A Prospective Phase I and II Trial of Abemaciclib + Nivolumab in Patients with Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma that Progressed or Recurred within Six Months after Platinum-based Chemotherapy

Washington University School of Medicine
Division of Oncology
660 South Euclid Avenue, Campus Box 8056
St. Louis, MO 63110

Protocol #: 201810019
Version Date: 09/10/2019

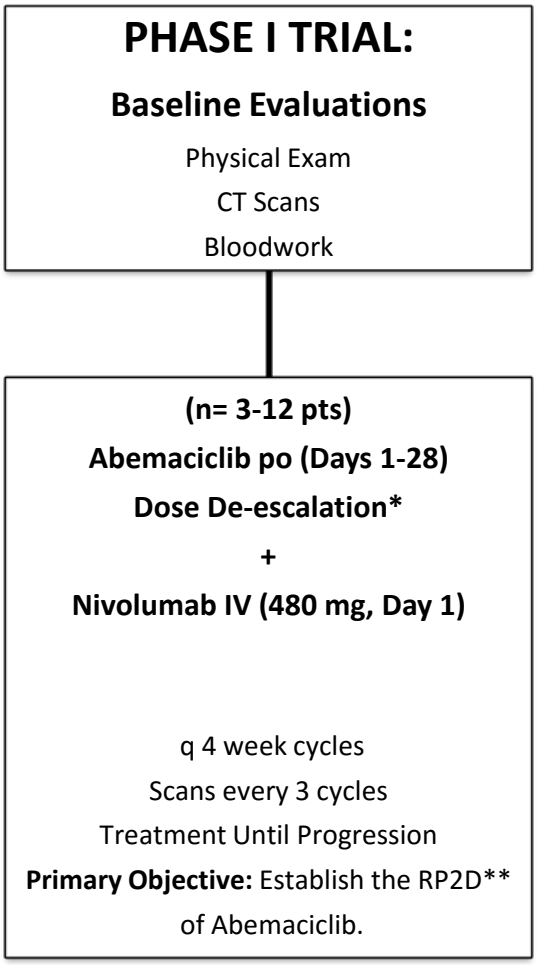
Principal Investigator: Douglas R. Adkins, MD
(314) 747-8475
dadkins@wustl.edu

Sub-Investigators	Modality
Miriam Jacobs, MD	Medical Oncology
Peter Oppelt, MD	Medical Oncology
Todd Fehniger, MD, PhD	Medical Oncology
Kevin Palka, MD	Medical Oncology
Esther Lu, PhD	Biostatistics
Jessica Ley, BS	Clinical Research Specialist
Sid Puram, MD	Otolaryngology/Head and Neck Surgery

Study Drug(s): Abemaciclib (Verzenio)
Nivolumab (Opdivo)

IND #: 141105 (EXEMPT)
ClinicalTrials.gov #: NCT03655444

SCHEMA



*Phase I: Abemaciclib De-Escalation Schedule

Dose Level	Abemaciclib Dose
1(Starting Dose)	150 mg bid
2	100 mg bid
3	50 mg bid

Three patients will be treated at each dose level. De-escalation to the next dose level will occur if 2 or more patients experience DLTs attributable to abemaciclib during cycle 1.

