (1.3% including all terms). These events can occur after the first dose to several months after the last dose of treatment. Mild irAEs are usually treated symptomatically and do not require dosing delays or discontinuation. Higher grade and persistent lower grade irAEs typically necessitate withholding or discontinuing treatment and administration of systemic steroids or other immunosuppressive agents (such as tumor necrosis factor blockers), when systemic steroids are not effective. Early recognition of irAEs and initiation of treatment are critical to reduce the risk of complications, since the majority of irAEs are reversible with the use of steroids and other immune suppressants

1.3.3 Clinical Efficacy

Efficacy data are available for a total of 655 P001 melanoma subjects treated with pembrolizumab and 540 P002 melanoma subjects treated with either pembrolizumab or chemotherapy. The data cutoff dates are 18-Apr-2014 for P001 melanoma subjects and 12-May-2014 for P002.

P001 is a, Phase I, first-in-human study of pembrolizumab monotherapy in subjects with progressive locally advanced or metastatic carcinomas, especially melanoma or non-small cell lung cancer (NSCLC). Through a series of amendments, P001 evolved into 4 phase II-like melanoma substudies, to include ipilimumab-refractory and ipilimumab-naïve patients, as well as 3 different pembrolizumab dose regimens (2mg/kg Q3W, 10mg/kg Q3W, and 10mg/kg Q2W). The primary efficacy endpoint is ORR. A secondary efficacy endpoint is disease control rate (DCR). The ORR and DCR analysis for 655 melanoma subjects who received pembrolizumab regardless of prior exposure to ipilimumab and across all dose levels tested, is as follows: overall, there were 44 complete responses and 159 partial responses. The ORR was 31% (95% CI: 28% to 35%). DCR was achieved in 51% of all subjects.

P002 is a partially blinded, randomized, Phase II pivotal study of 2 pembrolizumab dose regimens versus standard-of-care chemotherapy in subjects with melanoma refractory to ipilimumab. The two coprimary efficacy endpoints are progression-free survival and overall survival. A secondary efficacy endpoint is ORR. The 6-month PFS analysis for 361 subjects who received pembrolizumab was 34.3% (95% CI: 27.4 to 41.3%) and 37.7% (95% CI 30.6% to 44.8%) for the 2mg/kg and 10mg/kg dosing regimens, respectively, versus 15.6% (95% CI: 10.5% to 21.5%) for the control arm (chemotherapy). The ORR was 21% in the pembrolizumab 2mg/kg arm, 25% in the 10mg/kg arm, and 4% in the control arm.

1.4 Rationale for the Study

EGFR-targeted monoclonal antibodies such as cetuximab, have been shown to augment the host immune response to tumors, including HNSCC. Antibodies cause antibody-dependent cellular cytotoxicity (ADCC) and result in cross talk among immune cells, including natural killer (NK) cells and dendritic cells (DCs), which can prime tumor antigen-specific cellular immunity and generation of tumor antigen-specific T-lymphocyte responses.[45] As shown by Lee et al, interaction of cetuximab with EGFR on tumor cells and the Fc gamma receptor IIIa (FcγR IIIa) on NK cells enhances cross-presentation of EGFR by DC to cytotoxic T lymphocytes (CTLs). In

addition, HNSCC patients treated with cetuximab had higher numbers of circulating EGFR-specific T cells compared to cetuximab-naïve patients.[45] Understanding the role of adaptive immunity in cetuximab-mediated tumor regression is less well-defined, primarily due to a lack of appropriate experimental tumor cell lines responsive to cetuximab in immune-competent hosts. Recently, Yang et al developed an immune-reconstituted human tumor xenograft model and EGFR-dependent mouse cell line through which they were able to demonstrate that the therapeutic effect of cetuximab was dependent upon both innate and adaptive immunity, including CD8+ T cells, MyD88 and FcγR.[46]

Together, these data raise the intriguing possibility that the released inhibition of the adaptive immune response by PD-1 blockade coupled with ADCC and stimulation of the innate immune response by cetuximab may result in anti-tumor synergism that can be clinically exploited. For cetuximab-naïve patients, recruiting adaptive immunity may lead to better and more durable responses than observed with cetuximab alone, thus improving progression-free survival beyond current standard of care. Improved clinical efficacy could ultimately lead to registration trials of the combined drug therapy for this patient population.

Patients previously treated with anti-PD-1/PD-L1 therapy who initially achieved a therapeutic benefit have already demonstrated an ability of the immune system to respond to the tumor. We hypothesize that a lasting footprint of anti-PD-1/PD-L1 remains is counteracted by other regulatory factors. One potential means to exploit this change could include the combination of continued anti-PD-1 therapy with the addition of cetuximab, to determine if ADCC and stimulation of innate immunity in an already primed setting could induce further therapeutic response.

For cutaneous HNSCC, immunotherapy also represents an attractive treatment approach as these tumors possess pre-requisites, such as tumor-associated antigens and tumor specific immune response, which are needed for immune intervention. Cutaneous SCC has been shown to demonstrate loss of HLA-A, B-monomorphic determinants, down-regulation of total surface class I expression, and differential heavy chain and beta-2 microglobulin expression.[47] Further, cutaneous SCC tumor nests are often surrounded by mononuclear infiltrates (primarily T cells), suggesting tumor immunogenicity.[47] Finally, there is data to suggest that cutaneous SCC can abrogate immune recognition through the production of various immunosuppressive Th2 type cytokines, thus resulting in inhibition of the cell-mediated immune response, depletion of antigen-presenting cells (APC), and down-regulation of costimulatory molecules (CD80 and CD86) on APCs.[47] These data combined with known EGFR overexpression in cutaneous HNSCC suggest potential clinical activity with the combination of EGFR targeted therapy (cetuximab) and PD-1 inhibition (pembrolizumab).

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

1. To determine the clinical efficacy of pembrolizumab combined with cetuximab for patients with R/M HNSCC.
    a. Cohort 1 (PD-1/PD-L1 inhibitor-naïve, cetuximab-naïve): clinical efficacy defined as overall response rate.
    b. Cohort 2 (PD-1/PD-L1 inhibitor-refractory, cetuximab-naïve): clinical efficacy defined as overall response rate.
    c. Cohort 3 (PD-1/PD-L1 inhibitor-refractory, cetuximab-refractory): clinical efficacy defined as overall response rate.

d. Cohort 4 (cutaneous HNSCC): clinical efficacy defined as overall response rate.

2.2 Secondary Objectives

1. To determine 12 month progression-free survival probability.
2. To determine overall survival.
3. To determine duration of response.
4. To assess safety and tolerability of pembrolizumab combined with cetuximab.
5. To evaluate the correlation between molecular markers and disease outcome.

2.3 Endpoints

1. **Primary Endpoint** (for all cohorts): Overall response rate by 6 months, defined as the proportion of patients with partial or complete response in tumor burden as defined by RECIST.

Secondary Endpoints:

1. Progression-free survival probability (defined as probability of no disease progression or death from any cause) at 12 months from the time of study enrollment.
2. Overall survival, defined as time from study enrollment to death from any cause.
3. Duration of response, defined as time from documentation of tumor response to disease progression.
4. Safety and tolerability, defined as adverse events related to pembrolizumab and cetuximab (description, grade [CTCAE v4.03], seriousness).
5. Correlative analyses:
    a. Archival and/or newly obtained tumor specimens will be evaluated for biomarkers correlated with outcome to pembrolizumab or cetuximab, including PD-L1 expression, EGFR expression, p16 status, IDO expression, cyclin D1, bcl-xL and p53 status.
    b. Archival and/or newly obtained tumor specimens will be evaluated for immunophenotyping by flow cytometry:
        i. T cell subsets (CD3, CD4, CD8, CD25, FOXP3)
        ii. B cells (CD 19, CD20)
        iii. Macrophage I/II and myeloid-derived suppressor cells (MDSC) (CD16, CD68, CD206)
        iv. Natural killer cell activity (CD56, CD16)
6. T cell receptor (TCR) sequencing from blood obtained at baseline, at time of first radiographic disease assessment on study, and at time of disease progression.
7. Whole exome sequencing (for the purposes of neoantigen discovery) from newly obtained tumor specimen when feasible.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

Patients must meet all of the inclusion criteria to participate in this study.

