Abemaciclib and Pembrolizumab in Metastatic or Recurrent Head and Neck Cancer

Study Protocol & Statistical Analysis Plan

NCT03938337

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CLINICAL PROTOCOL	
Title:	**Phase II clinical trial of abemaciclib in combination with pembrolizumab in patients with metastatic or recurrent head and neck cancer**
Protocol Number:	
Study Sponsor	UAB Comprehensive Cancer Center
Study Support	Eli Lilly and Company
Principal Investigator:	Shih-Hsin Eddy Yang, MD, PhD
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PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone number
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Secondary Medical Monitor		

1. SYNOPSIS

Name of Company: Eli Lilly Pharma.	
Name of Investigational Product: Abemaciclib	
Name of Active Ingredient: Abemaciclib	
Title of Study: Phase II clinical trial of abemaciclib in combination with pembrolizumab in patients with metastatic or recurrent head and neck cancer	
Study center(s): This study will be performed at University of Alabama at Birmingham	
Principal Investigator: Dr. Shih-Hsin Eddy Yang, MD, PhD	
Studied period: Date first patient enrolled: 29 October 2019 Estimated date endpoint obtained: August 2021 Estimated date last patient completed: June 2021 Total number of estimated patients: 36 Estimated duration of treatment per patient: Until toxicity, progression or withdrawal.	**Phase of Development:** 2
Rationale: Pembrolizumab is an antibody that binds the programmed death receptor 1 (PD-1) and promotes anti-cancer immunity by inhibiting regulatory T-cell function to sensitize tumors to immune surveillance. Pembrolizumab is approved for the treatment of metastatic non-small cell lung cancer (NSCLC) that has progressed following platinum-based chemotherapy, metastatic melanoma and tumors that express high PD-L1. Abemaciclib represents a selective and potent small-molecule CDK4 and CDK6 dual inhibitor with a broad antitumor activity in preclinical pharmacology models, acceptable physical and pharmacokinetic (PK) properties, and an acceptable toxicity profile in nonclinical species. This compound demonstrates significant inhibition of tumor growth as monotherapy in multiple human xenograft models including models for: breast cancer, colorectal cancer, glioblastoma multiforme, acute myeloid leukemia, melanoma, mantle cell lymphoma (MCL), and non–small-cell lung cancer (NSCLC). Although characterized by a different constellation of genomic mutations, each of these human xenografts has an intact, functional Rb protein. Xenograft growth inhibition is generally dose dependent from 25 to 100 mg/kg following daily oral administration for 21 to 28 days. Additional nonclinical studies in xenograft models for human NSCLC and melanoma also show that abemaciclib	

may be used in combination with standard cytotoxic or targeted therapies to improve efficacy of these agents.

Immunotherapy (anti-PD-1/PD-L1) has been recently approved for patients with metastatic or recurrent squamous cell carcinoma of the head and neck. However, only a small percentage of patients experience long-term control, necessitating new therapeutic strategies. Recently, Goel et al. Nature 2017 showed preclinically and in breast tumors that CDK4/6 inhibitors stimulates production of type III interferons and hence enhances tumor antigen presentation. CDK4/6 inhibitors also suppressed the proliferation of regulatory T cells. These events promote cytotoxic T-cell-mediated clearance of tumor cells, which is further enhanced by the addition of immune checkpoint blockade. Based on these data, we propose a phase II trial in patients with metastatic or recurrent head and neck cancer who are eligible for anti-PD-1/PDL1 therapy investigating the combination of abemaciclib with pembrolizumab. Tumor & blood analysis for interferon gamma signature will be explored as possible biomarkers.

Objectives:

Primary:

- To assess the objective response rate of tumor lesions to abemaciclib in combination with pembrolizumab in patients with metastatic or recurrent squamous cell carcinoma of head and neck.

Secondary:

1) To assess safety and tolerability of abemaciclib in combination with pembrolizumab

2) To assess PFS and OS

3) To assess time to tumor response and duration of response

4) To assess objective response rate (ORR), complete response rate (CRR), best overall response (BOR), disease control rate (DCR) [response evaluation by investigator using immune related RECIST (iRECIST)]

Exploratory:

1) To assess MSI status, CDKN2A, RB, and CDK4/6 status

2) To assess gene expression related to immune pathway

Methodology:

Abemaciclib at 150 mg BD PO and Pembrolizumab will be given at 200 mg IV every 3 weeks.

Overall design:

This is an exploratory phase 2, open-label two-stage Simon MinMax design with a total of 18 evaluable patients (null hypothesis that ORR < 10% versus the alternative hypothesis that ORR >= 30 with alpha = 0.087 and power=0.8) in each cohort. The study will be conducted to test the efficacy and tolerability of combining abemaciclib with pembrolizumab in patients with metastatic or recurrent head and neck cancers eligible for immunotherapy. Based on the previous Phase Ib study (JPBJ, part E) where no DLTs or DLT-equivalent toxicities were reported, patients in this study will receive 150 mg abemaciclib orally q12 hours on days 1-21 (21 day cycle) with pembrolizumab 200mg IV on day 1 over every 21 day cycle. Two cohorts of patients will be enrolled:

Cohort 1: Recurrent or metastatic HNSCC patients who are anti-PD-1/PD-L1 naïve

Cohort 2: Recurrent or metastatic HNSCC patients with progressive disease on anti-PD-1/PD-L1 therapy.

Each cohort will enroll a maximum of 18 evaluable patients.

Patients will discontinue therapy upon confirmed progressive disease. Patients may continue therapy if they have stable disease or unconfirmed progressive disease. Patients may continue pembrolizumab at the investigator's discretion if the combination is not tolerated due to adverse events.

Disease response and progression will be assessed by the investigator (physical exam) and by using CT or MRI scans every 3 months based on Response Evaluation Criteria In Solid Tumors (RECIST) Version 1.1. The determination of disease progression for the study requires a confirmation of PD using iRECIST (ie, additional scans obtained at least 4 weeks later that qualify as PD by RECIST v1.1).

Number of Patients (planned):

About 36 patients with metastatic or recurrent squamous cell carcinoma of head and neck will be enrolled in the study.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

Histologically confirmed (core biopsy proven) metastatic advanced or recurrent squamous cell carcinoma of head and neck.

Adequate pulmonary and cardiac function

Available archived tissue of primary tumor or resected tumor specimen with adequate samples to generate 15 unstained slides.

Prior treatment with immune checkpoint inhibitor is not allowed in cohort 1 patients. Patients in cohort 2 should have failed or progressed on immune checkpoint inhibitor just prior to starting this study treatment. Patients should not receive any intervening systemic therapy after progression on immune checkpoint inhibitor.

ECOG PS = 0 or 1

Must have at least 1 target lesion

Life expectancy > 6 months

Adequate hematologic and end-organ function

- ANC $\geq 1500/mm^3$
- Platelet count $\geq 100,000/mm^3$
- Hb $\geq$ 8g/dl
- Creatinine $\leq$ 1.5 x ULN or Creatinine Clearance (CrCl) $\geq$ 60 ml/min
- Total Bilirubin $\leq$ 1.5 x ULN (except subjects with Gilbert syndrome, who can have total Bilirubin > 2.0 mg/dl)
- AST, ALT and alkaline phosphatase $\leq$ ULN

Agreement to remain abstinent or use appropriate contraception, among women of childbearing potential

Willingness and ability to consent for self to participate in study

Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures

Exclusion Criteria:

1. Autoimmune disease (Note: Vitiligo, type 1 diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, and conditions not expected to recur in the absence of an external trigger are permitted.)
2. Condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days prior to study treatment (Note: Inhaled and topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.)
3. History or active interstitial lung disease
4. Immunosuppression, of any kind
5. Major surgical procedure or significant traumatic injury within 4 weeks prior to study treatment, and must have fully recovered from any such procedure
6. Angina, myocardial infarction (MI), symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack TIA), arterial embolism, pulmonary embolism, percutaneous transluminal coronary angioplasty (PTCA), or coronary artery bypass grafting (CABG) within 6 months prior to study treatment
7. Known active viral or nonviral hepatitis or cirrhosis

8. Any active infection requiring systemic treatment, positive tests for Hepatitis B surface antigen.
9. History of gastrointestinal perforation or fistula in the 6 months prior to study treatment, unless underlying risk has been resolved (e.g., through surgical resection or repair)
10. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness.
11. Pregnancy or breastfeeding - Female patients must be surgically sterile (i.e., ≥6 weeks following surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) or be postmenopausal, or must agree to use effective contraception during the study and for 4 months following last dose of treatment. All female patients of reproductive potential must have a negative pregnancy test (serum or urine) within 7 days prior to study treatment. Male patients must be surgically sterile or must agree to use effective contraception during the study and for 4 months following last dose of treatment. The definition of effective contraception is provided in Section 2.6.1 of this protocol.
12. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for this study

Abemaciclib Investigational Product Dose and Administration:

Dosing will begin at 150 mg orally once daily dosing. Each patient will receive Abemaciclib for 3 weeks, then assessed, and then administered daily. Patients will receive treatment with Abemaciclib until there is(are) toxicity(ies) or disease progression on treatment. There will be no intra patient or interpatient dose escalation in dosing of Abemaciclib. Patients will take Abemaciclib in clinic on Day 1 of Cycle 1. Thereafter they can take the rest of the pills at home and even when they continue on cycle 2 and onwards.

Pembrolizumab Dose and Administration:

Pembrolizumab will be administered IV at 200 mg beginning on C1D1 and next dose after 3 weeks, in the absence of toxicity. Dose modification is not allowed.

Duration of Treatment:

Patients are eligible for treatment until unacceptable toxicity, or withdrawal of consent, or progression of disease on treatment. A patient should be withdrawn from study treatment if, in the opinion of the Investigator, it is medically necessary, or if it is the wish of the patient. In addition, patients will be withdrawn from treatment in the case of:

1. A need for surgery, radiation, or for other anticancer therapy not permitted by this protocol
2. Lost to follow-up or noncompliant with the protocol
3. Any Abemaciclib dose delay > 7 days during the 21 day DLT evaluation period
4. Pregnancy - Pregnant patients should be followed for the duration of the pregnancy and the outcome of the pregnancy should be documented.

5. Grade > 3 pneumonitis, any Grade 4 toxicity including colitis, AST or ALT > 5 times the ULN or total bilirubin > 3 times the ULN, Grade 4 hypophysitis that cannot be controlled with endocrine replacement therapy, Grade > 3 adrenal insufficiency that cannot be controlled with endocrine replacement therapy, Grade > 3 nephritis with serum creatinine > 3 times the ULN, encephalitis of any grade, type 1 diabetes mellitus with Grade 4 hyperglycemia, Grade > 3 infusion-related reactions, Grade 4 rash or suspected Stevens-Johnson syndrome or toxic epidermal necrolysis, any Grade > 3 non-hematologic treatment-related toxicity that recurs, any Grade 2 or 3 immune related toxicity that persists despite treatment modifications or corticosteroid treatment that cannot be reduced to 10 mg of prednisone or equivalent per day within 12 weeks

Parameters to be Assessed:

Safety:

Safety assessments will include physical examinations, vital signs, ECOG performance status, laboratory tests (complete blood counts [CBC] and serum chemistry), 12-lead electrocardiograms (ECGs), and additional studies as may be clinically indicated.

Exploratory Biomarkers:

Baseline archived tumor samples will be analyzed for PD-L1 expression via IHC. Mutational analysis will be performed via the Strata Oncology platform (Oncomine), which includes analysis of microsatellite stability and genetic alteration of the CDK4/6 pathway. Immune pathway gene expression will be performed using Nanostring immune pathways panel. This panel allows for the interrogation of immune repertoire as well as analysis of the IFN-g pathway, which has been shown to correlate with HNSCC response to immunotherapy (2). Additionally, blood will be collected at baseline, and day 1 of every cycle and analyzed for ctDNA, whole blood immune pathway/IFN-g pathway analysis. These will be used to correlate molecular profiling with responses.

Efficacy:

RECIST v1.1 and iRECIST will be applied to assess response and progression.

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Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADCC	Antibody-dependent T-cell-mediated cytotoxicity
ADR	Adverse drug reaction
AE	Adverse event
AFP	Alpha fetoprotein
AIDS	Acquired immune deficiency syndrome
ALK	Activin receptor-like kinase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APA	Anti-product antibody
AST	Aspartate aminotransferase
BP	Blood pressure
CABG	Coronary Artery Bypass Graft
CBC	Complete blood count
CD	Cluster of differentiation antigen
iCR	Immune Complete response
CRF	Case report form
iCPD	Immune Confirmed progressive disease
CT	Computed tomography
CTA	Clinical Trials Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CxDx	Cycle x Day x
DEHP	Diethylhexyl-phthalate
dL	Deciliter
DLT	Dose-limiting toxicity
EBUS	Endoscopic Bronchoscopic Ultrasound

ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
EGD	Esophagogastroduodenoscopy
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-linked immunosorbent assay
EOS	End of study
EOT	End of treatment
FDA	Food and Drug Administration
Fe	Iron studies
FFPE	Formalin fixed, paraffin-embedded
g	Gram
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HRA	Health Regulatory Authority
IB	Investigational Brochure
ICH	International Council on Harmonization
IEC	Independent ethics committee
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IM	Intramuscular
INR	International normalized ratio
IRB	Institutional review board
IUD	Intra-uterine device
IV	Intravenous

kDa	KiloDalton
kg	Kilogram
L	Liter
µL	Microliter
mg	Milligram
mL	Milliliter
MDSC	Myeloid derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
min	Minute
mm	Millimeter
mm Hg	Millimeters of mercury
MRI	Magnetic resonance imaging
ms	Millisecond
MTD	Maximum tolerated dose
NCI	National Cancer Institute
ng	Nanogram
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PET	Positron emission tomography
PFS	Progression-free survival
PlGF	Placental growth factor
PD-1	Programmed death receptor 1
PD-L1,PD-L2	Programmed death receptor ligands
PK	Pharmacokinetic
pM	Picomolar

PR	Partial response
PT	Preferred Term for adverse event in MedDRA
PTCA	Percutaneous transluminal coronary angioplasty
PUD	Peptic ulcer disease
QA	Quality assurance
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
ROS-1	Proto-oncogene tyrosine-protein kinase
RPTD	Recommended Phase 2 dose
SAE	Serious adverse event
sCD105	Soluble CD105/endoglin
SCID	Severe combined immunodeficient
SCLC	Small cell lung cancer
iSD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	Systemic Organ Class in MedDRA
SOP	Standard operating procedure
TGF	Transforming growth factor
TIA	Transient ischemia attack
TPS	Tumor proportion score
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
UPCR	Urine protein-creatinine ratio
iUPD	Immune Unconfirmed progressive disease
US	United States of America
VEGF	Vascular endothelial growth factor

2. BACKGROUND

2.1. Squamous Cell Carcinoma of Head and Neck (SCCHN)

Head and neck carcinomas (HNC) are the fifth most common cancer in the world and annual incidence appears to be increasing. In 2014, it was estimated that about 55,070 new cases of oral cavity, pharyngeal, and laryngeal cancers would occur, which would account for about 3% of new cancer cases in the United States. An estimated 12,000 deaths from HNC would occur during the same time period (1). SCCHN or a variant is the histologic type seen in more than 90% of these tumors. The four most common primary sites of SCCHN in the United States and Europe are the oral cavity, oropharynx, hypopharynx, and larynx. HNC are strongly associated with tobacco use and with excessive alcohol abuse in 80% of oral cancers. Other risk factors include HPV for oropharyngeal cancer, Epstein-Barr virus (nasopharyngeal), exposure to asbestos, and Barrett's esophagus in the case of hypopharyngeal cancer.