**RP2D: recommended phase 2 dose.

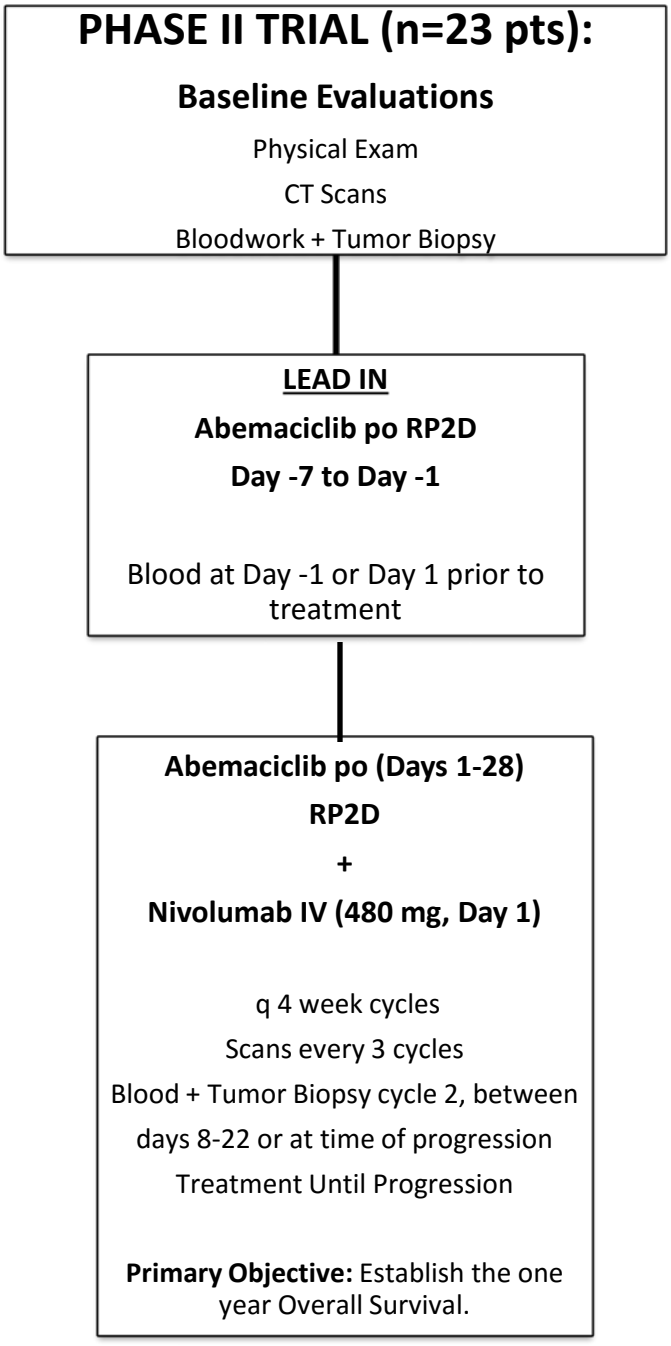

PHASE II TRIAL (n=23 pts):
Baseline Evaluations
Physical Exam
CT Scans
Bloodwork + Tumor Biopsy
LEAD IN
Abemaciclib po RP2D
Day -7 to Day -1
Blood at Day -1 or Day 1 prior to treatment
Abemaciclib po (Days 1-28)
RP2D
+
Nivolumab IV (480 mg, Day 1)
q 4 week cycles
Scans every 3 cycles
Blood + Tumor Biopsy cycle 2, between days 8-22 or at time of progression
Treatment Until Progression
Primary Objective: Establish the one year Overall Survival.

Table of Contents

1.0 BACKGROUND AND RATIONALE

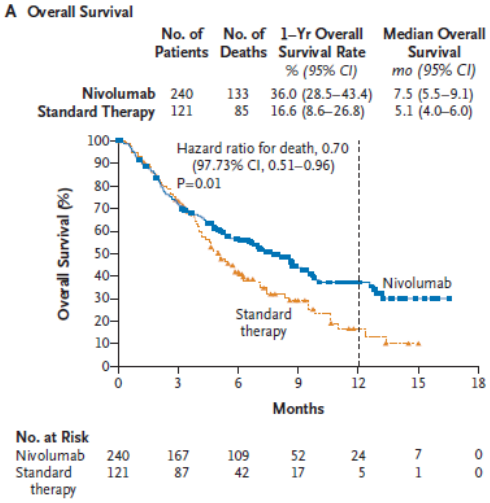
1.1 Head and Neck Squamous Cell Carcinoma

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer. Most patients (80%) present with locally advanced disease, and 50% of these patients are cured. However, 50% of these patients develop recurrent/metastatic (RM) disease within 18 months of completion of initial therapy. **The magnitude of the problem of RM-HNSCC is significant: in the USA alone, over 20,000 new cases of RM-HNSCC occur each year, while in the world, over 240,000 new cases of RM-HNSCC occur each year.**

Outcomes are poor for those patients who are not cured with initial therapy. The median overall survival (OS) of patients with RM-HNSCC treated with first line platin-based chemotherapy and cetuximab is 10 months[1]. Median OS for patients with platinum-refractory RM-HNSCC is 5 months and one year survival is only 17%. Novel effective therapies are needed for patients with RM-HNSCC.