1. Ability to understand and the willingness to sign a written informed consent.

2. Histologically or cytologically proven squamous cell carcinoma of the head and neck (lip, oral cavity, oropharynx, larynx, hypopharynx, non-EBV related nasopharynx, sinonasal, cutaneous), not amenable to curative intent therapy.

3. Platinum-refractory disease, or ineligible/unfit for platinum-based therapy

4. Patients must have at least one measurable site of disease as defined by RECIST v.1.1, determined by investigator review

5. Age ≥ 18 years.

6. Eastern Cooperative Oncology Group (ECOG) Performance status 0 or 1.

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

7. Patient has adequate organ and marrow function as defined below:
    - Absolute Neutrophil Count ≥ 1.0 x 10^9/L
    - Platelet count ≥ 75 x 10^9/L
    - Hemoglobin ≥ 8.0 g/dL
    - Total bilirubin ≤ 1.5 x institution's upper limit of normal
    - AST/SGOT and ALT/SPGT ≤ 2.5 X institutional upper limit of normal
    - Albumin ≥ 2.0 g/dL
    - Serum creatinine ≤ 1.5 x institution's ULN, or creatinine clearance ≥ 60 ml/min

8. Female patient of childbearing potential has a negative serum or urine pregnancy within 72 hours prior to receiving the first dose of study medication.

9. Female patient of childbearing potential agrees to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 4.6.2).

    Note: Females of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year, and are not on medications known to suppress menses.

10. Male patient with a partner of childbearing potential agrees to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

Additional Inclusion Criterion for Cohort 1 (PD-1/PD-L1 inhibitor-naïve, Cetuximab-naïve) and Cohort 2 (PD-1/PD-L1 inhibitor-refractory, Cetuximab-naïve):

1. Cetuximab-naïve patients may not have received cetuximab therapy in the recurrent/metastatic setting (treatment in curative setting permitted)

Additional Inclusion Criterion for Cohorts 2 and 3 (PD-1/PD-L1 inhibitor-refractory):

1. PD-1/PD-L1 inhibitor-refractory patients must have documented disease progression after prior response to anti-PD-1/PD-L1 therapy (response defined as stable disease, partial or complete response)

Additional Inclusion Criterion for Cohort 4 (Cutaneous HNSCC):

1. Cutaneous HNSCC must not be amenable to local treatment modalities, including surgery and/or radiation.

3.2 Exclusion Criteria

Patients meeting any of the exclusion criteria at baseline will be excluded from study participation.

1. Patient has salivary gland primary.

2. Patient is currently receiving or has received another investigational agent within 4 weeks prior to Day 1 of study.

3. Patient has received chemotherapy or radiotherapy within 4 weeks prior to Day 1 of study. Prior palliative radiotherapy to metastatic lesion(s) is permitted, provided there is at least one measurable lesion that has not been radiated.

4. Patient has received a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or baseline) from adverse events due to a previously administered agents.

5. Patient has had major surgery or insufficient recovery from surgical-related trauma or wound healing within 14 days of Study Day 1.

6. Patient has had a prior Grade ≥ 3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE > Grade 1.

7. Patient has had prior Grade 4 infusion reaction to cetuximab.

8. Patient has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or *in situ* cervical cancer.

9. Patient has known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

   Note: Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no

evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

10. Patient has an 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).
    Notes:
    - Patients with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment within the past 2 years are not excluded.
    - Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

11. Patient has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (>10mg prednisone daily, or steroid equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of pembrolizumab.

12. Patient has a known history of active TB (*Baccillus Tuberculosis*).

13. Patient has a known history of, or any evidence of active, non-infectious pneumonitis.

14. Patient has a known history of chronic interstitial lung disease.

15. Patient has an active infection requiring systemic therapy.

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

17. Patient has a known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

18. Patient is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial.

19. Patient has known active Hepatitis B infection (defined as presence of HepB sAg and/ or Hep B DNA), active hepatitis C infection (defined as presence of Hep C RNA) and/or known Human Immunodeficiency Virus (HIV) carrier (HIV 1/2 antibodies).

20. Patient has received a live vaccine within 30 days of study Day 1.
    Note: *Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.*

Additional Exclusion Criterion for Cohorts 1 (PD-1/PD-L1 inhibitor-naïve, cetuximab-naïve) and 4 (cutaneous):

1. Patient has received any prior immunotherapy with inhibitors of PD-1 or PD-L1.

4.0 TREATMENT PLAN

4.1 Study Design

This is a prospective, multi-center, open-label, non-randomized, multi-arm phase II trial to evaluate the efficacy of combination therapy with pembrolizumab and cetuximab for patients with recurrent/metastatic HNSCC. There will be four patient cohorts, including a PD-1/PD-L1 inhibitor-naïve, cetuximab-naïve arm (Cohort 1), a PD-1/PD-L1 inhibitor-refractory, cetuximab-naïve arm (Cohort 2), a PD-1/PD-L1 inhibitor-refractory, cetuximab-refractory arm (Cohort 3), and a cutaneous HNSCC arm (Cohort 4). A total of 83 patients (33 in Cohort 1, 25 in Cohort 2, 15 in Cohort 3, and 10 in Cohort 4) will be eligible to enroll. Patients will be enrolled at 4 sites: UC San Diego Moores Cancer Center, UC Los Angeles Jonsson Comprehensive Cancer Center, University of Michigan Comprehensive Cancer Center, and University of Washington Siteman Cancer Center.

All patients providing informed consent will be screened for eligibility. Adequate tumor biopsy tissue must be available for participation; tissue may be archival if newly obtained specimen is not feasible. Baseline assessments will include vital signs, physical exam, ECOG performance status evaluation, blood hematology and chemistries, urinalysis and tumor imaging. An extra sample of blood will be collected for correlative studies.

Upon study entry, all patients will receive cetuximab loading dose (400mg/m2 IV) on day 1, and 250mg/m2 IV on days 8 and 15 of cycle 1, followed by 250mg/m2 on days 1, 8 and 15 of each subsequent 21-day cycle. Pembrolizumab will be administered at a flat dose of 200mg IV on day 1 of each 21-day cycle. Treatment will be given until disease progression, unacceptable toxicity, investigator decision or patient withdrawal.

All patients will have regular evaluations for assessment of safety parameters and response as detailed in the study schedule of events. History and physical examination, adverse event assessment and routine bloodwork will be performed prior to every cycle. All patients will undergo imaging with CT, MRI, or PET/CT (CT must be diagnostic quality) within 4 weeks prior to study entry, and then every 9 weeks (±7 days) after treatment initiation. For patients who are clinically stable, a repeat scan will be required 4 weeks (±7 days) after initial radiographic findings of disease progression as a confirmatory assessment. Blood correlative studies will also be obtained at time of first radiographic disease assessment (± 7 days) and at time of disease progression (± 7 days).

An end of treatment visit for clinical evaluations and safety assessments will be performed approximately 28 days (± 7 days) after the last dose of study drug. Patients discontinuing study treatment will be followed every 3 months for disease and survival outcomes.

4.2 Treatment Dosage and Administration

4.2.1 Preparation and Administration of Pembrolizumab

Specific instructions for the preparation infusion fluid and administration of infusion solution are provided in the Pharmacy Manual.

Pembrolizumab is administered on an outpatient basis. 200 mg pembrolizumab will be administered as a 30 minute (-5 min/+10 min) intravenous (IV) infusion every 3 weeks.