Stage at diagnoses predicts survival rates and guides management in patients with SCCHN. The 2010 American Joint Commission on Cancer (AJCC) staging classification system is currently used as the basis for treatment decisions. Approximately 30% to 40% of patients present with early stage disease (stage I or II) and have 5-year survival rates approaching 80% with single-modality surgery or radiotherapy (2). Locally advanced disease (stage III/IV-A/IV-B) comprises approximately 60% of patients at diagnosis and has 5-year survival rates of approximately 50% to 60% with combined modality standard of care treatment. Notably, a recent publication attempting to refine stage and prognostic groups for HPV related non-metastatic (M0) oropharyngeal cancer found that with a refined prognostic model, patients with locally advanced disease had significantly improved survival prediction compared to seventh edition AJCC TNM staging (3). Approximately 10% of patients present with metastatic disease and have 5-year survival rates approaching 30% (1). Approximately 50% of patients with locally advanced SCCHN develop locoregional or distant relapses which are usually detected within the first 2 years of treatment (3). For this population, the prognosis is extremely poor with DCR estimating 45%, and median OS estimates of 6 to 9 months (4). For distant metastases, the usual pattern of spread is to lung, liver, and bone, although this pattern may be different in HPV-positive disease which can spread to a range of other sites including intra-abdominal lymph nodes, pleural cavity, bowel and brain. Chemotherapy is an integral part of the treatment of locally recurrent and metastatic SCCHN. Palliation is the main goal of treatment for patients with metastatic disease and locally recurrent disease not curable by radiation and/or surgery. The current standard of care for locally recurrent and/or metastatic SCCHN is concurrent platinum-based chemotherapy in patients with good performance status without severe comorbidities. The median OS is 7 to 10 months (5,6). In a phase 3 randomized trial of patients with recurrent or metastatic SCCHN, cetuximab plus 5-fluorouracil/cisplatin or 5-fluorouracil/carboplatin improved median OS compared to the standard of care chemotherapy doublet (10.1 months compared to 7.4 months [7]). A similar trial design was employed for the SPECTRUM study, which evaluated

panitumumab. Patients in both groups received up to six 3-weekly cycles of intravenous cisplatin (100 mg/m2) and 5-fluorouracil (1 g/m2 per day for 4 days), while those in the experimental group also received intravenous panitumumab. A total of 657 patients were randomized and the median overall survivals were 11.1 versus 9.0 months (hazard ratio [HR] 0.873; P=0.1403) in the panitumumab and control group, respectively (8). After failure of first-line platinum-based chemotherapy, cetuximab monotherapy in a phase 2 study demonstrated ORR 10% with a median OS of 5.8 months representing an increase of 2.5 months compared with platinum-refractory historical controls (4). Objective response to second-line cytotoxic chemotherapy are uncommon with little impact on prolonging OS (9). Locally advanced, metastatic and recurrent SCCHN remains an area of high unmet medical need. Therefore, clinical evaluation of novel therapeutic approaches such as modulation of the immune system is needed.

The Role of HPV

Genetic material from high risk-oncogenic strains (HPV types 16 and 18) is found in approximately 60% of oropharyngeal cancers arising from the palatine and lingual tonsils (9). Patients with locoregionally advanced HPV-positive oropharyngeal SCCHN treated with chemo radiation have better survival than do HPV-negative patients (10-12). The transforming potential of HPV infection is driven by viral proteins E6 and E7, which inactivate the tumor suppressor proteins p53 and pRb, which results in loss of cell cycle regulation, cellular proliferation, and chromosomal instability (13). Squamous cell carcinoma of the head and neck patients with tumors that are HPV-positive have an improved survival compared with SCCHN patients who are HPV-negative. A retrospective multivariate analysis of a randomized, phase 3 trial, Radiation Therapy Oncology Group 0129 originally designed to compare accelerated-fractionation to standard fractionation radiotherapy when delivered with concurrent cisplatin has been reported (12). This analysis revealed significantly improved 3-year survival among SCCHN patients who were HPV-positive compared with SCCHN patients who were HPV negative (84% vs. 57% respectively). Patients with HPV-positive tumors had a 58% reduction in risk of death compared with patients with HPV-negative tumors (HR 0.42, 95% confidence interval [CI 0.27, 0.66]). In a multicenter Eastern Cooperative Oncology Group (ECOG) study in which patients with newly diagnosed stage III or IV

SCCHN were treated with induction chemotherapy followed by chemoradiation, 60% of oropharynx primary tumors were found to be HPV-positive (14). The two-year PFS rate (86% vs.53%; p=0.02) and OS rate (95% vs. 62%; p=0.005) were also significantly better for patients with HPV-associated cancer compared to HPV-negative cancer. Another retrospective analysis of the SEER (Surveillance, Epidemiology, and End Results) data for patients with oropharyngeal cancer revealed a 4-fold higher median OS in patients who were HPV-positive compared with patients who were HPV-negative (131 months vs 20 months) (15). In contrast, the outcome for HPV-negative SCCHN patients has not improved despite intensification of standard chemotherapeutic agents and combinations. Novel therapeutic approaches are needed in this

population.

Etiologies of SCCHN

SCCHN is caused by the accumulation of multiple gene alterations modulated by genetic predisposition and chronic inflammation, enhanced by environmental influences such as tobacco and alcohol abuse (non-HPV related) or by infection with HPV (16). These etiologies involve a multistep process and result in alterations in both oncogenes and tumor suppressor genes.

Programmed Cell Death-1 (PD-1) in SCCHN

Recently a new class of monoclonal antibodies has been engineered to block or activate co-signaling pathways resulting in enhanced anti-tumor immunity. One of the most promising pathways for manipulation involves program death ligand 1 (PD-L1). PD-L1 expression is up regulated in solid tumors where it allows the tumor to evade attack by the immune system (17,18). Inhibition of the interaction between PD-1 receptors (expressed on activated T cells) and PD-L1 has been shown to enhance T-cell responses (19). Down-regulation of T-cells in SCCHN has been implicated in pathogenesis and progression of tumors (20,21). High levels of PD-1 expression have been demonstrated in human SCCHN tissue samples across multiple primary sites (22) on 46% to 87% of tumors (22-25). While most studies have analyzed surgical samples from initial diagnosis, one evaluation of oropharyngeal squamous cell samples included 28 recurrent tumors and 10 distant metastases of which 43% and 70% expressed PD-L1 respectively (25). PD-L1 expression was considered binarily positive in tumor cells if >5% staining (versus negative if 0 to 5% staining). These data suggest PD-L1 is expressed on SCCHN in the primary, recurrent, and metastatic settings and manipulation of the PD-L1: PD-1 pathway may be an important therapeutic target.

Given the importance of HPV in the etiology of oropharyngeal SCCHN, several studies have examined the correlation between HPV status and PD-L1 status. Three independent studies have revealed higher expression of PD-L1 in HPV-positive compared to negative patients: 70 vs 29% (26), 49.2% vs 34.1% (28), and 62.5% vs 40% (26). Additionally, a 12-gene chemokine signature identifying a subset of CD-8 enriched (T-cell enriched phenotype-high) tumors was developed in SCCHN tumors. T-cell enriched high phenotypes (TCIP-H) were found in 51% of HPV-positive-tumors and in 21% of HPV-negative tumors indicating that the TCIP-H population may be a particularly important target in SCCHN (27).

2.2. Anti-PD1 and Tumor Immunity

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. The inability of the immune system to control tumor growth does not appear to result from an inability to recognize the tumor as foreign. Tumor cells

have been shown to evade immune destruction despite displaying recognizable antigens on their surface and despite the presence of high-avidity T cells that are specific for these antigens.

Histologic evaluation of many human cancers shows extensive infiltration by inflammatory and immune cells, suggesting that the immune system responds less effectively to malignancy. These observations have led to the hypothesis that dominant mechanisms of immune tolerance or immune suppression are responsible for the immune system's inability to effectively respond in a way that consistently results in rejection.

There are a number of inhibitory mechanisms that have been identified to be involved in tumor-mediated immune suppression and include expression of the programmed death ligand-1 (PD-L1), which can engage the inhibitory receptor PD-1 on activated T cells; lack of function of antigen presenting cells and infiltration of FoxP3+ regulatory T cells (Treg), which can mediate extrinsic suppression of effector T cell function. Therefore, agents that target these negative regulatory pathways, and thereby allow the expansion of effectorT cells present in the tumor, may be beneficial in the clinic.

Combined Immune Checkpoint Inhibition

Blockade of immune inhibitory pathways is emerging as an important therapeutic modality for the treatment of cancer as evidenced by the clinical responses observed with antibodies to CTLA-4 and PD-1/PD-L1. Pembrolizumab, a fully human IgG4 antibody blocking PD-1, produced durable objective responses in patients with melanoma, NSCLC, and head and neck cancer. Although these single agents have antitumor activity, multiple immune inhibitory mechanisms are present concurrently within the tumor microenvironment, suggesting that combination therapies may be required for optimal therapeutic effect. For example, CTLA-4 and PD-1 appear to play complementary roles in regulating adaptive immunity. Whereas PD-1 contributes to T-cell exhaustion in peripheral tissues, CTLA-4 inhibits at earlier points in T-cell activation. In preclinical models, combined blockade of PD-1 and CTLA-4 achieved more pronounced antitumor activity than blockade of either pathway alone.

Pembrolizumab – Background information

Pembrolizumab (Keytruda™ [US]), a humanized monoclonal antibody against the PD-1 protein, has been developed by Merck & Co for the treatment of cancer. Pembrolizumab is approved for treatment of melanoma in several countries; in the US and EU it is approved for the treatment of advanced (unresectable or metastatic) melanoma in adults. Pembrolizumab has also been approved for treatment of non-small cell lung cancer (NSCLC) in several countries; in the US it is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with NSCLC and EGFR or ALK genomic tumor aberrations should also have disease progression on FDA-approved therapy for those aberrations prior to

receiving pembrolizumab. Most recently, pembrolizumab has gained accelerated conditional approval in the United States and several countries in the EU in the second line setting for recurrent/metastatic SCCHN with disease progression on or after platinum containing chemotherapy without any biomarker testing requirement based on the updated data of the phase 1b KEYNOTE-012 study (NCT01848834). Full approval is dependent on the OS outcome of the phase KEYNOTE 040 study.

Pembrolizumab has demonstrated initial clinical efficacy in single arm monotherapy trials in subjects with NSCLC, SCCHN, urothelial cancer, gastric cancer, triple negative breast cancer, and Hodgkin's Lymphoma as determined by response rate. Ongoing clinical trials are being conducted in other tumor types including hematologic malignancies. For study details, please refer to the pembrolizumab Investigator's Brochure.

The first dose-escalation phase 1 study involving subjects with solid tumors showed that pembrolizumab was safe at the dose levels tested (1 mg/kg of body weight, 3 mg/kg, and 10 mg/kg, administered every 2 weeks) without reaching a maximum tolerated dose (28). In addition, clinical responses were observed at all the dose levels (29). For additional information, refer to the pembrolizumab Investigator's Brochure.

Pembrolizumab in SCCHN

On 08 August 2016, pembrolizumab gained accelerated conditional approval in the United States and several countries in the EU in the second line setting for recurrent/metastatic SCCHN based on the results of a pooled analysis of 2 recurrent/metastatic squamous cell carcinoma head and neck cohorts from KEYNOTE 012 (NCT01848834). In one cohort, subjects with positive PD-L1 expression (defined as a proportion score of > 1% PD-L1 immunohistochemistry expression in tumor cells or stroma) received pembrolizumab 10 mg/kg every 2 weeks. In a second cohort, subjects with both positive and negative PD-L1 expression received pembrolizumab 200 mg every 3 weeks. The evaluable population (n = 173) was heterogeneous in terms of numbers of prior lines of therapy; however, most patients had received prior platinum therapy. The ORR in the entire population was 23.7% (24.1% in the HPV-negative subset and 23.6% in the HPV-positive subset). The median PFS was 2.2 months (95% CI: 2.0 to 3.6) and the median overall survival was reported to be 9.6 months (95% CI: 6.6 to not reached). Treatment was well tolerated with grade 3/4 drug-related adverse events occurring in 12.5% of patients (30).
A phase 2 clinical trial of single agent pembrolizumab in platinum and cetuximab failure subjects is currently being conducted (NCT02255097). The primary endpoint will be ORR by RECIST 1.1. A phase 3 clinical trial of pembrolizumab versus standard of care (methotrexate, docetaxel, or cetuximab) in recurrent or metastatic SCCHN subjects after treatment with platinum-based cetuximab therapy is being conducted (NCT02252042) with primary endpoint of OS. A third

study of pembrolizumab alone versus pembrolizumab plus platinum plus 5-Fluorouracil versus cetuximab plus platinum plus 5-Fluorouracil for first line treatment of recurrent or metastatic SCCHN is currently being conducted (NCT02358031). The primary endpoint of this study will be PFS by RECIST 1.1. For all three studies, subjects will receive pembrolizumab 200 mg intravenously on Day 1 of each 3 week cycle.

As existing data suggest 200 mg every 3 weeks as the appropriate dose for pembrolizumab and pembrolizumab is currently being tested at this fixed dose in ongoing head and neck cancer studies, this is the dose of pembrolizumab planned to be studied in this trial.

2.3. Abemaciclib Background

2.3.1. Cyclin D Kinase 3/4 inhibition in cancer

During the cell cycle, the G1 restriction point controls entry into S phase and is essential for maintaining control of cell division (31,32). The cyclin-dependent kinases (CDKs), CDK4 and CDK6, participate in a complex with D-type cyclins to initiate the transition through the G1 restriction point by phosphorylating and inactivating the retinoblastoma (Rb) tumor-suppressor protein. Alterations in this pathway occur frequently in human cancers and involve (1) loss of CDK inhibitors by mutation or epigenetic silencing, (2) mutation/overexpression of either CDK4 and CDK6 or cyclinD, or (3) inactivation of Rb. These alterations render cells less dependent on mitogenic signaling for proliferation. With the possible exception of those tumors with complete inactivation of Rb, which functions downstream of the CDK4 and CDK6–cyclinD complex, all of these cancers are potentially sensitive to pharmacologic inhibition of CDK4 and CDK6. From a therapeutic standpoint, the goal of inhibiting CDK4 and CDK6 with a small-molecule inhibitor is to prevent cell cycle progression through the G1 restriction point, thus arresting tumor growth.