1.2 Nivolumab in Platin-Refractory RM-HNSCC

Checkmate 141 was a randomized phase III trial that compared outcomes of patients with RM-HNSCC that had progressed or recurred within six months after platinum-based chemotherapy who were treated with nivolumab (anti-PD-1 antibody) or investigator's choice (IC) of chemotherapy (docetaxel, methotrexate or cetuximab)[2]. Median OS was 7.5 months in the nivolumab group and 5.1 months in the IC group (p=0.01). ***One-year survival was 36% in the nivolumab group and 17% in the IC group.*** Median progression-free survival (PFS) was not significantly different between the two groups (2.0 vs 2.3 months, respectively, p=0.32). Tumor response rate was 13% in the nivolumab group and 6% in the IC group.



This trial established nivolumab as the new standard therapy for patients with RM-HNSCC that had progressed or recurred within six months after platinum-based chemotherapy. However, the one year survival of only 36% with nivolumab emphasizes the need to develop strategies to improve these results.

1.3 CDK4/6 Inhibition is an Effective Therapeutic Strategy in RM-HNSCC

Because the genetics of HNSCC suggest a crucial role for CDK4/cyclin D in this disease[3], we performed a phase I trial to determine the dose limiting toxicity (DLT) and the maximum tolerated dose (MTD) of palbociclib combined with standard weekly doses of cetuximab in patients with RM-HNSCC[4]. We built upon the cetuximab platform because palbociclib targets a pathway associated with resistance to EGFR inhibitors.

A phase I trial using 3+3 design was performed to determine the DLT and MTD of palbociclib with standard dose weekly cetuximab. Palbociclib was administered orally days 1-21 every 28 days: dose level 1 (100 mg/d) and 2 (125 mg/d). Tumor response was assessed using RECIST 1.1.

Nine patients were enrolled across dose levels 1 (n=3) and 2 (n=6) and none experienced a DLT. The MTD of palbociclib was not reached. Six of nine patients had cetuximab-resistant and four of nine had platinum-resistant disease. Disease control (DC) occurred in 89% of patients, including partial response (PR) in two (22%) and stable disease in six (67%) patients. Five patients (56%) had measurable decreases in tumor target lesions. In platinum-resistant HNSCC, best tumor response was PR in 1 and DC in 3 patients. In cetuximab-resistant HNSCC, best tumor response was PR in 1 and DC in 5 patients.

This trial, the first to evaluate a CDK4/6 inhibitor in HNSCC, determined that palbociclib is an active agent in RM-HNSCC, even in platinum-resistant disease. Tumor responses in cetuximab-resistant disease suggest that monotherapy with a CDK4/6 inhibitor would result in tumor responses in this disease.

1.4 Selective CDK4/6 Inhibition with Abemaciclib

Abemaciclib is an oral selective CDK4/6 inhibitor administered on a continuous schedule[5-7]. Abemaciclib results in cell cycle arrest at the G_1 checkpoint and inhibits cell growth. Continuous inhibition of CDK4/6 results in sustained growth arrest and initiation of apoptosis or senescence[8]. Abemaciclib is 14 times more potent than palbociclib or ribociclib against cyclin D1/CDK4 than cycle D3/CDK6 in enzymatic assays[6-10]. **Compared to palbociclib, abemaciclib has greater potency as a CDK4/6 inhibitor and is administered on a continuous schedule. These advantages make abemaciclib an attractive option to inhibit CDK4/6 in HNSCC and could translate into improved and more durable tumor responses compared to palbociclib.**

In a phase I trial, the DLT of abemaciclib was fatigue[6]. Other (grade 3) toxicities included diarrhea (5%) and hematologic (10%). Tumor responses were seen in breast cancer, NSCLC and melanoma. In hormone-receptor positive breast cancer, the tumor response rate was 31%. The phase II MONARCH 1 trial confirmed the single agent activity of abemaciclib in refractory hormone-receptor positive breast cancer with a tumor response rate of 19.7%[8]. The phase III MONARCH 2 trial showed a significantly longer median PFS (16.4 vs 9.3 months) and better tumor response rate (48.1% vs 21.3%) with abemaciclib and fulvestrant compared to placebo and fulvestrant in refractory hormone-receptor positive breast cancer[11]. Diarrhea, neutropenia, nausea and fatigue were more common in the abemaciclib arm.