4.2.2 Preparation and Administration of Cetuximab

Specific instructions for the preparation infusion fluid and administration of infusion solution are provided in the Pharmacy Manual.

Cetuximab is administered intravenously once weekly via infusion pump or syringe pump with infusion rate not to exceed 10 mg/min. On cycle 1 day 1, patients will receive a loading dose of 400 mg/m^2 IV, then will receive 250 mg/m^2 IV weekly.

4.2.3 Monitoring of Dose Administration

Patients will be monitored during and after the infusion with assessment of vital signs at the times specified in the Schedule of Events.

Patients will be monitored for the presence of infusion-related reactions. Dose modification and toxicity management for infusion-related reactions are outlined in the dose modification section (Section 4.3).

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary.

4.2.4 Criteria for Starting Subsequent Cycles.

A cycle may be repeated every 21 days if the patient is without ongoing Grade 3 non-hematologic or Grade 4 hematologic toxicities attributable to study treatment.

4.3 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.03.

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 4-1 below. See Section 4.5.1 and Events of Clinical Interest (ECI) Guidance Document for supportive care guidelines, including use of corticosteroids.

Tables 4.2 and 4.3 should be used as guidelines for cetuximab dose modifications. Please refer to cetuximab label for additional information.

Table 4-1. Pembrolizumab Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Patient
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Patient
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism	2-4	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[2]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

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

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

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

Table 4-2. Cetuximab Dose Modification Guidelines for Infusion Reactions

NCI-CTCAE Grade	Dose Modification
1	Reduce infusion rate by 50%
2	
Non-serious grade 3	
Serious grade 3 (e.g. requiring hospitalization) or any grade 4	Immediately and permanently discontinue cetuximab

Table 4-3. Cetuximab Dose Modification Guidelines for Dermatologic Toxicity

Severe Acneiform Rash	Cetuximab Delay/Discontinuation	Outcome	Dose Modification
1st Occurrence	Delay infusion by 1-2 weeks	Improvement	Continue at 250mg/m2
		No improvement	Discontinue cetuximab
2nd Occurrence	Delay infusion by 1-2 weeks	Improvement	Reduce dose to 200mg/m2
		No improvement	Discontinue cetuximab
3rd Occurrence	Delay infusion by 1-2 weeks	Improvement	Reduce dose to 150mg/m2
		No improvement	Discontinue cetuximab
4th Occurrence	Discontinue cetuximab		

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). The reason for interruption should be documented in the patient's study record.

4.4 Concomitant Medications/Vaccinations

Concomitant medication also includes all prescription, over-the-counter (OTC), herbal supplements, blood transfusions, and IV medications. The patient needs to notify the investigational site about any new medications he/she takes after the start of the study drug.

All concomitant medications received within 7 days before the first dose of trial treatment and 28 days after the last dose of trial treatment should be recorded in the patient’s medical record. Concomitant medications administered after 28 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.3 and 7.6.

4.4.1 Permitted concomitant therapy

Medications required for treating adverse events and managing cancer symptoms, concurrent stable disease (e.g., controlled hypertension) and supportive care agents such as anti-emetics, erythropoietin, granulocyte growth factors, or blood transfusion, and pain medications are allowed. The patient needs to notify the investigational site about any new medications he/she

takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be recorded in the patient's medical record.

4.4.2 Prohibited concomitant therapy

Patients 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.
- Radiation therapy.
    - Note: Radiation therapy to a symptomatic lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology.

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

The Exclusion Criteria describes other medications which are prohibited in this trial.

4.5 Rescue Medications and Supportive Care

4.5.1 Supportive Care Guidelines for Pembrolizumab

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below (Table 4-2) and in greater detail in the ECI guidance document. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 4.3 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

Table 4-2. Supportive Care Guidelines

Event	Suggested Measures
Pneumonitis	• For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed. • Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
Diarrhea/Colitis	Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). • All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis. • For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids. • For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids. • When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Type 1 diabetes mellitus	**(if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
	• For **T1DM** or **Grade 3-4** Hyperglycemia
	  ○ Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
	  ○ Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

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

Hyperthyroidism or Hypothyroidism	Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
	
	• **Grade 2** hyperthyroidism events (and **Grade 3-4** hypothyroidism):
	  ○ In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
	  ○ In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
	• **Grade 3-4** hyperthyroidism
	  ○ Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

Hepatic	• For **Grade 2** events, monitor liver function tests more frequently until returned to

Event	Suggested Measures
	baseline values (consider weekly). ○ Treat with IV or oral corticosteroids • For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours. • When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
Renal Failure or Nephritis	• For **Grade 2** events, treat with corticosteroids. • For **Grade 3-4** events, treat with systemic corticosteroids. • When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Management of Infusion Reactions: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Table 4-3 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Table 4-3. Pembrolizumab Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 **Grade 3:** Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g.,	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilatory support indicated	Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

4.5.2 Supportive Care Guidelines for Cetuximab

Patients should be premedicated with an H1 antagonist (e.g. 50mg of diphenhydramine) intravenously 30-60 minutes prior to the first dose. Premedication for subsequent doses should be based upon clinical judgment and history of prior infusion reactions. Premedication with steroids may be administered on Cycle 1 Day 1, if required by institutional standards.

Serious infusion reactions, requiring medical intervention and immediate, permanent discontinue of cetuximab, include rapid onset of airway obstruction (e.g. bronchospasm, stridor, hoarseness), hypotension, shock, loss of consciousness, myocardial infarction and/or cardiac arrest.

Subjects should be monitored for 1 hour following cetuximab infusions in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (e.g. epinephrine, intravenous antihistamines, bronchodilators, oxygen, corticosteroids).

Guidelines for medical therapy for infusion reactions detailed in Table 4.3 above are also recommended for reactions due to cetuximab.

4.5.3 Magnesium Monitoring Guidelines for Cetuximab

NCI CTCAE Grade	Serum Magnesium		Guidelines for Management	Action
	mg/dL	mmol/L		
1	<LLL-1.2	<LLN-0.5	Consider replacement with IV magnesium sulfate 2-5 g in normal saline or D5W. Infusion schedule based on institutional guidelines.	Maintain dose and schedule
2	<1.2-0.9	<0.5-0.4	As above for grade 1 and consider prophylactic weekly infusion of magnesium and/or oral magnesium supplementation (e.g. magnesium oxide) if grade 2 or higher hypomagnesemia persists.	Maintain dose and schedule
3	<0.9-0.7	<0.4-0.3	As above for grades 1 and 2	Hold cetuximab until recovery to grade ≤2, then resume
4	<0.7	<0.3	As above for grades 1 and 2	Hold cetuximab until recovery to grade ≤2, then resume

Refer to approved product label for additional supportive care guidance.

4.6 Other Considerations

4.6.1 Diet

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

4.6.2 Contraception

Pembrolizumab may have adverse effects on a fetus *in utero*. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥ 45 years of age, has been free from menses for greater than 1 year and is not on medications known to suppress menses will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be 2 barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Patients should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study drug.

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

Patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in Section 7.6.2 Pregnancy and Lactation. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

4.6.3 Use in Pregnancy

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

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Study Chair. If a male patient impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Study Chair and to Merck and followed as described above and in Section 7.6.2.

4.6.4 Use in Nursing Women

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

4.7 Patient Withdrawal/Discontinuation from Study Treatment

In the absence of treatment delays due to adverse events, study treatment may continue until:

- Disease progression
- The patient experiences unacceptable adverse event(s) or those events listed in the dose modification guidelines that require discontinuation;
- The patient exhibits an inter-current illness that prevents further administration of study treatment,
- The patient has a confirmed positive serum pregnancy test;
- The patient or legal representative withdraws consent;
- The patient is noncompliant with trial treatment or procedure requirements;
- The patient is lost to follow-up;
- The patient dies;
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator;
- Administrative reasons.