2.3.2. Abemaciclib Background information

Abemaciclib represents a selective and potent small-molecule CDK4 and CDK6 dual inhibitor with a broad antitumor activity in preclinical pharmacology models, acceptable physical and pharmacokinetic (PK) properties, and an acceptable toxicity profile in nonclinical species. Formally, abemaciclib refers to the freebase whereas LSN2813542 refers to abemaciclib mesylate; however, abemaciclib is used for uniformity throughout this Investigator's Brochure (IB), except when important for experimental clarity. This compound demonstrates significant inhibition of tumor growth as monotherapy in multiple human xenograft models including models for: breast cancer, colorectal cancer, glioblastoma multiforme, acute myeloid leukemia, melanoma, mantle cell lymphoma (MCL), and non–small-cell lung cancer (NSCLC). Although characterized by a different constellation of genomic mutations, each of these human xenografts has an intact, functional Rb protein. Xenograft growth inhibition is generally dose dependent from 25 to 100 mg/kg following daily oral administration for 21 to 28 days. Additional nonclinical studies in xenograft models for human NSCLC and melanoma also show that abemaciclib may be used in combination with standard cytotoxic or targeted therapies to improve efficacy of these agents.

In nonclinical species, abemaciclib distributes efficiently to the brain and potentially provides a unique opportunity to treat primary brain tumors as well as cancers that have metastasized to the brain. As a result of its brain exposure, treatment with abemaciclib in a rat orthotropic brain tumor model produces statistically significant and dose-dependent improvement in survival. Abemaciclib demonstrates moderate-to-high bioavailability in preclinical species. In repeat-dose toxicokinetic studies, abemaciclib showed generally dose-dependent exposure with no gender differences. Abemaciclib is highly metabolized, and hepatic elimination plays a major role in the clearance of abemaciclib and its metabolites in rats, dogs, and humans. In humans, the terminal elimination half-life (t1/2) in plasma ranges from approximately 17 to 38 hours across the doserange tested. At a single dose of 200 mg, the mean apparent oral clearance (CL/F) is 38.3 L/hour with a high interindividual variability (105% coefficient of variation [CV]) and the apparent volume of distribution is large at 1300 L (96% CV). In the xenograft models and skin biopsies from patients, abemaciclib inhibited phosphorylated Rb (pRb) and topoisomerase II alpha (TopoIIα) at clinically relevant doses and exposures.

In preclinical species, the primary target organs for toxicity (associated with up to 3 months of continuous daily dosing) are bone marrow (resulting in pancytopenia), gastrointestinal tract, lymphoid tissues, and male reproductive tract. All of these changes demonstrated complete or partial reversibility during the recovery period. In humans, the most common (≥10%) treatment-emergent adverse events (TEAEs) possibly related to the study drug for patients who received single-agent abemaciclib include diarrhea, nausea, fatigue, neutropenia, vomiting, decreased appetite, leukopenia, thrombocytopenia, anemia, abdominal pain, and blood creatinine increased. Increased rates of skeletal and cardiac variations and malformations, accompanied by decreased fetal weights, were observed in an embryo–fetal development study of abemaciclib in rats.

2.4. Study Rationale

Immunotherapy (anti-PD-1/PD-L1) has been recently approved for patients with metastatic or recurrent squamous cell carcinoma of the head and neck. However, only a small percentage of patients experience long-term control, necessitating new therapeutic strategies. Recently, Goel et al. Nature 2017 showed preclinically and in breast tumors that CDK4/6 inhibitors stimulates production of type III interferons and hence enhances tumour antigen presentation. CDK4/6 inhibitors also suppressed the proliferation of regulatory T cells (33). These events promote cytotoxic T-cell-mediated clearance of tumour cells, which is further enhanced by the addition of immune checkpoint blockade.

Although the combination of Abemaciclib and Pembrolizumab is tested recently in Stage IV Non-Small Cell Lung Cancer patients, there is not much data available on combination of CDK 4/6 inhibitors and Anti-PD1 agents. Preliminary data from this Phase I study was presented at ESMO 2017 where combination of Abemaciclib and Pembrolizumab was tolerated well by NSCLC patients. Toxicities that were reported were as follows – Nausea (51.7%), diarrhea (51.7%), vomiting (41.4%), and decreased appetite (31%). 10 out of 24 patients treated with the

combination had Grade 3/4 treatment related Adverse events (AEs). Only 3 patient died although they were unrelated to drugs (2 due to disease progression and 1 due to stroke).

Based on these data, we propose a phase II trial in patients with metastatic or recurrent head and neck cancer who are eligible for anti-PD-1/PDL1 therapy investigating the combination of abemaciclib with pembrolizumab. Tumor & blood analysis for interferon gamma signature will be explored as possible biomarkers.

2.5. Population to be Studied

Patients with Stage IV metastatic or recurrent squamous cell carcinoma of Head and neck, progressed after treatment with systemic therapy.

2.6. Potential Risks and Benefits to Human Patients

2.6.1. Potential Risks

Abemaciclib

Based on clinical experience with abemaciclib, the adverse events of special interest (AESIs) are neutropenia, infections, diarrhea, blood creatinine increased, hepatic events (increases in aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), and embolism (mainly pulmonary embolism and deep vein thrombosis)); furthermore, pneumonitis is considered an adverse event (AE) of note.

Pembrolizumab

The most commonly observed adverse reactions to single-agent Pembrolizumab are fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, and pyrexia. Side effects of Pembrolizumab include immune-mediated disorders, such as hepatitis, colitis, pneumonitis, endocrinopathies, nephritis and renal dysfunction, skin reactions, and encephalitis, as well as infusion reactions. The most current Pembrolizumab investigator brochure should be referenced for the most complete and updated information.

Computed Tomography (CT) Scans

Patients will be exposed to a relatively small amount of radiation as a result of the CT scans required in this study. This degree of exposure has not been associated with harmful health effects. In addition, the frequency of CT scans performed in this study is similar to the standard of care frequency. Patients with a medical contraindication to CT scans or known iodinated contrast allergies may instead undergo magnetic resonance imaging (MRI). There is minimal risk of MRI imaging in patients able to undergo this type of exam including very rare reports of gadolinium-induce nephrogenic systemic fibrosis in patients with poor renal function.

Venipuncture

Patients could also experience side effects from venipuncture for tests that will be done as part of this study, including pain, tenderness, and bruising at the site of collection, and rarely infection may occur at the spot where the needle is inserted.

Other Risks

This study treatment may involve risks to unborn children and therefore patients should not become pregnant or father a baby while participating in this study. Patients should not nurse (breastfeed) while on this study. Women of childbearing potential must have a negative pregnancy test before taking part in this study.

Women must be of non-childbearing potential due to surgical sterilization (i.e., at least 6 weeks following surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) confirmed by medical history or menopause; or must agree to use 2 methods of effective and highly reliable methods of contraception at the same time (i.e., tubal sterilization, partner's vasectomy, intra-uterine device (IUD), male latex condom with or without spermicide, diaphragm with spermicide, cervical cap with spermicide, or vaginal sponge that contains spermicide) during study treatment (including during temporary breaks from treatment), and for at least 180 days after stopping Abemaciclib and at least 180 days after stopping Anti-PD1 treatment.

Men must agree to use 2 effective and highly reliable methods of contraception at the same time (i.e., vasectomy, male latex condom with or without spermicide, partner's tubal sterilization, partner's use of an IUD, partner's use of diaphragm with spermicide, cervical cap with spermicide, or vaginal sponge that contains spermicide) during study treatment (including temporary breaks from treatment), and for at least 180 days after stopping Abemaciclib and at least 180 days after stopping Anti-PD1. The long-term risk of infertility is unknown. Ovarian failure has been observed with other antiangiogenic agents.

2.6.2. Potential Benefits

Abemaciclib is an investigational product and its efficacy in combination with pembrolizumab has not been established. Pembrolizumab is approved for treatment of non-small cell lung cancer, melanoma, and head and neck cancer and any solid tumor that has high PD-L1 expression. It is expected that the administration of Abemaciclib and Pembrolizumab may result in clinical benefit (i.e. Tumor response).

2.7. Justification of the Dose, Schedule, and Route of Administration

The dose, schedule, and route of administration of Abemaciclib (150 mg BID) was selected based on safety, pharmacokinetics, and evidence of activity in the Phase 1b study (JBIF). Dose reduction is possible for treatment of adverse events, including anemia.

Pembrolizumab (Keytruda®) is an a human monoclonal PD-1 antibody that is approved by the FDA for a number of indications, including the treatment of metastatic NSCLC , Melanoma and

tumors with high PD-L1 expression, that have progressed following on or after standard of care treatment. This protocol is designed to administer Pembrolizumab 200 mg IV every 3 weeks.

2.8. Study Conduct

This clinical trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

3. TRIAL OBJECTIVES AND PURPOSE

The purpose of this study is to evaluate the efficacy, safety and tolerability of Abemaciclib in combination with Pembrolizumab.

Primary Objective:

- To assess the objective response rate (ORR) of tumor lesions to abemaciclib in combination with pembrolizumab in patients with metastatic or recurrent squamous cell carcinoma of head and neck.

Secondary Objectives:

1) To assess safety and tolerability of abemaciclib in combination with pembrolizumab
2) To assess PFS and OS
3) To assess time to tumor response and duration of response

Exploratory Objective:

1) To assess MSI status, CDKN2A, RB, and CDK4/6 status
2) To assess gene expression related to immune pathway

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

4.1.1. Overview

This is a single center, open-label, nonrandomized, Phase 2 study of Abemaciclib in combination with Pembrolizumab in patients with metastatic or recurrent squamous cell carcinoma of head and neck who have progressed on standard of care treatment.

All patients must sign and date a consent form prior to undertaking any study-related procedures. Prospective patients will be screened to determine if they qualify for the study within 28 days of enrollment. Patients will receive Pembrolizumab at 200 mg IV very 3 weeks starting on Cycle 1 Day 1 (C1D1) and will receive Abemaciclib starting on C1D1 at 150 mg PO BID Table 3 (see Abemaciclib Administration Section 6.1.5 and Pembrolizumab Administration Section 6.2.6).

Patients will receive study treatment until development of toxicity or disease progression on treatment or any reasons of withdrawal. Adverse events will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

Table 3: Study Drug Dosing Schedule

Cohort	Number of evaluable patients	Patient population	Abemaciclib (mg) PO BID	Pembrolizumab IV every 3 weeks starting C1D1
1	15	SCCHN who are Immunotherapy Naive	150	200 mg
2	15	SCCHN who progressed on Immunotherapy	150	200 mg

4.1.2. Eighteen patients will be enrolled in each cohort. For each cohort after 11 evaluable patients are enrolled (stage 1), an additional 7 evaluable patients will be enrolled (stage 2) if 2 or more patients respond. If there is one or no response,

then no further patients will be enrolled and the study will be terminated. Trial Procedures

All on-study procedures are permitted within the time window indicated in the Schedule of Assessments (Table 4).

4.1.2.1. Screening

The following screening procedures must be performed within 28 days prior to the first day of study therapy. Qualifying hematology, serum chemistry (including LFTs and thyroid-stimulating hormone [TSH] testing), coagulation, physical examination, ECG, pregnancy, and urinalysis collected within 7 days of Cycle 1 Day 1 (C1D1) do not need to be repeated. The following will be performed according to the Schedule of Assessments (Table 4).

- Patient signature and date on current Institutional Review Board (IRB)-approved informed consent form - Prior to undergoing any study-specific procedure, patients must read, sign, and date the current IRB)-approved informed consent form. Patients may sign consent prior to the 28-day screening period.
- Medical history, baseline signs and symptoms, drug allergies, primary diagnosis, and demographics
- Physical examination, including examination of all major body systems, ECOG and performance status.
- Vitals signs will be measured which will include - heart rate, temperature, blood pressure, respiratory rate, and weight. Height will also be measured at baseline visit.
- Hematology, coagulation (prothrombin time and INR), and serum chemistry (including liver function tests and TSH) to be performed locally
- Hepatitis B serology will be done for patients with history of hepatitis B infection in the past or are treated for active hepatitis infection
- Serum or urine pregnancy test for all females of childbearing potential to be performed locally
- Urinalysis to be performed locally - Microscopic analysis and/or urine protein-creatinine ratio (UPCR) should be performed as clinically indicated.
- CT or MRI scans of neck, chest, abdomen, and pelvis to detect spread of disease and for measurable target lesions.
- Bone scans are to be performed if metastases to bone are suspected at screening.
- Single tracing 12-Lead ECG (QT, PR, and QRS intervals and heart rate will be captured)
- Assessment of concomitant medications and treatments from 28 days prior to the start of study treatment
- Archival Tumor Tissue Specimens: Archival specimens (formalin-fixed, paraffin-embedded) of the primary cancer specimen for each study participant. It is preferable

that the entire paraffin block be submitted, but if this is not feasible, then at least 20 unstained slides are requested for immunohistochemical analysis (sections of ~ 5 microns are preferred).

- HPV status: HPV status will be collected from the pathological report for all patients. In case when this information is not available, HPV testing will be done on tumor tissue at the time of screening.

4.1.2.2. Study Drug Treatment Period

Qualifying hematology, blood chemistry (including TSH testing), coagulation, urinalysis, physical examination, ECG, and pregnancy test do not need to be repeated on C1D1 if acceptable screening assessments are performed within 7 days prior to the start of study therapy. On days of dosing, all assessments should be performed prior to dosing with Abemaciclib unless otherwise indicated in the Schedule of Assessments (Table 4). Patients will be eligible to receive Abemaciclib and Pembrolizumab until unacceptable toxicity, withdrawal of consent, progression of disease or end of study. Each cycle is 21 days in duration. The following will be performed according to the Schedule of Assessments (Table 4).

- Physical examination including examination of all major body systems, ECOG and performance status.
- Hematology, coagulation (prothrombin time and INR) and serum chemistry (including liver function tests and TSH) to be performed locally
- Urinalysis to be performed locally - Microscopic analysis and/or UPCR should be performed as clinically indicated.
- Serum or urine pregnancy test for all females of childbearing potential to be performed locally
- Vital signs will be evaluated before administration of Abemaciclib and pembrolizumab. These will include - heart rate, temperature, blood pressure, respiratory rate, and weight. These will be repeated on days mentioned in schedule of assessment (Table 4).
- Evaluation of Immunologic prognostic signature will be performed at baseline:
  - Flow cytometry for immune cells (circulation CD8+ T cells, MDSCs,)
  - Tumor mutation load
  - PD-L1 proportional score
  - Interferon-gamma gene signature

    Circulating tumor cell PD-L1 expression
- Administration of Abemaciclib: Abemaciclib will be administered at a starting dose of 150 mg twice daily and it is provided as 50-mg capsules. Abemaciclib should be taken twice daily (with at least 6-hour separating doses) at the same time each day with a glass of water. Patients should be instructed to swallow capsules whole and not open, chew, or crush. Intrasubject dose escalation of Abemaciclib is not permitted.