1.5 Rationale for the Combination of Abemaciclib and Nivolumab: "CDK4/6 Inhibition Triggers Anti-Tumor Immunity"

Abemaciclib, a CDK4/6 inhibitor, increases tumor immunogenicity by enhancing tumor antigen presentation and suppressing proliferation of regulatory T cells[12]. These effects are mediated by decreased expression of DNMT1. ***The functional significance of these effects include promotion of CD8 T cell mediated killing of tumor cells which is enhanced by the addition of PD-1 antibody.***

1.6 Study Synopsis and Aims

Nivolumab monotherapy is the current standard FDA approved therapy to treat RM-HNSCC that has progressed or recurred within six months after platinum-based chemotherapy; however, the benefit is modest. One year survival was only 36%, and median PFS 2.0 months and tumor response 13%. CDK4/6 inhibition is an effective therapeutic strategy in RM-HNSCC, and abemaciclib ***promotes CD8 T cell mediated killing of tumor cells which is enhanced by the addition of PD-L1 antibody.*** Based on these observations, we hypothesize that the combination of abemaciclib and nivolumab will increase the one year survival of patients with RM-HNSCC that had progressed or recurred within six months after platinum-based chemotherapy, compared to historical data with nivolumab monotherapy.

In phase I of the trial, **we aim to explore the safety and feasibility of abemaciclib in combination with nivolumab in patients with RM-HNSCC.** A dose de-escalation study design will be used to determine the recommended phase II dose (RP2D) of abemaciclib given with the standard dose of nivolumab.
In phase II of the trial, we aim to determine if abemaciclib and nivolumab will improve the one year survival from 36% (historical comparison with nivolumab) to 60% (abemaciclib + nivolumab) in patients with RM-HNSCC that had progressed or recurred within six months after platinum-based chemotherapy. Patients will be treated with abemaciclib at the RP2D in combination with standard doses of nivolumab. If this aim is met, genome

sequencing, bulk and single cell RNAseq, and selected protein expression and deep cellular phenotyping will be performed on tumor tissue and blood obtained before and during treatment with abemaciclib and nivolumab. These biomarker data will be correlated with survival and tumor response to abemaciclib and nivolumab.

2.0 OBJECTIVES

2.1 Primary Objectives

1) Phase I: Determine the RP2D of abemaciclib combined with a fixed dose of nivolumab in patients with RM-HNSCC.

2) Phase II: Determine the OS of patients with RM-HNSCC that progressed or recurred within six months of platinum-based therapy who are treated with abemaciclib and nivolumab.

2.2 Secondary Objectives

1) Phase II: Determine the best tumor response rate for patients with RM-HNSCC who are treated with abemaciclib and nivolumab.

2) Phase II: Determine the duration of tumor response for patients with RM-HNSCC who are treated with abemaciclib and nivolumab.

3) Phase II: Determine the progression-free survival (PFS) for patients with RM-HNSCC who are treated with abemaciclib and nivolumab.

4) Phase II: Determine the adverse events (AEs) associated with the combination of abemaciclib and nivolumab.

5) Phase II-Lead In: Characterize the changes in peripheral blood lymphocyte subsets before and after one week of abemaciclib monotherapy.

2.3 Exploratory Objectives

1) Phase II: Collect and store pre-treatment and on-treatment tissue and blood specimens from patients for correlative studies, including studies of tumor heterogeneity that may define the malignant, stromal, and immune response with treatment.

2) Phase II: Monitor quality of life (QOL) as documented by QOL measurements using the FACT H&N and EORTC QLQ-C30 assessment tools.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. Incurable RM-HNSCC, defined as disease not amenable to cure by surgery and/or radiation therapy (or patient declines or is ineligible for surgery and/or radiation therapy).