4.8 End of Study Treatment and Follow Up

After the last dose of study treatment, each patient will be followed for 28 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.1). Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Patients who discontinue for reasons other than progressive disease will have post-treatment follow-up approximately every 3 months for disease status until disease progression, initiation of a non-study cancer treatment, withdrawal of consent or lost to follow-up.

After documented disease progression, each patient will be followed approximately every 3-6 months by review of medical records, telephone, or review of the Social Security Index for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

4.9 Patient Withdrawal/Discontinuation from Study Criteria

Patients may be removed from study participation for the following reasons:

- The patient or legal representative withdraws consent for follow-up;
- The patient is lost to follow-up;
- The patient dies;
- It is the decision of the investigator.

5.0 STUDY PROCEDURES

Refer to the study Schedule of Events for procedures.

All patients will be closely monitored for safety and tolerability during all cycles of therapy, at study treatment completion/early study treatment discontinuation, and during the follow-up period.

5.1 Definitions of Study Assessments

a. Medical history

A medical history and details regarding the disease for which the patient has enrolled in this study 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. Any clinically significant changes from Screening (e.g. worsening severity or abnormal findings) are considered to be adverse events (AEs).

b. Demographics

The patient's demographic profile of date of birth, gender, race, and ethnicity will be obtained unless the patient declines.

c. Review of eligibility criteria

Review of eligibility criteria as described in Section 3 to ensure patient qualification for study entry and adjuvant study treatment.

d. Concomitant Medication

All concomitant therapy, including anesthetic agents, vitamins, homeopathic/herbal remedies, nutritional supplements, received by patients from seven days prior to the first day of study treatment until 28 days after the last study dose (or until the start of a new treatment, whichever comes first) will be recorded in the patient's medical record. If a reportable adverse event deemed related to study intervention (see Section 7) occurs within 28 days after last study dose and the patient has not started a new treatment, recording of concomitant medications related to the treatment of that adverse event should continue until resolution of the adverse event.

e. Physical exam

The investigator or qualified designee will perform a complete physical examination during screening, which should include the evaluation of general appearance; evaluation of head, eyes, ears, nose, and throat (HEENT); and cardiovascular, pulmonary, abdominal, musculoskeletal, skin, lymph nodes, neurological, and genitourinary systems. Subsequent exams may be directed as appropriate.

Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as adverse events if clinically significant.

f. Vital Signs and height

Vital signs should include temperature, pulse, blood pressure and weight. Height will only be collected at screening.

g. Performance status

Performance status is evaluated by the ECOG scale.

h. Adverse event assessment

Baseline assessment of subject status for determining adverse events. See Section 7 for Adverse Event monitoring and reporting.

i. Laboratory Assessments

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5-1.

Table 5-1. Laboratory tests

Hematology	• Complete Blood Count (CBC) with differential
	  ○ hemoglobin,
	  ○ hematocrit,
	  ○ platelet count,
	  ○ white blood cell count,
	  ○ percentage or absolute differential count

Chemistry	• Comprehensive metabolic panel (CMP)
	  ○ albumin
	  ○ alkaline phosphatase
	  ○ aspartate aminotransferase (ALT)
	  ○ alanine aminotransferase (AST)
	  ○ bicarbonate (CO_2)
	  ○ blood urea nitrogen (BUN)
	  ○ calcium
	  ○ chloride
	  ○ creatinine
	  ○ glucose
	  ○ potassium
	  ○ sodium
	  ○ total protein
	  ○ total bilirubin
	• Thyroid stimulating hormone (TSH)
	• Magnesium

Pregnancy Test	• Urine human chorionic gonadotropin (HCG) or serum βHCG
Urinalysis	○ Blood, ○ Glucose, ○ Protein, ○ Specific gravity ○ Microscopic exam (*if abnormal*)
If clinically indicated	• Hepatitis B: HepB sAg and/ or Hep B DNA • Hepatitis C: Hep C RNA PCR • HIV

j. Blood collection for correlative studies

See Section 5.5 for details.

k. Tumor assessment

Radiologic assessment is performed by MRI or CT (neck and chest, abdomen/pelvis as indicated) or PET/CT. If a PET/CT is performed, the CT must be of diagnostic quality. The same radiographic technique should be used throughout the study. However, a patient who develops a contraindication to undergo an MRI scan during study treatment may remain on study and undergo contrast enhanced CT scans.

l. Tumor biopsy and tissue collection

See Section 5.5 for details.

5.2 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 21 days prior to registration unless otherwise stated. The screening procedures include:

- Written informed consent *(within 28 days)*.
- Review of inclusion and exclusion criteria.
- Complete medical/oncology history.
- Demographics.
- Documentation of concomitant medications.
- Complete physical examination, including vital signs and height.
- Performance status assessment.
- Laboratory tests *(within 7 days; pregnancy test within 72 hours)*.
- Blood collection for correlative studies.
- Documentation of tumor staging *(within 28 days)*.
- Tumor biopsy tissue collection for correlative studies *(within 42 days)*.

5.3 Procedures During Treatment

5.3.1 Cycle 1 Day 1 (±3 days)

- Focused physical exam, including vital signs, ECOG performance status assessment and weight
- Assess for adverse events
- Update concomitant medications
- Collect blood samples for CBC with differential, CMP, Magnesium

5.3.2 Each Additional Cycle, Day 1 (±3 days)

- Focused physical exam, including vital signs, ECOG performance status assessment and weight
- Assess for adverse events
- Update concomitant medications
- Collect blood samples for CBC with differential, CMP, Magnesium

5.3.3 Thyroid studies and Urinalysis (±3 days)

- Collect blood sample for TSH at cycle 2, cycle 4, then every 3 cycles thereafter (ie. cycle 7, 10, etc.). Obtain urinalysis (dipstick) every 3 cycles following treatment initiation (ie. cycle 4, 7, 10 etc). Urine microscopic examination should be performed if dipstick abnormal.

5.3.4 Additional Blood Collection for Correlative Studies (±7 days)

- At time of first radiographic disease assessment on treatment
- At time of disease progression

5.3.5 Imaging (every 9 weeks ±7 days after treatment initiation)

- MRI, CT (neck, chest; abdomen/pelvis when indicated) or PET/CT (CT must be diagnostic quality)
- For patients who are clinically stable, a repeat scan will be required 4 weeks (±7 days) after initial radiographic findings of disease progression as a confirmatory assessment.

5.3.6 End of Treatment Visit *(28 days after last dose, ± 7 days)*

- Focused physical exam, vital signs, ECOG performance status, weight
- Documentation of concomitant medications and adverse events.
- Collect blood samples for CBC with differential, CMP, TSH, Magnesium.
- Obtain urinalysis. Urine microscopic examination should be performed if dipstick abnormal.

5.4 Follow-up Procedures

Patients discontinuing study treatment will be followed every three months after the last dose of study treatment until death with:

- Tumor assessments if they discontinued from study treatment without disease progression- until disease progression or initiation of a new anti-cancer therapy, and
- Survival contacts via medical record review, telephone call, or review of the Social Security Index.

5.5 Correlative Studies

The goal of the planned laboratory correlative studies is to further characterize the biology of PD-L1 blockade, to gain a better understanding of the impact of pembrolizumab on the tumor's immunophenotype, and explore potential biomarkers which may correlate with response to pembrolizumab and cetuximab.

5.5.1 Sample Collection Guidelines

Specimens should be collected as outlined below and ALL samples should be labeled with the following:

- Protocol number
- Institution
- Patient's de-identified study number
- Date of biopsy or surgery

5.5.1.1 Newly obtained tumor tissue

Newly obtained tumor tissue will be collected when feasible, preferably from a diagnostic core biopsy, within 28 days of initiating study treatment.

Samples collected for research will be obtained from only material in excess of that needed for routine clinical care as determined by a staff pathologist.