- Administration of Pembrolizumab: Administer 200 mg as an IV infusion over 60 min on Day 1 of cycle 1 and over 30 min thereafter starting cycle 2, as described in the Pembrolizumab investigator brochure.
- Assessment of adverse events (AEs)
- Assessment of concomitant medications and concomitant treatments

4.1.3. Follow-up

Safety Follow-up

All subjects will complete a safety follow-up visit approximately 30 (+7) days after the last dose of study treatment. Serious adverse events and any concomitant medications associated with serious adverse events observed by the investigators or reported by the subjects that occur through 90 (+7) days after the cessation of all study treatment or 30 (+7) days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, will be reported to Eli Lilly and recorded in the CRF.

Long-term Follow-up

After the safety follow-up visit, all subjects will enter the long-term follow-up. Subjects will be followed for survival and subsequent anticancer therapies every 12 weeks (± 28 days) **from safety follow-up** for approximately 36 months after the last subject is enrolled. In addition, Abemaciclib/Pembrolizumab related adverse events that occur through the end of the long-term follow-up will be reported.
For subjects who discontinue study treatment without documented PD and have not **initiated a new** anticancer therapy, every effort should be made to continue monitoring tumor response status by clinical and radiographic tumor assessments.

Table 4: Schedule of Assessments

Protocol Activities	Screening	Cycle 1 [21 days]		Cycles 2 -4	Cycles 5 onwards	EOT	Follow-up[a]
	Day -28	Day 1	Day 15	Day 1	Day 1		
Baseline Documentation							
Informed Consent	X						
Medical/Oncology History	X						X
Baseline Signs and Symptoms	X						
Physical Examination	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X
Laboratory Studies							
Hematology	X	X	X	X	X	X	X
Coagulation	X	X					
Blood Chemistry including TSH, LFTs	X	X	X	X	X	X	X
Serology for Hepatitis B and C	X						
Pregnancy Test[b]	X	X		X	X	X	
Urinalysis	X	X		X	X	X	

Protocol Activities	Screening	Cycle 1 [21 days]		Cycles 2 -4	Cycles 5 onwards	EOT	Follow-up[a]
	Day -28	Day 1	Day 15	Day 1	Day 1		
HPV status	X[g]						
Treatment with Study Drug							
Abemaciclib (150 mg) Dosing[e]		X		X	X		
Pembrolizumab (200 mg IV)		X		X	X		
Tumor Assessments							
CT or MRI Scans	X				X		X
Other Clinical Assessments							
12-Lead ECG	X						
Concomitant Medications/Treatments	X	X	X	X	X		
Adverse Events		X	X	X[d]	X[d]	X	X
Special Laboratory Assessments							
Immunologic prognostic signatures[f]	X						
Archival Tumor Tissue	X						

Protocol Activities	Screening	Cycle 1 [21 days]		Cycles 2 -4	Cycles 5 onwards	EOT	Follow-up[a]
	Day -28	Day 1	Day 15	Day 1	Day 1		
Blood for ctDNA	X	X		X		X	

a Refer section 4.1.3 for frequency of follow-up (safety and long-term)

b when applicable

c Sample will be collected from resected tumor tissue after operation

d Staging scans will be done after every completion of 4 cycles (3 months)

e BID PO dosing Abemaciclib

f Includes Flow cytometry for immune cells (circulation CD8+ T cells, MDSCs,), Tumor mutation load, PD-L1 proportional score, Interferon-gamma gene signature, Circulating tumor cell PD-L1 expression

g HPV testing will be done on tumor tissue at baseline only for those patients where HPV status is not available.

5. SELECTION AND WITHDRAWAL OF PATIENTS

5.1. Patient Inclusion Criteria

1. Histologically confirmed (core biopsy proven) metastatic or recurrent squamous cell carcinoma of head and neck
2. Adequate pulmonary and cardiac function
3. Available archived tissue of primary tumor or resected tumor specimen with adequate samples
4. Prior treatment with immune checkpoint inhibitor is not allowed in cohort 1 patients. Patients in cohort 2 should have failed or progressed on prior immune checkpoint inhibitor.
5. ECOG PS = 0 or 1
6. Patients who received chemotherapy must have recovered (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≤1) from the acute effects of chemotherapy except for residual alopecia or Grade 2 peripheral neuropathy prior to randomization. A washout period of at least 21 days is required between last chemotherapy dose and randomization (provided the patient did not receive radiotherapy).
7. Patients who received adjuvant radiotherapy must have completed and fully recovered from the acute effects of radiotherapy. A washout period of at least 14 days is required between end of radiotherapy and randomization.
8. The patient is able to swallow oral medications.
9. Adequate hematologic and end-organ function
10. ANC ≥ 1500/mm^3
11. Platelet count ≥ 100,000/mm^3
12. Hb ≥ 8g/dl (Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator. Initial treatment must not begin earlier than the day after the erythrocyte transfusion).
13. Creatinine ≤ 1.5 x ULN or Creatinine Clearance (CrCl) ≥ 60 ml/min
14. Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert syndrome, who can have total Bilirubin ≤ 2.0 x ULN and direct bilirubin within normal limits are permitted.)
15. AST and ALT and alkaline phosphatase ≤ ULN
16. Agreement to remain abstinent or use appropriate contraception, among women of childbearing potential
17. Willingness and ability to consent for self to participate in study
18. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures

5.2. Exclusion Criteria:

1. Autoimmune disease (Note: Vitiligo, type 1 diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement,

and conditions not expected to recur in the absence of an external trigger are permitted.)

2. Condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days prior to study treatment (Note: Inhaled and topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.)
3. Preexisting medical condition(s) that would preclude participation in this study (for example, interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis or a preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea).
4. Immunosuppression, of any kind
5. Prior treatment with CDK 4/6 inhibitor
6. Major surgical procedure or significant traumatic injury within 4 weeks prior to study treatment, and must have fully recovered from any such procedure
7. Personal history of any of the following conditions: syncope of cardiovascular etiology, ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest
8. Angina, myocardial infarction (MI), symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack TIA), arterial embolism, pulmonary embolism, percutaneous transluminal coronary angioplasty (PTCA), or coronary artery bypass grafting (CABG) within 6 months prior to study treatment
9. Known active viral or nonviral hepatitis or cirrhosis
10. Any active infection requiring systemic treatment, positive tests for Hepatitis B surface antigen or Hepatitis C ribonucleic acid (RNA).
11. History of gastrointestinal perforation or fistula in the 6 months prior to study treatment, unless underlying risk has been resolved (e.g., through surgical resection or repair)
12. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness.
13. Pregnancy or breastfeeding - Female patients must be surgically sterile (i.e., ≥6 weeks following surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) or be postmenopausal, or must agree to use effective contraception during the study and for 4 months following last dose of treatment. All female patients of reproductive potential must have a negative pregnancy test (serum or urine) within 7 days prior to study treatment. Male patients must be surgically sterile or must agree to use effective contraception during the study and for 4 months following last dose of treatment. The definition of effective contraception is provided in Section 2.6.1 of this protocol.
14. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for this study

5.3. Patient Withdrawal Criteria

A patient should be withdrawn from study treatment if, in the opinion of the Investigator, it is medically necessary, or if it is the wish of the patient. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome. Data to be collected at the end of study visit are described in the Schedule of Assessments (Table 4). Patients will be followed for at least 28 days after the last dose of study drug (Abemaciclib or Pembrolizumab) for AEs. If the patient withdraws consent, no further evaluations should be performed, and no attempts should be made to collect additional data. In addition, patients will be withdrawn from treatment in the case of:

1. Lost to follow-up or noncompliant with the protocol
2. Pregnancy - Pregnant patients should be followed for the duration of the pregnancy and the outcome of the pregnancy should be documented.
3. Arterial thrombosis of any grade (including cerebrovascular ischemia, cardiac ischemia/infarction, or peripheral or visceral arterial ischemia) or Grade 3 or 4 venous thrombosis (including pulmonary embolism)
4. Grade > 3 pneumonitis, any Grade 4 toxicity including colitis, AST or ALT > 5 times the ULN or total bilirubin > 3 times the ULN, Grade 4 hypophysitis that cannot be controlled with endocrine replacement therapy, Grade > 3 adrenal insufficiency that cannot be controlled with endocrine replacement therapy, Grade > 3 nephritis with serum creatinine > 3 times the ULN, encephalitis of any grade, type 1 diabetes mellitus with Grade 4 hyperglycemia, Grade > 3 infusion-related reactions, Grade 4 rash or suspected Stevens-Johnson syndrome or toxic epidermal necrolysis, any Grade > 3 non-hematologic treatment-related toxicity that recurs, any Grade 2 or 3 immune related toxicity that persists despite treatment modifications or corticosteroid treatment that cannot be reduced to 10 mg of prednisone or equivalent per day within 12 weeks

5.4. General Guidelines

Eligible patients will be entered on study at Kirklin clinic and UAB Hospital. Site clinical research coordinator (CRC) will ensure study agent availability before enrolling patients. Following enrollment and registration by site CRC, patients should begin protocol treatment within 28 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be cancelled. The Study Monitor should be notified of cancellations as soon as possible.

5.5. Registration Process

The Clinical Trials Network Monitoring Office (CTNMO) of the UAB Comprehensive Cancer Center (CCC) coordinates investigator-initiated clinical trials under Good Clinical Practice conditions at UAB to achieve timely study subject enrolment. Once a study subject has been screened and deemed eligible for study entry by the site CRC, a study-specific number is assigned to the study subject and a Registration Form is completed. Queries regarding data accuracy are forwarded from the CTNMO to the site CRC for clarification or correction.

6. TREATMENT OF PATIENTS

6.1. Description of Abemaciclib Study Drug

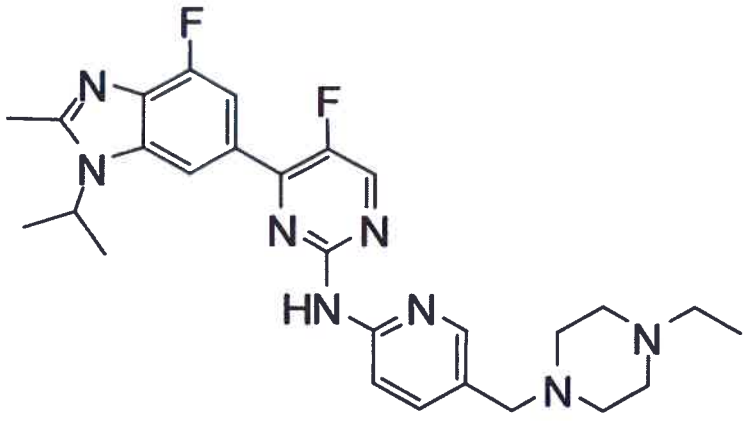
Abemaciclib is an oral, selective, and potent ATP-competitive inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6, respectively). CDK4 and CDK6 promote cell growth by facilitate ing the progression of cells from the G1 to the S-phase of the mammalian cell cycle. This promotion of cell growth occurs primarily by counteracting the effects of a growth suppressor protein known as the retinoblastoma (Rb) protein, whereby the reversal of Rbmediated suppression is achieved by the phosphorylation of this protein by CDK4 and/or CDK6.

The CDK4/CDK6-Rb pathway is commonly altered in cancer cells, whereby the activation of this pathway contributes to enhanced growth. Accordingly in cancer cells, abemaciclib inhibits CDK4/CDK6-dependent phosphorylation of Rb, which subsequently blocks proliferation by inhibiting the progression of these cells from the G1 phase into the S and G2/M phases of the cell cycle.

Abemaciclib showed antitumor activity within multiple preclinical pharmacology models and an acceptable toxicity profile in nonclinical species. Abemaciclib has been shown to significantly inhibit tumor growth in multiple murine xenograft models for human cancer.

6.1.1. Abemaciclib Composition

The chemical name of Abemaciclib is (2-Pyrimidinamine, N-[5-[(4-ethyl-1-piperazinyl)methyl]-2-pyridinyl]-5-fluoro-4-[4-fluoro-2-methyl-1-(1-ethylethyl)-1Hbenzimidazol-6-yl]-N-(5-((4-ethylpiperazin-1-yl)methyl)pyridin-2-yl)-5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-amine and the structural formula is presented in Figure 2. Abemaciclib has a molecular formula of $C_{27}H_{32}F_2N_8$ and a molecular weight of 506.60.



Structure of abemaciclib.

6.1.2. Abemaciclib Dose Levels

Abemaciclib Subjects in Part 1 of the study will be administered Abemaciclib according to cohort enrollment. The starting dose of Abemaciclib for combination immunotherapy cohorts is 150 mg BID daily.

Table 5: Study Drug Dosing Schedule

Cohort	Number of evaluable patients	Patient population	Abemaciclib (mg) PO BID	Pembrolizumab IV every 3 weeks starting C1D1
1	15	SCCHN who are Immunotherapy Naive	150	200 mg
2	15	SCCHN who progressed on Immunotherapy	150	200 mg

6.1.3. Abemaciclib Packaging and Labeling

Abemaciclib will be provided by Lilly. Clinical trial materials will be labeled according to the country's regulatory requirements.

6.1.4. Abemaciclib Storage and Shipping

Abemaciclib drug product should be stored at ambient conditions (15°C-30°C or 59°F-86°F).

6.1.5. Abemaciclib Administration

Abemaciclib will be administered at a starting dose of 150 mg twice daily and it is provided as 50-mg capsules. Abemaciclib should be taken twice daily (with at least 6-hour separating doses) at the same time each day with a glass of water. Patients should be instructed to swallow capsules whole and not open, chew, or crush.

Doses of Abemaciclib will be self-administered except on cycle 1 day 1 when it will be administered at the study clinic. Thereafter patients will take Abemaciclib at home as instructed by the treating physician. Abemaciclib will be given daily while Pembrolizumab will be administered at every 21 days as long as subjects do not have toxicity, disease progression or have not met any criteria for study withdrawal. Patient can take Abemaciclib at home even when they come to clinic for Pembrolizumab infusion on day 1 of cycle 2 onwards. Intrasubject dose escalation of Abemaciclib is not permitted.

Table 6: Ideal Dosing Schema for Study Drugs and Abemaciclib Premedications

Sequence	Drugs	C1D1 and onwards
1	Abemaciclib PO (BID)	150 mg
2	Pembrolizumab IV over 60 minutes on day 1 cycle and over 30 min q3weeks	200 mg

6.1.6. Abemaciclib Dose Modification/Dose Delays

6.1.6.1. Rationale for Dose modifications

Independent of the determination of tolerability during the study, subjects may require individual modification of Abemaciclib or Pembrolizumab or modifications of Abemaciclib, Pembrolizumab, combination regimen if necessitated by drug-related or unrelated AEs, including irAEs or DLTs.