When possible, 4 core biopsies should be taken for lesions > 1.5 cm, otherwise 2 cores should be taken.

- If 4 cores are obtained, 1 core should be fresh frozen and the rest should be formalin-fixed paraffin embedded (FFPE).

- If < 4 cores are obtained, tissue for research should be FFPE after being divided into the research and diagnostic documentation blocks according to the Pathology staff's specifications.

Ten (10) unstained sections (4-5 micron slices) or one (1) 20 micron roll-ups from FFPE tissue are desired.

Fresh frozen samples should be stored in liquid nitrogen and FFPE samples at room temperature until shipment.

5.5.1.2 Peripheral Blood Mononuclear Cells (PBMCs)

Blood for PBMCs will be collected prior to study treatment at screening (may be collected at the same time as blood drawn for routine laboratory tests).

Blood samples will be collected in two heparin green top tubes (approximately 20 ml).

Additional blood sample collections will be performed at:

- time of first radiographic disease assessment on treatment, (± 7 days)
- time of disease progression (± 7 days)

Samples should be processed the day of collection according to the PBMC isolation protocol in the Laboratory Manual.

PBMCs should be stored in LN2 until shipment.

5.5.1.3 Buffy Coat

Blood samples will be collected in one EDTA purple top tube (approximately 10 ml) prior to study treatment at screening (may be collected at the same time as blood drawn for routine laboratory tests).

Additional blood samples will be collected in one EDTA purple top tube (approximately 10 ml) at:

- time of first radiographic disease assessment, (± 7 days)
- the time of disease progression (± 7 days)

Samples should be processed the day of collection according to the buffy coat isolation protocol in the Laboratory Manual.

Samples should be stored at -80°C until shipment.

5.5.2 Specimen Shipping

Samples should be batched and shipped overnight for receipt on weekdays only during normal business hours to the Coordinating Site UCSD laboratory at the following address:

Attn: Sharmeela Kaushal
Moores Cancer Center, 3345/3G, GG
3855 Health Sciences Drive
La Jolla, CA 92093-0819
Phone: 858-822-7661

PBMC and buffy coat samples should be shipped on dry ice. FFPE tumor tissue (archived or newly obtained) can be shipped at room temperature. Please notify the Study Coordinator prior to shipment so it can be expected.

5.5.3 Specimen Analyses

Analyses will be performed at the direction of the study chair, Dr. Sacco.

Tumor specimens (archived and/or newly obtained) will be evaluated by immunohistochemistry (IHC) for such biomarkers as:

- PD-L1 expression
- EGFR expression
- p16
- tumor infiltrating lymphocytes
- IDO expression
- cyclin D1
- bcl-xL
- p53

PBMCs will be analyzed by flow cytometry for the following immune cell markers:

- T cell subsets (CD3, CD4, CD8, CD25, FOXP3)
- B cells (CD 19, CD20)
- Macrophage I/II and myeloid-derived suppressor cells (MDSC) (CD16, CD68, CD206),
- Natural killer cell activity (CD56, CD16)

Buffy coat samples will be analyzed for T cell receptor (TCR) sequencing.

Fresh frozen core biopsies (when available) will undergo whole exome sequencing for neoantigen discovery.

Additional biomarkers may be examined as new information arises.

5.5.4 Specimen Banking

Patients at UCSD will be co-consented to the UCSD Moores Cancer Center Biorepository, where samples will be retained in for analysis and future cancer research. Specimens will be stored indefinitely or until they are used up. Samples will be labeled with the protocol number, subject's de-identified study number and collection date. The link between study number and medical record number will be viewed over a password secured encrypted server-client.

Patient samples from participating sites will be stored locally per institutional protocol. The study research coordinator at each local site will review their subject's medical record for demographic and clinical information pertaining to the subject's general medical history, diagnosis, and outcomes of any treatments received. This information will be transmitted to and retained by the Coordinating Site UCSD. Samples and data extracted from the subject's medical record will be coded with a de-identified study number so that the subject's name and identifying information will be removed. A log that links the subject's name and identifiers to the study number will be maintained in a secure database distinct from the secure database into which the subject's clinical information will be entered by study personnel.

Potential research collaborators outside of UCSD who approach the Moores Cancer Center for clinical specimens will be required to complete an agreement (Material Transfer Agreement or recharge agreement) stating that the specimens will only be released for use in disclosed research, and any specimen left over from research will either be returned to the Cancer Center or destroyed. Any data obtained from the use of clinical specimen will be the property of UCSD for publication and any licensing agreement will be strictly adhered to. These outside

collaborators may include for-profit biotechnology corporations interested in collaborating with UCSD investigators in research diagnostic, prognostic assays and drug development. Any future studies using these samples will require separate IRB approval or exemption.

The specimens, DNA, and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the subject that there is the potential for financial gain by UCSD, the investigator or a collaborating researcher or entity.

If patients later decide they do not want their specimens collected to be used for future research, they may tell this to the local site principal investigator, who will inform the Study Chair Dr. Sacco. Dr. Sacco will use her best efforts to stop any additional studies and to destroy the specimens. Samples stored in the Biorepository will be destroyed; for samples that have been disseminated outside of the Biorepository, Dr. Sacco will contact the recipient to notify them of the need to halt further research and destroy specimens.

6.0 Measurement of Effect

6.1 Safety/tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 4.03 (http://ctep.cancer.gov/reporting/ctc.html) for reporting of adverse events.

6.2 Antitumor Effect

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria. See Appendix A.

6.2.1 Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation.

6.2.2 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment until objective tumor progression or death.

6.2.3 Time to Progression

Time to progression is defined as the duration of time from start of treatment until objective tumor progression.

6.2.4 Overall Survival

Overall survival is defined as the duration of time from start of treatment to death.

7.0 ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental

intervention, whether or not related to the intervention. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the investigational agent, is also an AE.

Progression of the cancer under study or events which are unequivocally due to disease progression should not be reported as an AE during the study (unless it is considered to be drug related by the investigator).

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

As far as possible, each adverse event should be evaluated to determine:

- duration (start and end dates)
- severity (grade)
- seriousness
- relationship to study agent
- action taken (i.e., none, study agent modification, medical intervention)
- outcome (i.e., resolved without sequelae, resolved with sequelae, ongoing)

Adverse events monitoring begins at the time of initiating study treatment through ***90 days*** following the last administration of study treatment or study discontinuation/termination, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to pembrolizumab or cetuximab.

Note: Serious adverse events must be recorded in the case report forms for this 90 day-period; however, non-serious adverse events need only be recorded through 28 days post last study drug administration.

All patients experiencing an adverse event at least possibly related to study treatment will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any clinically significant abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

7.2 Severity

All adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE v4.03 is available at http://ctep.cancer.gov/reporting/ctc.html

If no CTCAE grading is available, the severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities; intervention not indicated.
Moderate (grade 2): the event causes discomfort that affects normal daily activities; minimal, local or noninvasive intervention indicated.
Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status; intervention indicated.
Life-threatening (grade 4): the patient was at risk of death at the time of the event; urgent intervention indicated.
Fatal (grade 5): the event caused death.

7.3 Seriousness

A "serious" adverse event is defined in regulatory terminology as any untoward medical occurrence that:

1. **Results in death.**
   If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
2. **Is life-threatening.**
   (the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
3. **Requires in-patient hospitalization or prolongation of existing hospitalization**.
   Note: Hospitalization (including hospitalization for an elective procedure) for a preexisting condition which has not worsened does not constitute a serious adverse event.
4. **Results in persistent or significant disability or incapacity**. Substantial disruption of one's ability to conduct normal life functions.
5. **Is a congenital anomaly/birth defect.**
6. **Is an important medical event.**
   Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".
   For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

7.4 Relationship

Attribution categories for adverse events in relationship to protocol therapy are as follows:

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

The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the AE based upon the available information.

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

Exposure: Is there evidence that the subject was actually exposed to the 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 pembrolizumab? Is the time of onset of the AE compatible with a drug-induced effect?

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 pembrolizumab 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; or (2) the AE resolved/improved despite continuation of pembrolizumab.

Rechallenge: Was the subject re-exposed to pembrolizumab 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.

7.5 Prior experience

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in the current known adverse events listed in the agent clinical experience section of this protocol or the current Investigator's Brochure.

7.6 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Study Chair and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220). Events of clinical interest for this trial include:

7.6.1 Overdose of Pembrolizumab

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

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

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

7.6.2 Pregnancy and Lactation

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

7.6.3 Elevated Lab Values

The purpose of the following elevated lab value criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology:

- AST or ALT ≥ 3X the institutional ULN
- total bilirubin lab ≥ 2X the institutional ULN
- alkaline phosphatase < 2X the institutional ULN

7.7 Expedited Reporting Requirements for Adverse events

Serious adverse events, or a follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time study treatment initiation through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, requires expedited reporting as described below.

7.7.1 Expedited Reporting to Site Principal Investigator and Study Chair

The Study Chair and Site Principal Investigator must be notified within 24 hours of learning of any serious adverse events (SAEs).

7.7.2 Expedited Reporting to Merck

Merck must be notified within 2 working days of learning of any SAEs or non-serious Events of Clinical Interest:

Merck Global Safety
Attn: Worldwide Product Safety;
FAX: 215-993-1220

The Study Chair will submit a copy of all 15 Day FDA Reports to Merck Worldwide Product Safety at the time of submission to FDA.

7.7.3 Expedited Reporting to Regulatory Authorities

A. The **Institutional Review Board (IRB) of each site** must be notified by the site principal investigator according to their local policies.

B. The **UCSD Human Research Protections Program (HRPP)** and **Moores Cancer Center Data and Safety Monitoring Board (DSMB)** must be notified within 10 business days of “any unanticipated problems involving risk to subjects or others” (UPR).

The following events meet the definition of UPR:

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
5. Any breach in confidentiality that may involve risk to the subject or others.
6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

C. The **FDA** must be notified by the Study Chair according to the following timelines:

- within 7 calendar days of any unexpected fatal or life-threatening adverse event with possible relationship to study drug, and
- within 15 calendar days of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

7.8 Routine Reporting Requirements for Adverse events

A. The **IRB of each site** must be notified by the site principal investigator according to their local policies.

B. The **UCSD HRPP** must be notified of any adverse events that are not unanticipated problems involving risk to subjects or others (non-UPRs) at the time of the annual Continuing Review.

C. The **FDA** must be notified by the Study Chair of all non-serious adverse events annually at the time of the annual report.

8.0 AGENT INFORMATION

8.1 Pembrolizumab

Please refer to the Product Label and Investigator's Brochure for more comprehensive information.

Other Names: MK-3475, Keytruda®

Mechanism of Action:
Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor

models, blocking PD-1 activity resulted in decreased tumor growth.

Availability: Clinical supplies are provided by Merck & Co., Inc. and will be affixed with a clinical label in accordance with regulatory requirements.

Dosage Forms and Strengths:
For injection: 50 mg lyophilized powder in a single-use vial for reconstitution.
Injection: 100 mg/ 4mL (25mg/mL) solution in a single-use vial.

Preparation:
Pembrolizumab will be prepared according to the product label unless otherwise directed in the Pharmacy Manual.

Storage and stability:
The product does not contain a preservative.
Store the reconstituted and diluted solution from the KEYTRUDA 50mg vial either:

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

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

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

Do not freeze.

Route of administration for this study: **Administer infusion solution intravenously** over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter. Do not co-administer other drugs through the same infusion line.

Side effects:
Please refer to the Product Label for full side effect details.

8.1.1 Study Drug Accountability and Disposition

The Study Chair and site Principal Investigators are responsible for ensuring accountability for the investigational agent, including reconciliation of materials and maintenance of drug records.

Dispensing and administration of pembrolizumab will be recorded following institutional practices. An accurate accounting will be available for verification. Accountability records will include:

- Confirmation of delivery to the site
- Inventory at the site

- Dispensing for each patient
- Return or alternative disposition of unused study drug

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

8.2 Cetuximab

Please refer to the Product Label for more comprehensive information.

Other Names: Erbitux®

Mechanism of Action:
Cetuximab binds specifically to the EGFR on both normal and tumor cells, and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, such as transforming growth factor-alpha. Cetuximab can mediate antibody-dependent cellular cytotoxicity (ADCC), with in vitro assays and in vivo animal studies demonstrating that cetuximab inhibits the growth and survival of tumor cells expressing EGFR.

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

Dosage Forms and Strengths:
100mg/50 mL, single-use vial.
200mg/100 mL, single-use vial.

Preparation:
Cetuximab will be prepared according to the product label unless otherwise directed in the Pharmacy Manual.

Storage and stability:
- Single use vials are stored under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze.
- Preparations of cetuximab in infusion containers are stable for up to 12 hours at 2° C to 8° C (36° F to 46° F) and up to 8 hours at controlled room temperature (20° C to 25° C; 68° F to 77° F). Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2° C to 8° C. Discard any unused portion of the vial.

Route of administration for this study: Intravenous infusion over 60-120 minutes.

Side effects:
Please refer to the Product Label for full side effect details.

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Populations

All subjects who undergo at least one dose of the study treatment will be included in the analysis population. If applicable, "Intention-to-treat" analyses will be performed for an endpoint. If the endpoints for a subject cannot be assessed (for example, a subject dies early prior to the 6 months assessments), it will be considered to be an event that does not favor the study therapy (e.g., disease progression for the primary outcome).

The Safety population will consist of all patients who have received at least one dose of pembrolizumab.

9.2 Sample Size and Primary Analysis

Cohort 1 (Cetuximab-naïve and PD-1/PD-L1 inhibitor naive arm):
The primary efficacy endpoint is overall response (CR or PR, see Appendices section 2 for definition) rate by 6 months. Overall response rate will be assessed when the last accrued patient has been observed for 6 months.

For cetuximab-naïve and pembrolizumab-naïve patients, recruiting adaptive immunity may lead to better and more durable responses than observed with cetuximab alone, thus improving response rate beyond current standard of care. Phase II data of cetuximab monotherapy for R/M HNSCC (irrespective of HPV status) indicates that response rate is approximately 10%. [9-10] Phase Ib data of pembrolizumab monotherapy for R/M HNSCC (irrespective of HPV status) suggests a response rate of 20%.[43-44]We are thus estimating our null rate to be 20%.

A Simon's minimax two-stage design will be used for this cohort. The primary outcome is response rate (CR/PR) by 6 months. If the response rate is ≤20%, we will consider the treatment as not meeting the threshold of going further. We will test the null hypothesis H0: p≤20% against the alternative hypothesis H1: p>20%, where p is the response rate after six months of starting treatment. The two stage design proposed below will have an 80% power to reject the null hypothesis and conclude that the true response rate is above 20%, if the true response rate is ≥40%, at 5% significance level. The study design is described in detail is as follows:

Stage 1: 18 subjects will be accrued; accrual will be held until the response results for all the 18 subjects are known for the first six months. The trial will be terminated at Stage 1 if ≤ 4 of the 15 subjects have any response by 6 months; otherwise it will continue to Stage 2.

Stage 2: 15 more patients will be accrued. We will reject the therapy if, among all the 33 (18+15) subjects, the number of patients who have a response is ≤ 10; if >10 patients have a defined response by RECIST (see Appendices section 2), the treatment will be successful. It will be concluded that our study treatment is associated with a response in more than 20% of patients.

Early stopping probability: Under this design, if the null hypothesis is true, the probability of stopping the trial early will be 71.6%.

The sample size calculation was done using PASS version 14.0.3.