6.1.7. Abemaciclib Drug Accountability

The Investigator must maintain an accurate accounting of Abemaciclib supplies. During the study, the following information must be recorded:

- Date of receipt, quantity, and lot number of the Abemaciclib study drug received.
- Identification number of the patient to whom the product is dispensed.
- The date(s) and quantity of the product dispensed.
- Dates and quantity of product returned, lost, or accidentally or deliberately destroyed.

Investigational Drug Accountability Logs should be maintained by the site and must be readily available for inspection.

6.1.8. Abemaciclib Study Drug Handling and Disposal

The Investigator must maintain an accurate accounting of the Abemaciclib product that is used. During the study, the following information must be maintained:

- Identification number of the patient to whom the product is dispensed.
- Lot number dispensed.
- The date(s) and quantity of the product dispensed.

6.2. Description of Pembrolizumab

See the most recent version of the Pembrolizumab investigator brochure.

6.2.1. Pembrolizumab Composition

See the most recent version of the Pembrolizumab investigator brochure.

6.2.2. Pembrolizumab Dose Level

200 mg will be administered IV every 3 weeks, starting on Cycle 1 Day 1 (C1D1).

6.2.3. Pembrolizumab Packaging and Labeling

See the most recent version of the pembrolizumab investigator brochure.

6.2.4. Pembrolizumab Storage

See the most recent version of the Pembrolizumab investigator brochure.

6.2.5. Pembrolizumab Preparation

Commercially available Pembrolizumab will be utilized in this study. Pembrolizumab should be prepared according to the most recent version of the package insert.

6.2.6. Pembrolizumab Administration

Administer Pembrolizumab 200 mg IV over 60 minutes on Days 1 (every 3 weeks) of each 21-day cycle until progression, with any dose modifications done per the investigator brochure. Pembrolizumab is administered before Abemaciclib and Abemaciclib premedications.

6.2.7. Pembrolizumab Drug Accountability

The Investigator must maintain an accurate accounting of the Pembrolizumab product that is used. During the study, the following information must be maintained:

- Identification number of the patient to whom the product is dispensed.
- Lot number dispensed.
- The date(s) and quantity of the product dispensed.

6.2.8. Pembrolizumab Drug Handling and Disposal

The Site Pharmacist will be responsible for documenting the destruction (according to institutional requirements) of used or expired vials.

6.3. Dose modifications of Study drugs

6.3.1. Planned Dose modifications

Intrasubject dose escalations are not permitted. Table 7 describes Abemaciclib dose reductions that may occur due to any related AEs.

There will be no dose reductions of Pembrolizumab allowed for the management of toxicities of individual subjects. Doses of Pembrolizumab may be delayed for toxicity management.

Table 7: Allowable Abemaciclib Dose Modifications for Toxicity Attributed to Abemaciclib

Cohort	Current Dose	Dose Reduction
1 and 2	150 mg BID	100 mg BID

6.3.2. Criteria and Procedure for interruption

In some circumstances, it may be necessary to temporarily interrupt study treatments as a result of AEs that may have an unclear relationship to the study drug(s). If an interruption is necessary, both study treatments should be interrupted.

Any dose interruptions of > 2 weeks for LFT abnormalities must be discussed with the medical monitor before resuming treatment. Treatment with both study drugs should be withheld for drug-related Grade 4 hematologic toxicities, nonhematological toxicity ≥ Grade 3 (including laboratory abnormalities), and severe or life-threatening AEs.

At enrollment, patients should receive instructions on the prompt management of diarrhea. In the event of diarrhea, supportive care measures should be initiated as early as possible. These include the following:

- At the first sign of loose stools, the patient should initiate antidiarrheal therapy (e.g. loperamide) and notify the investigator for further instructions and appropriate follow up.
- Patients should also be encouraged to drink fluids (e.g., 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours.
- Refer to Table 8 for additional information for diarrhea management and dose modification.

Table 8 summarizes the dose administration guidance for Pembrolizumab and Abemaciclib that should be implemented with the indicated drug-related AEs.

Except in cases of emergency, it is recommended that the investigator consult with the sponsor's medical monitor (or other representative of the sponsor) before temporarily interrupting therapy for reasons other than Protocol-mandated medication hold. Additionally, the investigator must notify the sponsor's medical monitor and study project manager via email or during safety teleconferences before restarting study drug that was temporarily interrupted because of an AE.

Dose modifications for hematologic and nonhematologic AEs may be managed per institutional guidelines.

Elevation of serum creatinine is very common with abemaciclib, and is due to a pharmacological inhibitory effect of the drug on renal tubular transporters of creatinine, which reduces creatinine excretion by the kidney. The rise in serum creatinine occurs within

the first 28-day cycle of abemaciclib, and the serum creatinine remains elevated but stable throughout the treatment period. The creatinine elevation seen with abemaciclib is reversible upon treatment discontinuation. Renal function (Glomerular Filtration Rate) is not impacted, and other measures of GFR that do not rely on serum creatinine (such as cystatin C calculated GFR) are not affected. If there are other indications of renal injury (e.g., proteinuria, progressive rise in serum creatinine, etc.), or if a patient has a need for precise GFR assessment (such as concomitant medications that effect kidney function), other measures should be used to assess renal function, as creatinine may not be a reliable indicator. Elevation of serum creatinine is observed with abemaciclib, and is due to a pharmacological inhibitory effect of abemaciclib on renal tubular transporters without affecting glomerular function. The rise in serum creatinine (mean increase, 0.2 mg/dL) occurs within the first 28-day cycle of abemaciclib, and remains elevated but stable throughout the treatment period, and were reversible upon treatment discontinuation. Alternative markers (such as BUN, cystatin C level, or cystatin C calculated GFR) which are not based on creatinine, may be considered to determine whether renal function is impaired.

It is important to note that some AEs will overlap with potential irAEs. In these cases, both the AE and irAE guidance within the applicable appendix should be reviewed to determine the most appropriate management of study medications.

Table 8. Dose modification guidelines for Drug Related Adverse Events for Combination Immunotherapy

Toxicity	**Grade**	**Hold Treatment (Y/N)**	**Timing for treatment restart**	**Dose Schedule for treatment restart**		**Discontinue subject (after medical monitor approval)**
				Abemaciclib	**Pembrolizumab**	
Hematologic Toxicity	1,2	No	N/A	N/A	N/A	N/A
	3	Yes	Toxicity resolves to ≤ Grade 2	Resume at same dose soon after toxicity resolves to ≤ Grade 2	Resume at same dose from day 1 of upcoming cycle after toxicity resolves to ≤ Grade 2	N/A

	Recurrent grade 3 or grade 4	Yes	Toxicity resolves to ≤ Grade 2	Resume at next lower dose soon after toxicity resolves to ≤ Grade 2.	Restart same dose from day 1 of upcoming cycle for the following events: Grade 4 neutropenia lasting <= 7 days, Grade 4 lymphopenia or leukopenia. For all other Grade 4 hematologic toxicities, treatment with Pembrolizumab may not be restarted (Note: in case Pembrolizumab is discontinued permanently, Abemaciclib should be discontinued as well)	Toxicity does not resolve within 4 weeks of last infusion. Permanent discontinuation should be considered for any severe or life-threatening event.
	Patient requires administration of a blood cell growth factor	Yes	At least 48hours after last dose of blood cell growth factor and until toxicity	Resume at next lower dose unless the dose was already reduced for the toxicity that led to use of the	N/A	Toxicity does not resolve within 4 weeks of last infusion. Permanent discontinuation should be considered

			resolves to ≤ Grade 2	growth factor		for any severe or life-threatening event.
Non-hematologic toxicity	1	No	N/A	N/A	N/A	N/A
	2	Consider holding for persistent symptoms	Toxicity resolves to <= Grade 1 or baseline	Restart at same dose soon after toxicity resolves to < Grade 1	Restart at same dose from day 1 of upcoming cycle after toxicity resolves to ≤ Grade 1	Toxicity does not resolve within 4 weeks of last infusion
	3[a]	Yes[a]	Toxicity resolves to <= Grade 1 or baseline	Resume at next lower dose soon after the toxicity resolves to < Grade 1	Restart at same dose[a] from day 1 of upcoming cycle after toxicity resolves to ≤ Grade 1.	Toxicity does not resolve within 4 weeks of last infusion. Permanent discontinuation should be considered for any severe or life-threatening event.
	4	Yes	Toxicity resolves to <= Grade 1 or baseline	Resume at next lower dose soon after the toxicity resolves to < Grade 1	Restart only as noted[b]. For all other Grade 4 non-hematologic toxicities, treatment with Pembrolizumab may not be restarted.	Toxicity does not resolve within 4 weeks of last infusion. Permanent discontinuation should be

					(Note: in case Pembrolizumab is discontinued permanently, Abemaciclib should be discontinued as well)	considered for any severe or life-threatening event.
ALT increase	Grade 1 (>ULN-3.0 x ULN) Grade 2 (>3.0-5.0 x ULN)	No	N/A	N/A	N/A	N/A
	Persistent or Recurrent Grade 2, or Grade 3 (>5.0-20.0 x ULN) that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Yes	Toxicity resolves to <= Grade 1 or baseline	Resume at next lower dose soon after toxicity resolves to <u>< Grade 1</u>	Restart at same dose from day 1 of upcoming cycle after toxicity resolves to <u>≤ Grade 1</u>	See above for non-hematologic toxicity
	Grade 4 (>20.0 x ULN)	Yes, discontiue abemaciclib	N/A	N/A	Restart at same dose from day 1 of upcoming cycle after toxicity resolves to <u>≤ Grade 1</u>	See above for non-hematologic toxicity
Diarrhea	1	No	N/A	N/A	N/A	N/A

	2	Yes if toxicity dose not resolve within 24 hours to <u>< grade 1</u>	Toxicity resolves to <= Grade 1 or baseline	Resume at same dose soon after toxicity resolves to <u>< Grade 1</u>	Restart at same dose from day 1 of upcoming cycle after toxicity resolves to <u>≤ Grade 1</u>	See above for non-hematologic toxicity
	2 persists or recurs after resuming same dose despite maximal supportive measures	Yes	Toxicity resolves to <= Grade 1 or baseline	Resume at next lower dose soon after toxicity resolves to <u>< Grade 1</u>	Restart at same dose from day 1 of upcoming cycle after toxicity resolves to <u>≤ Grade 1</u>	See above for non-hematologic toxicity
	3 or 4 or requires hospitalization	Yes	Toxicity resolves to <= Grade 1 or baseline	Resume at next lower dose soon after toxicity resolves to <u>< Grade 1</u>	Restart at same dose from day 1 of upcoming cycle after toxicity resolves to <u>≤ Grade 1</u>	See above for non-hematologic toxicity

Note: Subjects who experience a recurrence of the same severe life threatening AE at the same grade or greater treatment should be discontinued from study treatment

[a] The following exception for asymptomatic amylase or lipase do not require a dose delay. Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestation of pancreatitis. It is recommended to consult with the medical monitor for Grade 3 amylase or lipase abnormalities.

[b] Isolated Grade 4 lipase or amylase abnormalities not associated with symptoms or clinical manifestations of pancreatitis. Medical monitor should be consulted for any grade 4 amylase or lipase abnormality.

6.3.3. Procedures for Subjects exhibiting Immune-Related Adverse Events

This section is meant to apply to suspected irAEs from Abemaciclib, Pembrolizumab or the combination.

Immune-related AEs may be defined as an AE of unknown etiology, associated with drug exposure and consistent with an immune phenomenon. Immune-related AEs may be predicted based on the nature of the Pembrolizumab or Abemaciclib compounds, their mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes before labeling an AE as an irAE. Subjects who develop a ≥ Grade 2 irAE should be discussed immediately with the sponsor.

General recommendations to managing irAEs not detailed elsewhere in the Protocol are detailed in Table 9. Recommendations for management of specific immune-mediated AEs such as pneumonitis, enterocolitis, hepatitis, dermatitis, neuropathies, endocrinopathies, and other immune-mediated AEs are detailed in the sections below.

Table 9. General Approach to Handling Immune Related Adverse Events

irAE	**Withhold/discontinue Pembrolizumab or Abemaciclib**	**Guidance for restarting study treatment**	**Supportive care**
Grade 1	No Action	Not applicable	Provide supportive treatment
Grade 2	May withhold/discontinue Pembrolizumab or Abemaciclib per Investigator's dicretion	May return to treatment if improves to Grade 1 or resolves within 6 weeks. If AE resolves within 4 weeks, subject may restart at same dose and schedule for both Pembrolizumab and Abemaciclib. For AE that does not resolve within 4 weeks, Abemaciclib should be reduced to 100 mg BID, but Pembrolizumab	Consider systemic corticosteroids in addition to appropriate symptomatic treatment

		may be restarted at same dose and schedule. If AE dose not resolve within 6 weeks, then study treatment with both study drugs should be discontinued or discussed with medical monitor.	
Grade 3	Withhold or discontinue both Pembrolizumab and Abemaciclib. Discontinue if unable to reduce corticosteroid dose to < 10 mg/day of prednisone or equivalent within 6 weeks of toxicity.	Any restart of study treatment must be discussed with study monitor before restarting treatment	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May use 1 to 2 mg/kg of Prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to ≤ Grade 1 or tapered over at least 4 weeks in most cases.
Grade 4	Discontinue Pembrolizumab and/or Abemaciclib	Not applicable. Any exceptions require medical monitor approval	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May use 1 to 2 mg/kg of Prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to ≤ Grade 1 or tapered over at least 4 weeks in most cases.

6.3.3.1. Procedures and Guidelines for Pneumonitis

Subjects with symptomatic pneumonitis should immediately stop receiving Pembrolizumab and Abemaciclib and have an evaluation. The evaluation may include bronchoscopy to rule out other causes such as infection. If the subject is determined to have study drug associated pneumonitis, the suggested treatment plan is detailed in Table 10.

Table 10. Recommended Approach to Handling Non-infectious Pneumonitis

Study Drug(s) Associated Pneumonitis	**Withhold/Discontinue Pembrolizumab and Abemaciclib**	**Guidance for restarting Study Treatment**	**Supportive Care**
Grade 1 (asymptomatic)	No action	Not applicable	Intervention not indicated[a]
Grade 2	Withhold Pembrolizumab and Abemaciclib	First episode of Pneumonitis: • If improves to near baseline: - Decrease the dose of Abemaciclib to 100 mg BID, and for Pembrolizumab, restart at same dose and schedule for subsequent cycles. • If not improved after 2 weeks or worsening permanently, discontinue	Systemic corticosteroids are indicated. Taper if necessary[a].

		Pembrolizumab. Discuss with medical monitor if restart with Abemaciclib is permitted (Note: in case Pembrolizumab is discontinued permanently, Abemaciclib should be discontinued as well). Second episode of Pneumonitis: • Permanently discontinue Pembrolizumab and Abemaciclib if upon rechallenge subject develops pneumonitis ≥ Grade 2	
Grades 3 and 4	Discontinue Pembrolizumab and Abemaciclib	Not applicable. Any exceptions require medical monitor approval.	Systemic corticosteroids are indicated. The use of infliximab may be indicated as appropriate. See Appendix C for additional recommendations .