Cohort 2 (PD-1/PD-L1 inhibitor-refractory, Cetuximab-naïve):

The primary efficacy endpoint is overall response (CR or PR, see Appendices section 2 for definition) rate by 6 months. Overall response rate will be assessed when the last accrued patient has been observed for 6 months.

Patients previously treated with anti-PD-1/PD-L1 therapy who initially achieved a therapeutic benefit have already demonstrated an ability of the immune system to respond to the tumor. We hypothesize that a lasting footprint of anti-PD-1/PD-L1 remains is counteracted by other regulatory factors. One potential means to exploit this change could include the combination of continued anti-PD-1 therapy with the addition of cetuximab, to determine if ADCC and stimulation of innate immunity in an already primed setting could induce further therapeutic response. Cetuximab monotherapy results in a 10% response rate in cetuximab-naïve patients.[9-10]

Therefore, based on a null rate of 10%, a minimum clinically meaningful benefit we would reasonably accept is an increase in response rate from 10% to 30%. A Simon's minimax two-stage design will also be used for this cohort. The primary outcome is tumor response (CR or PR) rate by 6 months. If the response rate is ≤10%, we will consider the treatment as not meeting the threshold of going further. We will test the null hypothesis H0: p≤10% against the alternative hypothesis H1: p>10%, where p is the response rate after six months of study treatment. The two-stage design proposed below will have an 80% power to reject the null hypothesis and conclude that the true response rate is above 10%, if the true rate is 30%, at 5% significance level. The study design is described in detail is as follows:

Stage 1: 15 subjects will be accrued; accrual will be held until the response results for all the 15 subjects are known for the first six months. The trial will be terminated at Stage 1 if ≤1 of the 15 subjects have any response by 6 months; otherwise it will continue to Stage 2.

Stage 2: 10 more patients will be accrued. We will reject the therapy if, among all the 25 (15+10) subjects, the number of patients who have a defined response is ≤5; if ≥6 patients have a defined response by RECIST (see Appendices section 2), the treatment will be successful. It will be concluded that our study treatment is associated with a response in more than 10% of patients.

Early stopping probability: Under this design, if the null hypothesis is true, the probability of stopping the trial early will be 54.9%.

Cohort 3 (PD-1/PD-L1 inhibitor-refractory, Cetuximab-refractory):
The primary efficacy endpoint is overall response (CR or PR, see Appendices section 2 for definition) rate by 6 months. Overall response rate will be assessed when the last accrued patient has been observed for 6 months.

We expect 0% response rate among the cetuximab- refractory and PD-1/PD-L1 inhibitor refractory patients if they were treated again with a single agent.

A Simon's minimax two-stage design will also be used for this cohort. The primary outcome is tumor response (CR or PR) rate by 6 months. If the response rate is ≤1% (we used 1% instead of 0% to ease calculation), we will consider the treatment as not meeting the threshold of going further. We will test the null hypothesis H0: p≤1% against the alternative hypothesis H1: p>1%, where p is the response rate after six months of study treatment. The two-stage design proposed below will have an 80% power to reject the null hypothesis and conclude that the true

response rate is above 1%, if the true rate is 20%, at 5% significance level. The study design is described in detail is as follows:

Stage 1: 10 subjects will be accrued; accrual will be held until the response results for all the 10 subjects are known for the first six months. The trial will be terminated at Stage 1 if none of the 10 subjects have any response by 6 months; if there is at least one response, it will continue to Stage 2.

Stage 2: 5 more patients will be accrued. We will reject the therapy if, among all the 15 (10+5) subjects, the number of patients who have a defined response is ≤1; if ≥2 patients have a defined response by RECIST (see Appendices section 2), the treatment will be successful. It will be concluded that our study treatment is associated with a non-zero response in this type of patients.

Early stopping probability: Under this design, if the null hypothesis is true, the probability of stopping the trial early will be 90.4%.

Final efficacy analyses for cohorts 1, 2 and 3 will calculate the UMVUE, p-value and 95% CI for the response rates.[48-49]The calculation will be performed using R *clinfun* package (www.r-project.org).

Cohort 4 (Cutaneous HNSCC arm)
The primary efficacy endpoint is overall response (CR or PR) rate by 6 months. Overall response rate will be assessed when the last accrued patient has been observed for 6 months.

We would like to evaluate clinical activity in a cohort of patients with cutaneous HNSCC, where there is no well-defined standard of care. Given the paucity of data regarding response rates to systemic treatment in this patient population, we have arbitrarily chosen a sample size of 10 patients. We will use the exact method to estimate two-sided 95% CIs of the response rates. If we are able to demonstrate clinical activity with combination cetuximab-pembrolizumab, we would then pursue a larger trial with the use of a control arm.

9.3 Rationale for Historic Control Arm

For the cetuximab-naïve arm (primary endpoint is response rate), there are phase II trials with well-annotated patient populations comparable to our proposed cohort from which response rates are clearly defined and can be extrapolated.[9-10] Therefore, we think it is reasonable to utilize this published data as our reference.

For the PD-1/PD-L1 inhibitor refractory arms (cohorts 2 and 3), there is currently no data evaluating the use of cetuximab following failure on anti-PD-1/PD-L1 therapy.

For the cutaneous HNSCC arm, there is no well-established standard of care and there is a paucity of data regarding efficacy of platinum or EGFR-based treatment regimens. If we are able to establish clinical activity of pembrolizumab-cetuximab combination therapy in this disease setting, a subsequent multi-site registration trial could then include randomization.

9.4 Interim Safety Analysis

Both agents have independently demonstrated good tolerability with generally non-overlapping toxicity profiles. One phase II trial evaluating the combination of pidilizumab (humanized anti-PD-1 monoclonal antibody) with rituximab (a monoclonal anti-CD20 antibody) demonstrated the combination was well-tolerated with no treatment-related grade 3/4 toxicities or treatment discontinuation due to toxicity.[50] A second study recently reported the safety data combining pembrolizumab (200mg IV flat dose) with necitumumab (EGFR inhibitor) at varying dose levels (including full dose of 800mg) in patients with stage IV non-small cell lung cancer.[51] There were no observed dose-limiting toxicities with full doses of anti-PD1 with EGFR inhibition. Further, the safety profile was noted to correspond to the individual profiles for both drugs, with no additive toxicities. While we do not anticipate this regimen will be toxic, the safety of this specific combination has not been otherwise formally evaluated. Therefore, we will perform an interim safety analysis after the first 10 patients (across all the cohorts) have been enrolled and completed one cycle (21 days) of treatment. Any subjects experiencing unacceptable toxicity will be identified and the nature of the unacceptable toxicity will be determined. We will stop the study if, among these 10 patients, there is at least one death that is possibly/probably/definitely associated with the study treatment. If four or more of the 10 patients develop grade 3-4 non-hematologic toxicities, the study will be placed on hold pending further discussion with the UCSD Moores Cancer Center Data and Safety Monitoring Board.

9.5 Accrual

A minimum of 4 patients with R/M HNSCC (cetuximab-naive) are evaluated monthly at each of the 4 institutions included in this study. A minimum of 2 patients with R/M HNSCC (PD-1/PD-L1 inhibitor-refractory) are evaluated monthly at each of the 4 institutions. A minimum of 2 patients with cutaneous HNSCC are evaluated monthly at each of the 4 institutions. We therefore anticipate this study would require no more than 12 months to accrue.

9.6 Secondary Efficacy Analyses

Secondary analysis will present PFS and response rates over the course of the study, duration of response, and overall survival. We will estimate median survival times together with their 95% confidence intervals, and report number of events, as well as Kaplan Meier plots with 95% confidence bands.

9.7 Secondary Safety Analyses

Analyses will be performed for all patients having received at least one dose of study treatment. The proportion of subjects experiencing adverse events, serious adverse events, and treatment delays will be summarized. Tolerability will be assessed based on dosage delays and discontinuation due to adverse events.

All AEs will be listed, documenting the course, outcome, severity, and relationship to the study treatment. Incidence rates of AEs and the proportion of subjects prematurely withdrawn from the study due to AEs will be shown**.**

9.8 Analysis of Biomarkers

All tests will be 2 sided at the 5% significance level unless otherwise indicated below.

We will perform T cell receptor (TCR) sequencing from blood obtained at baseline, at time of first radiographic disease assessment on study, and at time of disease progression. We will examine the T cell repertoire at each time point to determine if there is a specific clone that has preferentially expanded. The analysis of clonal expansion will be blinded to patient response

status; for the primary analysis patients will be categorized as having clonal expansion or not. We hypothesize that specific clones will be responsive to immunostimulation and thus that patients in which clonal expansion occurs will have improved progression-free survival. The primary analysis will compare PFS for those with and without clonal expansion using a log-rank test.

We will measure expression of genes such as EGFR, p16, IDO, cyclin D1, bcl-xL and p53 from newly obtained and/or archived tumor specimens as these genes may represent potential prognostic markers. Log-rank tests will be used to explore the association between expression levels and time to progression free survival and overall survival. In these analyses, expression level will be categorized into quartiles or tertiles. Adjustment for the multiple comparisons will use a step down approach. To consider all the predictors multivariately, L_1-regularized Cox models will be built using LASSO or Elastic net.[52-53] Integrated Brier scores will be used for model comparisons.[54]

We will analyze newly obtained and/or archival tissue for the following:
1). PD-L1 expression by immunohistochemistry
2). Immunophenotyping by flow cytometry:

- T cell subsets (CD3, CD4, CD8, CD25, FOXP3)
- B cells (CD 19, CD20)
- Macrophage I/II and myeloid-derived suppressor cells (MDSC) (CD16, CD68, CD206)
- Natural killer cell activity (CD56, CD16)

Log-rank tests will be used to explore the association between expression levels and time to progression-free survival and overall survival. In these analyses, expression level will be categorized into quartiles or tertiles. Adjustment for the multiple comparisons will use a step down approach.

Whole exome sequencing (for the purposes of neoantigen discovery) from newly obtained specimens (at time of study enrollment, when feasible) will also be performed. This analysis is exploratory in nature.

10.0 STUDY MANAGEMENT

10.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed according to UCSD conflict of interest policy.

10.2 Institutional Review Board (IRB) Approval and Consent

The IRB should approve the consent form and protocol prior to any study-related activities. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must

include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

10.3 Required Documentation For Multi-site Studies

Before the study can be initiated at any site, the following documentation must be provided to the UCSD Moores Cancer Center Clinical Trials Office:

- A copy of the official IRB approval letter for the protocol and informed consent.
- A copy of the IRB-approved consent form
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation. (NOTE: this is required if UCSD holds the IND. Otherwise, the affiliate Investigator's signature on the protocol is sufficient to ensure compliance)
- CAP and CLIA Laboratory certification numbers and institution lab normal values.
- Executed clinical research contract.

10.4 Patient Registration

All patients must be registered with the UCSD Moores Cancer Center Clinical Trials Office before enrollment to the study. Prior to registration, eligibility criteria must be confirmed with the UCSD Study Coordinator. To register a patient, call (858)-246-0357 Monday through Friday, 8:00am-4:30pm Pacific Time. Study sites other than UCSD must fax informed consent documentation, completed eligibility checklist, and all source documentation for eligibility confirmation to the UCSD Clinical Trials Office (Fax: 858-822-5380).

Patients will be given a unique sequential study number at the time of enrollment. UCSD will fax the outside study site for confirmation of patient registration, the patient's study number, and ability to start study treatment.

10.5 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), subjects who have provided written informed consent must also sign a subject authorization to release medical information to the study Sponsor and allow a regulatory authority, or Institutional Review Board access to subject's medical information relevant to the study.

10.6 Data and Safety Monitoring/Auditing

In addition to adverse event monitoring and clinical oversight by the Study Chair, site principal investigator and co-investigators, quality assurance of the study will be performed by the UCSD Moores Cancer Center Clinical Trials Office internal monitor. Monitoring intervals will be dependent upon risk-based assessments.

This study will also use the UCSD Moores Cancer Center Data Safety and Monitoring Board (DSMB) to provide oversight in the event that this treatment approach leads to unforeseen

toxicities. Data from this study will be reported annually and will include:

1) the protocol title, IRB protocol number, and the activation date of the study.
2) the number of patients enrolled to date.
3) the date and site of patients' enrollment.
4) a summary of all adverse events regardless of grade and attribution.
5) a response evaluation for evaluable patients when available.
6) a summary of any recent literature that may affect the ethics of the study.

10.7 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, investigators are required to conduct their research according to the plans reviewed and approved by the IRB.

10.7.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate apparent immediate hazards/risks to trial subjects without prior IRB approval. Any such emergency modification implemented must be noted and reported to the IRB along the lines of a protocol deviation or violation, depending on the nature of the modification.

10.7.2 Protocol Violations

Any unplanned variance from an IRB approved protocol is considered a violation and must be reported to the IRB in a timely fashion. For the UCSD IRB:

A. Major violations must be reported to the IRB within 10 working days of awareness of the violation.
Major violations include:
- Instances that have harmed or increased the risk of harm to one or more research participants.
- Instances that have damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

B. Minor violations may be reported to the IRB at the time of the continuing review.
Minor violations have no substantive effect on the risks to participants or on the scientific integrity of the research plan or the value of the data collected.

10.8 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Study Chair. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRBs at each site and submitted to the FDA by the Study Chair for approval prior to implementation.

10.9 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient

consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.10 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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Appendix A. Response Evaluation Criteria in Solid Tumors (RECIST)

Tumor assessments will be made according to the schedule of assessments. Response and progression will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines [Eisenhauer et al. 2009].

1 Measurability of Tumor at Baseline

1.1 Definitions

At baseline, tumor lesions will be categorized as follows:

1.1.1 Measurable

Tumor lesions: must be accurately measured in at least one dimension (longest diameter in the plane of measurements is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measureable).
- 20 mm by chest X-ray.

Malignant lymph nodes: to be considered pathologically enlarged and measurable, a lymph node must be >= 15 mm in *short* axis when assessed by CT scan. At baseline and in follow-up, only the *short* axis will be measured and followed.

1.1.2 Non-measurable

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

1.1.3 Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic

lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2 Specifications by methods of measurements

1.2.1 Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

1.2.2 Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and P10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

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

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a

potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

2 Tumor Response Evaluation

2.1 Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).
Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of P15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20mm· 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement. All other pathological nodes (those with short axis P10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed.

A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2.2 Response criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

2.2.1 Evaluation of target lesions

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

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

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

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2.2.2 Special notes on the assessment of target lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned in this circumstance as well). This default value is derived from the 5mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.2.3 Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

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

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

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

2.2.4 Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e.an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

2.2.5 New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new'

bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow- up:
If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

2.3.1 Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.
When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Appendix Table 1. Time point response: patients with target (+/- non-target) disease.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR

CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Inevaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Appendix Table 2. Time point response: patients with non-target disease only.

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	Inevaluable
Unequivocal PD	Yes or No	PD
Any	Yes	PD

2.3.2 Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

2.3.3 Best overall response: all time points

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

Appendix Table 3. Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR

CR	PR	SD, PD OR PR
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	Inevaluable	SD provided minimum criteria for SD duration met, otherwise inevaluable
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	Inevaluable	SD provided minimum criteria for SD duration met, otherwise inevaluable
inevaluable	Inevaluable	Inevaluable

2.3.4 Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

2.4 Confirmatory measurement/duration of response

2.4.1 Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, i.e. in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

2.4.2 Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

2.4.3 Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.