6.3.3.2. Procedures and Guidance for Enterocolitis

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

should be ruled out and endoscopic evaluation should be considered for persistent or severe symptoms.

Recommendations for management of enterocolitis are shown in Table 11.

Table 11. Recommended Approach for Handling Enterocolitis

Study drugs(s) associated with Enterocolitis	**Withhold/Discontinue Pembrolizumab and Abemaciclib**	**Guidance for restarting study treatment**	**Supportive care**
Grade 1	No Action	Not Applicable	All subjects who experience diarrhea 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. An antidiarrheal can be started.
Grade 2	Withhold Pembrolizumab and Abemaciclib	May return to treatment if improves to Grade 1. If AE resolves within 4 weeks, subject may restart at the same dose and schedule for both Pembrolizumab and Abemaciclib. For an AE that does not resolve within 4 weeks, Abemaciclib should be reduced	An anti-diarrheal should be started. If symptoms are persistent for > 1 week, systemic corticosteroids should be initiated (eg. 0.5-1 mg/kg per day of prednisone or equivalent). When symptoms improve to ≤ Grade 1, corticosteroids taper should be started and

		to 100 mg BID, but Pembrolizumab may be restarted at same dose and schedule. If AE does not resolve within 6 weeks, study treatment with both study drugs should be discontinued or discussed with medical monitor.	continued over at least 1 month.
Grades 3 and 4	Discontinue Pembrolizumab and Abemaciclib	Not applicable. Any exceptions require medical monitor approval	Treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg per day of prednisone or equivalent. Systemic corticosteroids are indicated. The use of infliximab may be indicated as appropriate. When symptoms improve to <= Grade 1, corticosteroid taper should be started and continued at least 1 month.

6.3.3.3. Procedures and Guidance for Hepatitis

Liver chemistry tests (hepatic transaminase and bilirubin levels) should be monitored and signs and symptoms of hepatotoxicity should be assessed before each dose of Pembrolizumab and Abemaciclib. In subjects with hepatotoxicity, infectious or malignant causes should be ruled out and frequency of LFT monitoring should be increased until resolution. Recommendations for management of hepatitis are shown in Table 12. See Section 8.2.2 for reporting requirements for certain cases that may be considered SAEs.

Table 12. Recommended Approach to Handling Hepatitis

Study drug(s) Associated Hepatitis	**Withhold/Discontinue Pembrolizumab and Abemaciclib**	**Guidance for restarting study treatment**	**Supprotive Care**
Grade 1	No action	Not applicable	Increase frequency of LFT monitoring to twice per week until LFTs return to baseline
Grade 2	Withhold Pembrolizumab and Abemaciclib	If AE resolves to <= Grade 1 or baseline within 4 weeks, subject may restart at same dose and schedule for both Pembrolizumab and Abemaciclib. For an AE that does not resolve with 4 weeks, Abemaciclib should be reduced to 100 mg BID, but Pembrolizumab may be restarted at the same dose level and schedule. If AE does not resolve within 6 weeks, study treatment with both study drugs should be discontinued.	Increase frequency of LFT monitoring to twice per week until LFTs return to baseline. If elevation persists for > 1 week, systemic corticosteroids should be initiated (eg. 0.5 mg/kg per day of prednisone or equivalent). When symptoms improve to <= Grade 1, cortocsteroids taper should be started and continued over at least 1 month.

Grades 3 and 4	Discontinue Pembrolizumab and Abemaciclib	Not applicable. Any exceptions require medical monitor approval.	Increase frequency of LFT monitoring to every 1-2 days. Treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg per day of prednisone or equivalent. When symptoms imorove to <= Grade 1, corticosteroid taper should be started and continued over at least 1 month.

6.3.3.4. Procedures for Immune Mediated Dermatitis

Monitor subjects for signs and symptoms of dermatitis such as rash and pruritus. Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune mediated. Recommendations for management of dermatitis are shown in Table 13.

Table 13. Recommended Approach for Handling Dermatitis

irAE	**Withhold/Discontinue Pembrolizumab and Abemaciclib**	**Guidance for restarting study treatment**	**Supportive care**
Grade 1	No action	Not applicable	For mild to moderate dermatitis, such as localized rash and pruritus, treat symptomatically. Administer topical or systemic corticosteroids if

			there is no improvement of symptoms within 1 week.
Grade 2	No action	Not applicable	For mild to moderate dermatitis, such as localized rash and pruritus, treat symptomatically. Administer topical or systemic corticosteroids if there is no improvement of symptoms within 1 week.
Grades 3 and 4	Withhold Abemaciclib and/or Pembrolizumab in subjects with moderate to severe signs and symptoms of rash. Permanently discontinue Abemaciclib and Pembrolizumab I subjects with Stevens-Johnson syndrome, toxic epidermal necrolysis or rash complicated by full thickness dermal ulceration or by necrotic, bullous, or hemorrhagic manifestations.	If AE resolves to baseline within 4 weeks, subject may restart at the same dose and schedule for both Pembrolizumab and Abemaciclib. For an AE that does not resolve within 4 weeks, Abemaciclib should be reduced to 100 mg BID, but Pembrolizumab may be restarted at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment with both study drugs should be discontinued or discussed with medical monitor.	Administer systemic corticosteroids at a dose of prednisone or equivalent. When dermatitis is controlled, corticosteroid tapering should occur over a period of at least 1 month.

6.3.3.5. Procedures for Immune Mediated Neuropathies

Subjects should be monitored for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Recommendations for management of neuropathies are shown in Table 14.

Table 14. Recommended approach for Handling Neuropathies

irAE	**Withhold/Discontinue Pembrolizumab and Abemaciclib**	**Guidance for restarting study treatment**	**Supportive care**
Grade 1	No action	Not applicable	Provide symptomatic treatment
Grade 2	May withhold Pembrolizumab and Abemaciclib	If Ae resolves to <= Grade 1 or baseline within 4 weeks, subject may restart at the same dose level and schedule for both Pembrolizumab and Abemaciclib. For an AE that does not resolve within 4 weeks, Abemaciclib should be reduced to 100 mg BID, but Pembrolizumab may be restarted at same dose level and schedule. If AE does not improve within 4 weeks, Abemaciclib should	Consider systemic corticosteroids in addition to appropriate symptomatic treatment.

		be reduced 1 dose level, but Pembrolizumab may be restarted at the same dose level and schedule. If AE does not resolve within 6 weeks, study treatment with both study drugs should be discontinued or discussed with medical monitor.	
Grades 3 and 4	Discontinue Pembrolizumab and Abemaciclib	Not applicable. Any exceptions require medical monitor approval.	Consider initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg per day prednisone or equivalent for severe neuropathies. Institute medical interventions as appropriate for management of severe neuropathy.

6.3.3.6. Procedures for Immune Mediated Endocrinopathies

Subjects should be monitored for clinical signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism. Subjects may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension or with nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate etiology has been identified, signs or symptoms of endocrinopathies should be considered immune-mediated.

Thyroid function tests and clinical chemistries should be monitored at the start of treatment, before each dose, and as clinically indicated based on symptoms. In a limited number of subjects, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland. Recommendations for management of endocrinopathies are shown in Table 15.

Table 15. Recommended approach for handling Endocrinopathies

irAE	**Withhold/Discontinue Pembrolizumab and Abemaciclib**	**Guidance for restarting study treatment**	**Supportive care**
Grade 1	No action	Not applicable	Provide symptomatic treatment
Grade 2	May withhold Pembrolizumab and Abemaciclib	If AE resolves within 4 weeks, subject may restart at the same dose and schedule for both Pembrolizumab and Abemaciclib. For an AE that does not resolve within 4 weeks, Abemaciclib should be reduced to 100 mg BID, but Pembrolizumab may be restarted at the same dose level and schedule. If AE does not resolve within 6 weeks, study treatment with both study drugs should be discontinued.	Initiate systemic corticosteroids treatment at a dose of 1 to 2 mg/kg per day of prednisone or equivalent and initiate appropriate hormone replacement therapy.

Grade 3	Withhold or discontinue both Pembrolizumab and Abemaciclib	If AE resolves or is controlled within 4 weeks, subject may restart at the same dose and schedule for both Pembrolizumab and Abemaciclib. For an AE that does not resolve within 4 weeks Abemaciclib should be reduced 1 dose level, but Pembrolizumab may be restarted at the same dose and schedule. If AE does not resolve within 6 weeks, study treatment with both study drugs should be discontinued or discussed with medical monitor	Consider initiating systemic corticosteroids treatment at a dose of 1 to 2 mg/kg per day of prednisone or equivalent and initiate appropriate hormone replacement therapy.
Grade 4	Discontinue both Pembrolizumab and Abemaciclib	Not applicable. Any exceptions require medical monitor approval	Consider initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg per day of prednisone or equivalent and initiate appropriate hormone replacement replacement therapy.

6.3.3.7. Procedures for Other Immune Mediated Adverse Reactions, including Ocular manifestations.

Abemaciclib and Pembrolizumab should be permanently discontinued for severe immune-mediated adverse reactions. Systemic corticosteroids treatment should be initiated at a dose of 1 to 2 mg/kg per day of prednisone or equivalent for severe immune-mediated adverse

reactions. Corticosteroid eye drops should be administered to subjects who develop uveitis, iritis, or episcleritis. Abemaciclib and Pembrolizumab should be permanently discontinued for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

6.3.3.8. Therapy for Febrile Neutropenia

Patients experiencing febrile neutropenia, especially with diarrhea or dyspnea, should be managed in a hospital setting according to standard procedures, with the urgent initiation of IV antibiotic therapy. Events that require a patient to be hospitalized are considered SAEs

6.3.3.9. Growth Factor Therapy

Growth factors should not be administered to a patient to satisfy study inclusion criteria. Growth factors may be administered in accordance with ASCO guidelines (Smith et al. 2015). Dosing of abemaciclib must be suspended if the administration of growth factors is required and must not be recommenced within 48 hours of the last dose of growth factors having been administered. Following the administration of growth factors, the dose of abemaciclib must be reduced to 100 mg BID on recommencement, if a dose reduction for the specific event necessitating the use of the growth factors has not already occurred.

6.4. Criteria for permanent discontinuation of study drug(s)

Subjects may withdraw consent at any time for any reason or be withdrawn from the study at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the sponsor if enrollment into the study is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

Subjects must be withdrawn from the study treatment for the following reasons:

- In the investigator's medical judgment, further participation would be injurious to the subject's health or well-being.
- The subject becomes pregnant.
- Consent is withdrawn by the subject or legal representative (such as parent or legal guardian).
- The study is terminated by the sponsor.
- The study is terminated by the local health authority or IRB/IEC.
- The subject has experienced an unacceptable toxicity or a toxicity that does not recover in 6 weeks. Investigators who wish to continue treatment after a treatment delay of 6 weeks should consult with the sponsor's medical monitor for approval.

- Noncompliance with study treatment or procedure requirements.
- The subject is lost to follow-up.

6.5. Study Completion

6.5.1. Study completion criteria

Subjects will be considered completing the study if they met any of the following criteria:

- Subject dies and a date of death is available.
- Subject is known to have died; however, the date of death cannot be obtained.
- (NOTE: every effort must be made to obtain the date of death.)
- Consent is withdrawn for any further contact related to this study.
- Toxicities that result in treatment stoppage and do not resolve in 4 weeks.
- Subjects may choose to withdraw from the study at any time without penalty of jeopardizing their health care or loss of benefits to which the subject is otherwise entitled. Every reasonable effort should be made to determine the reason a subject withdraws prematurely, and this information should be recorded in the eCRF.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority or IRB or IEC.

6.5.2. Withdrawal procedures

In the event that any subject discontinues study drug and, subsequently, withdraws from the study before completion, regardless of reason, reasonable efforts should be made to have the subject return for the EOT procedures to be completed. The date the subject was withdrawn from the study and the specific reason for withdrawal will be recorded in the eCRF.

If a subject is withdrawn from the study:

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal must be documented in the subject's medical record and in the eCRF.
- The EOT or early termination visit should be performed.
- Subjects must be followed for safety until the time of the follow-up visit or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer.

6.6. Concomitant Medications

No other approved or investigational anticancer treatment will be permitted during the study period. No other investigational drug may be used during treatment on this protocol, and concurrent participation in another clinical trial is not allowed.

Patients who receive nonsteroidal anti-inflammatory drugs (NSAIDs) on study should also receive peptic ulcer disease (PUD) prophylaxis with a histamine-2 (H2) blocker or proton pump inhibitor.

Narcotic analgesics, NSAIDs, ketorolac and triptans (e.g., sumatriptan) may be offered as needed for relief of pain or headaches. Antihistamines and decongestants may be offered for the treatment of sinus congestion.

Antibiotic prophylaxis should be used for invasive dental procedures.

Packed red blood cells, colony stimulating factors, and platelet transfusions should be administered as clinically indicated.

6.7. Treatment Compliance

All infusions (Anti-PD1 and Chemotherapy) and oral intake of Abemaciclib will occur at the investigational site under the direct supervision of the Investigator or his or her designee.

6.8. Patient Enrollment

Patients will be manually enrolled by site CRC in Oncore database and assigned an 8-digit patient number. This 8-digit number will be used to identify patients throughout their participation in the trial. A regulatory binder will be provided and will include detailed instructions for the manual enrollment process.

6.9. Beginning and End of the Study

The study begins when the first subject signs the informed consent. The end of the study may be designated as the timepoint when all subjects have discontinued the study. At this point a database lock of the study may occur to allow the analysis of the study data.

6.10. Management of Infusion Reactions From Pembrolizumab

Since Pembrolizumab contains only human Ig protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms.

All Grade 3 or 4 infusion reactions should be reported within 24 hours to the medical monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to National Cancer Institute (NCI) CTCAE (version 4.0) guidelines. In Phase 2, for those experiencing an infusion reaction, infusion time may be increased to 60 minutes. Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated) Remain at bedside and monitor subject until recovery from symptoms. The

following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (or acetaminophen) at least 30 minutes before additional Pembrolizumab administrations.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, nonsteroidal anti inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for $\geq$ 24 hours)

Stop the Pembrolizumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (or acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further Pembrolizumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the eCRF. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (or acetaminophen) should be administered at least 30 minutes before additional Pembrolizumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Grade 4: life threatening; pressor or ventilator support indicated).

Immediately discontinue infusion of Pembrolizumab. Begin an IV infusion of normal saline, and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Pembrolizumab will be permanently discontinued.

Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

7. ASSESSMENT OF EFFICACY

7.1. Radiologic Tumor Assessment

The primary efficacy assessment will be best overall response by RECIST v1.1/ iRECIST as defined in Table 17 and Seymour et al [1]. iRECIST introduces the criterion of unconfirmed progressive disease (iUPD) to prevent the discontinuation of study treatment for cases of pseudoprogression. If the criteria for iUPD have never been met, principles should follow RECIST 1.1. However, if the criteria for iUPD have been met, the next timepoint response could be:

- iUPD: no change noted in any category of lesion
- iSD, iPR, or iCR. Here, iUPD (followed by iCPD) should occur again
- iCPD, if the category in which iUPD was met at the last timepoint response shows a further increase in tumor burden as evidenced (as applicable) by a $\geq$ 5 mm increase in sum of measures of target or new target lesions, further increase in non-target or new non-target lesions, or an increase in the number of new lesions.

Investigators will make treatment decisions based on these assessments. All lesions will be classified as target or non-target lesions at the Screening visit. Each lesion designation will be maintained through the course of the study.

The same method and technique should be used to characterize each identified and reported lesion at Screening, during the study treatment period, and at the End of Study visit. Imaging-based evaluation over clinical examination is the required technique when both could be used to assess the antitumor effect of the treatment. Clinical Oncology review of all tumor measurements is desired.

Whenever possible, clinical evaluation of superficial lesions should not be used as the sole form of measurement. However, when necessary, color photograph with metric caliber is acceptable. Tumor evaluation by positron emission tomography (PET) scan or by ultrasound may not substitute for CT or MRI scans.

Radiological tumor assessments will be performed at Screening, as outlined in the Schedule of Assessments (Table 4), and whenever disease progression is suspected. Another tumor assessment will be performed at the End of Study visit if an assessment has not been performed within the prior 8 weeks. All patient files and radiological images must be available for CRF source verification.

Table 17: Assignment of Timepoint Response Using iRECIST

	Timepoint Response with no previous iUPD in any category	**Timepoint response with previous iUPD in any category[a]**
Target lesions: iCR; non-target lesions: iCR; new lesions: no	iCR	iCR
Target lesions: iCR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iPR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iSD; non-target lesions: non-iCR/non-iUPD; new lesions: no	iSD	iSD
Target lesions: iUPD with no change, or with a decrease from last timepoint; non-target lesions: iUPD with no change, or decrease from last timepoint; new lesions; yes	Not Applicable	New lesions confirm iCPD if new lesions were previously identified and they have increased in size (≥ 5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD
Target lesions: iSD, iPR, iCR; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in the size of non-target disease (does not need to meet RECIST 1.1 criteria for unequivocal progression)
Target lesions: iUPD; non-target lesions: non-iCR/non-iUPD, or iCR; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures ≥ 5mm; otherwise, assignment remains iUPD

	Timepoint Response with no previous iUPD in any category	**Timepoint response with previous iUPD in any category[a]**
Target lesions: iUPD; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures ≥ 5mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression)
Target lesions: iUPD; non-target lesions: iUPD; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified target lesion iUPD sum of measures ≥ 5mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified
Target lesions: non-iUPD or progression; non-target lesions: non-iUPD or progression; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of an increase in the size or number of new lesions previously identified

[a]Previously identified in assessment immediately before this timepoint.
Target lesions, non-target lesions, and new lesions defined according to RECIST 1.1 principles; if not pseudoprogression occurs, RECIST 1.1 and iRECIST categories for complete response, partial response, and stable disease would be the same.

8. ASSESSMENT OF SAFETY

8.1. Safety Parameters

Safety will be characterized in terms of the incidence, timing, severity graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03), seriousness, and drug-relatedness of adverse events (AEs) and laboratory abnormalities. In addition, physical examination, vital signs, and ECOG performance status will be serially monitored. Laboratory safety analyses will be based on the local laboratory data, and will include hematology (including iron studies at baseline), serum chemistry (including liver and kidney function, and TSH), urinalysis, serum or urine pregnancy testing, and coagulation profile (baseline only). Serum will also be assessed for immunogenicity to Abemaciclib (including anti-product antibody titers). In addition, single tracing 12-lead ECGs will be performed at the time points indicated in the Schedule of Assessments (Table). QT, PR and QRS intervals and heart rate will be captured. ECGs will also be collected as clinically indicated throughout the study.

8.1.1. Laboratory Safety Assessments

Abnormal and clinically significant laboratory tests should be recorded as adverse events. To meet the definition of clinically significant, the test result generally requires a change in medical management (e.g., new medication, unplanned treatment, additional tests, etc.).

8.1.1.1. Hematology, Serum Chemistry, Coagulation, and Pregnancy Test

Assessments will be performed at the time points indicated in the Schedule of Assessments (Table 4) and analyzed at local laboratories. Investigators may have additional blood tests performed for the purpose of planning treatment administration, or for following AEs, as clinically indicated.

- Hematology: Complete blood count (CBC) with differential and platelet count.
- Coagulation: Prothrombin time and International Normalized Ratio (INR).
- Serum Chemistry: Total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, lipase, amylase, sodium, potassium, bicarbonate, chloride, calcium, phosphorus, blood urea nitrogen, creatinine, magnesium, thyroid stimulating hormone (TSH), and glucose.
- Pregnancy Test: Serum or urine pregnancy tests will be performed locally on all female patients of childbearing potential. Patients must be surgically sterile (i.e., ≥ 6 weeks following surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) or be postmenopausal, or must agree to use effective contraception during the study and for ≥ 180 days following last dose of study drug (Abemaciclib or Pembrolizumab, which occurs later). The definition of effective contraception is provided in Section 2.6.1 of this protocol.

8.1.1.2. Urinalysis

Urinalysis (without microscopic analysis, unless indicated) will be performed at time points indicated in the Schedule of Assessments (Table 4) and analyzed by local laboratories. Microscopic analysis, urine protein-creatinine ratio (UPCR), and 24-hour urine collection for protein should be performed as clinically indicated.

8.1.2. Physical Examination

A physical examination including, but not limited to, general appearance, head, eyes, ears, nose, throat, neck, heart, chest, abdomen, musculoskeletal, extremities, skin, lymph nodes, neurological genitourinary (as appropriate), and rectal (as appropriate) will be assessed at time points indicated within the Schedule of Assessments (Table 4). The physical examination will include examination of known and suspected sites of disease.

8.1.3. Vital Signs

Heart rate, temperature, blood pressure, respiratory rate, and weight will be assessed at time points indicated within the Schedule of Assessments (Table 4). Height will be assessed only at the Screening visit. Heart rate, temperature, blood pressure, and respiratory rate will also be assessed before Pembrolizumab and abemaciclib administrations as described in Section 4.1.2.2 and the footnotes of the Schedule of Assessments (Table 4).

8.1.4. Performance Status

The ECOG scale will be used to assess performance status at Screening and at time points indicated within the Schedule of Assessments (Table 4).

8.1.5. Electrocardiogram (ECG)

A single tracing 12-lead tracing will be used for all ECGs. It is preferable that the machine used has a capacity to calculate standard intervals automatically. ECG will be performed at the time points indicated in the Schedule of Assessments (Table 4) and as clinically indicated throughout the study.

8.2. Adverse Events

All observed or volunteered AEs regardless of suspected causal relationship to study drug (Abemaciclib and Pembrolizumab) will be reported as described below.

8.2.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a trial patient who is administered a drug or biologic (medicinal product); the event may or may not have a causal relationship with the medicinal product. Examples of AEs include, but are not limited to the following:

- Clinically significant symptoms and signs including:
  - Worsening of signs and symptoms of the malignancy under study drug treatment (Note: Disease progression with or without worsening of signs and symptoms assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs unless the outcome is fatal during the study or within the safety reporting period for the study.)
  - Signs and symptoms resulting from drug overdose, abuse, misuse, withdrawal, sensitivity, dependency, interaction, or toxicity
  - All treatment-emergent possibly related and unrelated illnesses, including the worsening of a preexisting illness
  - Injury or accidents - Note that if a medical condition is known to have caused the injury or accident (e.g., hip fracture from a fall secondary to dizziness), the

medical condition (dizziness) and the outcome of the accident (hip fracture from a fall) should be reported as 2 separate AEs.

  - Symptoms or signs resulting from exposure *in utero*

- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat confirmatory test)
- Laboratory abnormalities that meet any of the following criteria (Note: Merely repeating an abnormal test, in the absence of any of the below conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.)
  - Test result that is associated with accompanying symptoms
  - Test result that requires additional diagnostic testing or medical/surgical intervention
  - Test result that leads to a change in study drug (Abemaciclib or Pembrolizumab) dosing other than protocol-stipulated dose adjustments or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy
  - Test result that is considered to be an AE by the Investigator or ELI LILLY

8.2.2. Serious Adverse Events

An AE that meets one or more of the following criteria/outcomes is classified as a serious /ae (SAE):

- Results in death
- Is life-threatening (i.e., at immediate risk of death)
- Requires in patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly/birth defect
- Other Important Medical Events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependence or drug abuse.

Serious also includes any other AE that the Investigator or sponsor judges to be serious, or which is defined as serious by the Health Regulatory Authority (HRA) in the country in which the event occurred.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal during the study or within the safety reporting period for the study. Hospitalizations due to signs and symptoms of disease

progression should not be reported as SAEs. However, if the malignancy has a fatal outcome during the study or within the safety reporting period for the study, then the AE leading to death must be recorded as an SAE with CTCAE Grade 5.

The onset date of an SAE is defined as the date on which the event initially met serious criteria (e.g., the date of admission to a hospital). The end date is the date on which the event no longer met serious criteria (e.g., the date the patient was discharged from a hospital).

8.2.2.1. Hospitalization

AEs associated with in-patient hospitalization, or prolongation of an existing hospitalization, are considered serious. Any initial admission, even if the duration is less than 24 hours, is considered serious. In addition, any transfer within the hospital to an acute/intensive care unit is considered serious (e.g., transfer from the psychiatric wing to a medical floor or transfer from a medical floor to a coronary care unit). However, the following hospitalizations **should not** per se constitute a serious AE:

- Rehabilitation facility admission
- Hospice facility admission
- Respite care
- Skilled nursing facility admission
- Nursing home admission
- Emergency room visit, including observation unit visit
- Outpatient same day surgery/procedure
- Hospitalization or prolongation of hospitalization in the absence of precipitating clinical adverse events as follows:
  - Admission for treatment of preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition
  - Social admission
  - Administrative admission (e.g., for yearly physical exam)
  - Protocol-specified admission during a clinical trial
  - Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery)
  - Preplanned treatments or surgical procedures that are not related to an SAE
- Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. The medical condition for which the procedure was performed should be reported if it meets the definition of an AE (e.g., acute appendicitis that begins during the AE reporting period should be reported as an AE and the appendectomy should be recorded as a concomitant treatment).

8.3. Reporting Adverse Events

8.3.1. Eliciting Adverse Event Information

The Investigator is to report all directly observed AEs and all AEs reported by the study patient using concise medical terminology. In addition, each study patient will be questioned about AEs at each clinic visit following initiation of treatment. The question asked will be, or words to the effect, "Since your last clinic visit have you had any health problems?"

8.3.2. Adverse Event Reporting Period

Safety information for each patient will be collected from the date of informed consent. AEs occurring prior to the initiation of the study treatment with Pembrolizumab and/or Abemaciclib study drug will be considered " baseline-emergent adverse events," will be recorded on corresponding CRFS and will not be retained for patients who fail screening. The AE reporting period for this study begins when the patient has received even a portion of the first dose of Pembrolizumab or Abemaciclib study drug and ends 28 days after the last dose of the latest study treatment (i.e., Pembrolizumab or Abemaciclib study drug) is administered.

All AEs that occur in study patients during the AE reporting period specified in the protocol must be reported to ELI LILLY, whether or not the event is considered study treatment-related. In addition, any known untoward event that occurs beyond the AE reporting period that the Investigator assesses as possibly related to either investigational medication/product should also be reported as an AE.

8.3.3. Reporting Requirements

Each AE is to be classified by the Investigator as SERIOUS or NONSERIOUS. This classification of the gravity of the event determines the reporting procedures to be followed. If an SAE occurs, reporting will follow local and international regulations, as appropriate.

The Investigator must notify the Sponsor of any AE that meets any one of the criteria for an SAE immediately upon learning of the event. Any subsequent revisions that are made to information pertaining to serious suspected adverse drug (Abemaciclib or Pembrolizumab) reactions (e.g., change in grade, etc.), including a change in attribution to study drug from "not related" to "suspected adverse drug reaction" should also be communicated to Eli Lilly and Merck immediately.

Following notification, the Investigator will report the SAE via the AE CRF via the data management system. The initial AE CRF is to be updated with more detailed AE information within **5 calendar days** of the event onset.

In the rare event that the Investigator is not immediately aware of an SAE (e.g., if the study patient seeks urgent medical attention elsewhere), the Investigator is to notify the Sponsor immediately upon learning of it and document his/her first awareness.

All serious adverse events and those non-serious events assessed by the Investigator as suspected reactions (i.e., at least possibly related) to a Eli Lilly investigational medicinal product must be followed, even after the patient's withdrawal from study, until the event is either resolved, improved to the patient's pre-treatment baseline or better, stable without

anticipated future change, or the patient is lost to follow-up, or, in the case of a suspected adverse reaction, later determined to be not related to the Eli Lilly investigational medicinal product.

SAEs that are unexpected and associated with use of the study medication will be reported to the US Food and Drug Administration (FDA) and the participating clinical site by Eli Lilly via MedWatch forms. For SAEs which are fatal or life-threatening, unexpected, and associated with use of the study drug (Abemaciclib or Pembrolizumab), a 7-Day Alert Report will be submitted to the FDA within 7 calendar days of receipt of the SAE information. For all other SAES that are unexpected and associated with use of the study drug (Abemaciclib or Pembrolizumab), a written report will be made no more than 15 calendar days from the date Eli Lilly learns of the event. Participating clinical sites will be notified of these events in parallel with FDA notification.

All AEs, including SAEs, are to be reported on the AE CRFs.

8.3.4. Recording Adverse Events in the Case Report Forms

The Investigator is to report all directly observed AES and all AEs reported by the study patient. In addition, each study patient will be questioned about AEs. All AEs that meet the criteria specified in Section 8.2.1 are to be recorded on patient source documents and on the CRFs. AEs should be reported using concise medical terminology on the CRFs.

8.3.5. Grading of Adverse Event Severity

To report AEs on the CRFs, the Investigator will use the severity grading as described in NCI CTCAE (Version 4.03). Every effort should be made by the Investigator to assess the AE according to CTCAE criteria. If the Investigator is unable to assess severity because the term is not described in NCI CTCAE (Version 4.03), then severity of MILD, MODERATE, SEVERE, LIFE-THREATENING, or FATAL may be used to describe the maximum intensity of the AE, as guided by Table 8. Note that the selection of the most appropriate verbatim term for AEs is not restricted to only those toxicities represented in NCI CTCAE. For purposes of consistency, these intensity grades are defined as follows:

Table 18: Adverse Event Grading

Grade	Non-CTCAE Severity	Definition
1	Mild	Does not interfere with patient's usual function
2	Moderate	Interferes to some extent with patient's usual function
3	Severe	Interferes significantly with patient's usual function
4	Life-Threatening	Results in immediate risk of patient's death
5	Fatal	Results in patient's death

Note the distinction between the severity and the seriousness of an AE. A severe AE is not necessarily a serious AE. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it met one of the criteria for serious events.

8.3.6. Relationship to Tretament Drugs (Abemaciclib, and Pembrolizumab)

In this study, there are 2 study drugs; the investigational drug Abemaciclib is given in combination with the approved drug Pembrolizumab. The relationship of each AE to each study drug will be made independently for each of the 4 study drugs and should be guided in part by the known safety profile of each drug, including the Abemaciclib IB, and the Pembrolizumab IB. The relatedness should be classified by the Investigator using the following guidelines:

- Suspected Adverse Reaction: There is a reasonable possibility that study drug caused the AE (i.e., there is evidence to suggest a causal relationship between study drug and the AE).
- Not Related: There is no reasonable possibility that the AE is associated with study drug.

AEs related to study drug are considered Adverse Drug Reactions (ADR).

8.3.7. Expectedness

All AEs and ADRs are considered "unexpected" if not listed in the Abemaciclib IB, Pembrolizumab IB or Cisplatin/Docetaxel PI. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected ADRs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

8.3.8. Exposure in Utero

If any study patient (or partner of a study patient) becomes or is found to be pregnant during the study or within 90 days of discontinuing the investigational medication/product, the Investigator must report the information to ELI LILLY, or designee via the Pregnancy Notification Report Form within 24 hours of awareness of the pregnancy. This must be done irrespective of whether an AE has occurred. The information submitted should include the anticipated date of delivery.

The Investigator will follow the pregnant patient (or partner of a study patient) until completion of the pregnancy or until pregnancy termination (i.e., induced abortion) and then notify Eli Lilly, or its designee, of the outcome within 5 days or as specified below. The Investigator will provide this information as a follow-up to the initial report. The reason(s) for an induced abortion must be specified.

The Investigator should follow procedures for reporting an SAE if pregnancy outcome meets criteria for an SAE (e.g., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]).

In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth and the Pregnancy Outcome Report Form should be completed (i.e., no minimum follow-up period of a presumably normal infant must pass before a Pregnancy Outcome Report Form

can be completed). The "normality" of an aborted fetus can be assessed by gross visual inspection unless pre-abortion laboratory findings are suggestive of a congenital anomaly.

Additional information about pregnancy outcomes that are classified as SAEs follows:

- "Spontaneous abortion" includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 1 month that the Investigator assesses as possibly related to the *in utero* exposure to the study drug should also be reported.

8.3.9. Follow-up of Unresolved Adverse Events

All AEs should be followed until resolved, improved to the patient's pre-treatment baseline severity or better, or the patient's participation in the study is completed, whichever occurs first. All serious adverse events and those non-serious events assessed by the Investigator as suspected reactions (i.e., at least possibly related) to a Abemaciclib must be followed, even after the patient's withdrawal from study, until the event is either resolved, improved to the patient's pre-treatment baseline or better, stable without anticipated future change, or the patient is lost to follow-up, or, in the case of a suspected adverse reaction, later determined to be not related to the ELI LILLY investigational medicinal product. Any increase or decrease in AE grade should be recorded as a new adverse event. All AEs should also be documented on the AE CRF.

8.4. Safety Monitoring

Data and Safety Monitoring Plan

Dr. Eddy Yang will function as the sponsor of the trial at UAB. The UAB Comprehensive Cancer Center Data and Safety Monitoring Plan (DSMP) instituted by the CTNMO will monitor subjects treated at UAB in the trial. The Clinical Trials Monitoring Committee (CTMC) on a weekly basis will closely monitor adverse reactions observed during treatment. The CTMC is responsible for data and safety monitoring of the trial and adherence to the DSMP. The independent Quality Assurance Committee (QAC) is responsible for oversight of the operation of CTMC, including adherence to the DSMP. Reports from the CTMC are reviewed annually by the QAC.

These committees will monitor safety throughout this study and all studies of Abemaciclib via the following activities:

- Surveillance for SAEs according to regulatory guidelines
- Routine monitoring of non-serious AES as they are recorded in the CRFs and the source documents at study sites

Toxicity information that may affect the treatment of patients on this study will be promptly communicated in writing to all participating Abemaciclib clinical sites, as well as institutions participating in this clinical trial.

9. OTHER ASSESSMENTS

9.1. Other Laboratory Assessments

9.1.1. Immunologic Prognostic Signatures

Blood will be drawn for exploratory analysis of interferon signature using Nanostring. Samples will be sent to Center for Clinical and Translational Sciences (CCTS) laboratory for storage. See separate laboratory manual for specific collection, storage, and shipping information.

9.1.2. Archival Tumor Specimens

Archival specimens (formalin-fixed, paraffin-embedded) of the primary cancer and/or metastatic cancer specimen for each study participant will be obtained. It is preferable that the entire paraffin block be submitted, but if this is not feasible, then at least 20 unstained slides are requested for immunohistochemical analysis (sections of ~ 5 microns are preferred). Samples will be stored at room temperature. See separate laboratory guide for further collection and shipment information.

10. STATISTICS

10.1. Statistical Design/Sample Size

The study design is based on a two-stage Simon MinMax design (Simon, 1989) enrolling total of 18 evaluable patients (null hypothesis that ORR < 10% versus the alternative hypothesis that ORR >= 30 with alpha = 0.087 and power=0.8) will be enrolled in each cohort.

Definition of Analyzed Study Populations:

The following study populations will be considered when reporting study results:

- The study population for safety includes all patients receiving at least a portion of 1 dose of either study drug (Abemaciclib and Pembrolizumab).
- The study population for efficacy will include all safety population patients who have baseline and follow-up tumor measurements as required for assessment by iRECIST.

Only those patients who are deemed ineligible (e.g., do not satisfy eligibility criteria) or who receive no study drug (i.e., no Abemaciclib or Pembrolizumab) will be eliminated from the analysis. Ineligible patients who receive therapy will not be included in the assessment of efficacy endpoints, but their data will be included in the assessment of all AE reporting.

10.2. Data Analysis

Descriptive statistics (such as means, medians, standard deviations, and ranges for continuous data and percentages for categorical data) will be used to summarize patient characteristics, treatment administration/compliance, immunogenicity, efficacy, pharmacokinetic parameters, protein biomarkers, and archival tumor tissue by each cohort. Data will also be displayed graphically, where appropriate. Individual patient data listing will be provided.

10.2.1. Analysis of Primary Objective

• ORR (CR+PR) and corresponding 95% confidence interval based on the Clopper-Pearson will be calculated for each cohort.

10.2.2. Analysis of Secondary Objective

The Kaplan-Meier method will be used to summarize OS, PFS, time to tumor response, DOR, (response evaluation by investigator using irRECIST).
• Subject incidence of treatment-emergent and treatment-related adverse events (all adverse events, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, adverse events and serious adverse events leading to discontinuation of treatment, and adverse events defined as events of interest) and laboratory abnormalities

Dose-limiting toxicities (DLTs) will be summarized by category (hematologic and non-hematologic) and by Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) and System Organ Class (SOC).

All AEs with an onset after initiation of treatment will be considered as treatment-emergent AEs. A preexisting condition that worsens after study drug treatment will also be considered as a treatment-emergent AE. All AEs will be coded by MedDRA SOC and PT.

The number and percentage of patients with the following types of treatment-emergent AEs will be summarized: all AEs, all SAEs, AEs related to study drug (Abemaciclib and Pembrolizumab), AEs resulting in study drug discontinuation, and clinically significant laboratory abnormalities. Non-treatment-emergent serious AEs will be presented separately from treatment-emergent AEs. Deaths will be reported with demographic information.

10.2.3. Exploratory Analysis

PD-1/PD-L1 expression will be quantified for each patient who received at least 1 dose of study drug and will be listed. Expression will be determined by immunohistochemistry (IHC). Other markers that may relate to efficacy or toxicity of Abemaciclib may also be explored.

Mutational analysis will be performed via the Strata Oncology platform (Oncomine), which includes analysis of microsatellite stability and genetic alteration of the CDK4/6 pathway.

Immune pathway gene expression will be performed using Nanostring immune pathways panel. This panel allows for the interrogation of immune repertoire as well as analysis of the IFN-g pathway, which has been shown to correlate with HNSCC response to immunotherapy (2).

Additionally, blood will be collected at baseline and day 1 of every cycle and analyzed for ctDNA, and whole blood immune pathway/IFN-g pathway analysis will be performed using the Nanostring platform.

We will correlate molecular profiling with responses.

10.3 Interim Analysis

For each cohort after 11 evaluable patients are enrolled (stage 1), an additional 7 evaluable patients will be enrolled (stage 2) if 2 or more patients respond. If there is one or no response, then no further patients will be enrolled.

Stopping Rule:
Stage 1:
Stop and accept the null hypothesis if the response rate is less than or equal to 1/11. Otherwise, continue to stage 2. The probability of stopping for futility is 0.697 when Ho is true and 0.113 when Ha is true.

Stage 2:
Stop and accept the null hypothesis if the response rate is less than or equal to 3/18. Otherwise, stop and reject the null hypothesis.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

All data entered on CRFs/electronic CRFs (eCRFs) must be verifiable within the patients' source documents (written or electronic record). UAB PI, CTNMO, QAC, ELI LILLY representatives and appropriate regulatory authorities will have direct access to the original source records for the duration of the agreed study record retention period. Printouts of source records that are electronically obtained and stored will not be acceptable for audit/inspection unless provided as certified exact copies and the data remains as meaningful and useful as in its original electronic state.

Legally protected patient identification and other personal health information must be securely stored with limited access by the participating institutions. No authority will receive access to electronic source record for monitoring purpose on site or remotely. Only paper copies of source documents that have been signed and dated by PI will be used as source documents for monitoring by authorities outside UAB.

12. QUALITY CONTROL AND QUALITY ASSURANCE

CTNMO and QAC committee at UAB will conduct monitoring periodically during the trial to ensure that GCPs and all aspects of the protocol are being followed.

The trial site will also be subject to possible inspection by the institutional review board (IRB) or independent ethics committee (IEC) or other appropriate regulatory authority. The trial site is also subject to quality assurance audits performed by UAB CTNMO and QAC.

It is important that the Investigator(s) and their relevant personnel are available during the monitoring visits, audits, and inspections and that sufficient attention, time, and support is devoted to the process.

UAB CTNMO and QAC will be governed by applicable regulations, GCP standards, and internal standard operating procedures (SOPs) for the conduct of monitoring visits and quality assurance (QA) audits.

13. ETHICS

13.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the Investigator to have approval of the study protocol, protocol amendments, informed consent forms, advertisements from the IRB/IEC, and any other patient-distributed materials before potential patients are consented for participation on the trial. All correspondence and other evidence of appropriate and timely communications with the IRB/IEC should be retained in the Investigator/site files. Copies of all IRB/IEC approvals should also be forwarded to ELI LILLY.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the Investigator must notify the IRB/IEC and ELI LILLY in writing within 5 business days after the implementation.

13.2. Ethical Conduct of the Study

The trial will be performed in accordance with the protocol, applicable local regulatory requirements and laws, and the International Council on Harmonization (ICH) Guideline on Good Clinical Practice (GCP), which supports the application of ethical principles that have their origin in the Declaration of Helsinki (see ICH E6, § 2.1).

13.3. Written Informed Consent

The informed consent form language must be agreed upon by UAB PI and the IRB/IEC and must be in compliance with ICH GCP, local regulatory requirements, and legal requirements. The informed consent information must not be changed without prior approval by UAB PI and the IRB/IEC. The informed consent form used in this trial, and any changes made during the course of the study, must be approved by both the IRB/IEC and UAB PI, before use.

It is the responsibility of the Investigator to give each patient full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. This information must be provided to the patient prior to undertaking any protocol-specified procedure. Patients must be informed about their right to withdraw from the trial at any time. Furthermore, it is the responsibility of the Investigator to ensure all patients are appropriately informed before obtaining their signed and dated consent. Signatures from the Investigator conducting the informed consent discussion should also be obtained, prior to undertaking any trial-related procedure. Consent by a legally authorized representative is not permitted. Should an impartial witness be needed, ICH E6 requirements for impartial witnesses will apply.

The Investigator will retain the original of each patient's signed consent form in the Investigator/site files.

13.4. Patient Compensation

Patients will not be compensated for participation in this study; this will be outlined in the patient informed consent form.

14. DATA HANDLING AND RECORDKEEPING

14.1. Inspection of Records

CRFs/eCRFs are required and should be completed for each patient who receives treatment with Abemaciclib. Screen failure CRF's will not be collected. Nevertheless, records of potential patients identified and screened shall be retained on site screening logs. The completed original CRFs/eCRFs are the sole property of UAB Comprehensive Cancer Center and should not be made available in any form to third parties without written permission from UAB PI (except for authorized representatives of the HRA and in accordance with Health Insurance Portability and Accountability Act [HIPAA] regulations).

It is the Investigator's responsibility to ensure completion and to review and approve all CRF data. The investigator will sign off on his/her data per patient. These signatures serve to attest that the Investigator has reviewed and approved the information contained on the CRFs and that the information is complete, accurate, and true. At all times, the Investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs.

The use of electronic CRFs (eCRFs) to capture study data using automated computerized data capture systems does not change the principles and requirements for collecting study data. The Investigator still retains final personal responsibility for eCRF data and any associated data pertaining to it (e.g., metadata including any record of change to the originally recorded data). The Investigator's signed approval of the eCRF data serves to attest that the electronic data and all of its associated metadata (including changes) has been reviewed and accepted as complete, accurate, and true for each patient in the study.

14.2. Retention of Records

To allow for appropriate evaluations and/or audits by regulatory authorities, the UAB PI agrees to keep records, including the identity of all participating patients (sufficient information to link records, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, source documents, and detailed records of treatment disposition. The Investigator should retain these records according to local regulations or as specified in the Clinical Trial Agreement, whichever is longer.

If the Investigator relocates, retires, or for any reason withdraws from the study, then ELI LILLY should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution. The Investigator must inform ELI LILLY of any such transfer of responsibilities and properly identify the person or institution assuming the responsibility. The responsible institution must obtain UAB PI's written permission before disposing of any records.

15. DEFINITION OF END OF TRIAL

15.1. End of Trial

End of trial is defined as the time at which all patients enrolled in the study have completed the treatment follow-up period.

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15.2. Discontinuation Criteria

Premature termination of this trial may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems.

16. PUBLICATION OF TRIAL RESULTS

Publication of trial results is discussed in the Clinical Trial Agreement.

17. FINANCING AND INSURANCE

Financing and Insurance are discussed in the Clinical Trial Agreement.

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19. APPENDICES

19.1. Appendix 1: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

The NCI CTCAE (Version 4.03) should be used to assess adverse events and may be reviewed on-line at the following NCI website:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

19.2. Appendix 2: ECOG Performance Status

Grade	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	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	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.