2. Disease Evaluation:
   a. Phase I: evaluable or measurable disease.
   b. Phase II: measurable disease, defined as lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with CT scan, as ≥ 20 mm by chest x-ray, or ≥ 10 mm by clinical exam.

3. Prior Treatment:
   a. Phase I: any number of lines of prior therapy for RM-HNSCC.
   b. Phase I: prior therapy with inhibitors of CDK4/6 or PD-L1/PD-1 is acceptable.
   c. Phase II: RM-HNSCC that progressed or recurred within six months of platinum-based therapy (given for curable or incurable disease).
   d. Phase II: prior therapy with inhibitors of CDK4/6 or PD-L1/PD-1 is not acceptable.

4. 18 years of age or older.

5. Performance status 0-1 (ECOG: Appendix 1).

6. Adequate blood and organ function as defined:
   a. Absolute neutrophil count ≥ 1,500/mcL
   b. Platelets ≥ 100,000/mcL
   c. Hemoglobin ≥ 8.0 g/dL
   d. Total bilirubin ≤ 1.5 x ULN
   e. AST(SGOT) ≤ 3 x IULN and ALT(SGPT) ≤ 3 x IULN
   f. Creatinine ≤ 2 x ULN OR creatinine clearance ≥ 40 mL/min/1.73 m^2
   g. INR ≤ 1.5 x ULN and PTT ≤ 1.5 x ULN (Patients are allowed to be on anticoagulation)

7. Able to swallow oral medication.

8. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) beginning 14 days prior to first dose of abemaciclib, through the dosing period, and for at least 28 days after.

9. Signed IRB approved written informed consent document.

3.2 Exclusion Criteria

1. Phase II: prior inhibitors of CDK4/6 or PD-L1/PD-1 for treatment of incurable HNSCC.

2. Radiation within 14 days of treatment start (patients who received radiotherapy must have completed and fully recovered from the acute effects of radiotherapy); Chemotherapy, targeted or investigational therapy within 21 days of treatment start.

3. History of other malignancy ≤ 1 year prior to consent with the exception of completely resected skin carcinoma or other cancers with a low risk of recurrence.

4. Ongoing toxicity attributed to prior anti-cancer therapy that is > grade 1, except alopecia or peripheral neuropathy.

5. Active central nervous system metastases: defined as currently receiving radiation therapy to metastatic CNS disease. Once radiation therapy is completed, patients with CNS disease are eligible if they meet all other criteria for enrollment.

6. History of severe allergic reactions attributed to agents used in the study.

7. Serious uncontrolled inter-current illness within the 3 months prior to study entry or psychiatric illness/social situations that would limit compliance with study requirements.

8. Serious and/or uncontrolled preexisting medical condition(s) that, in the judgment of the investigator, would preclude participation in this study (i.e., interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, severe renal impairment [e.g. estimated creatinine clearance <30ml/min], 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).

9. Active systemic bacterial infection (requiring intravenous [IV] antibiotics at time of initiating study treatment), fungal infection, or detectable viral infection (such as known human immunodeficiency virus positivity or with known active hepatitis B or C [for example, hepatitis B surface antigen positive]. Screening is not required for enrollment.

10. 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.

11. Pregnant and/or breastfeeding. Patient must have a negative serum pregnancy test within 7 days of first dose of treatment.

12. Active serious autoimmune disease requiring systemic immunosuppression (biologics, prednisone equivalent dose > 20 mg/day).

13. Current use of strong CYP3A inhibitors or inducers.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center OnCore database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

5.0 TREATMENT PLAN

5.1 Phase I: Dose De-Escalation

Abemaciclib will be administered po bid (with or without food) on Days 1 through 28 of every 4-week cycle. Patients will be asked to complete a drug diary Nivolumab 480 mg will be given intravenously (IV) over 30 minutes on Day 1 of every 4-week cycle. Abemaciclib dose levels are shown in the table below. Nivolumab dosing will not change.

5.1.1 Phase I Abemaciclib Dose De-Escalation Plan

Dose Level	Dose (mg bid)
1 (Starting Dose)	150
-1	100
-2	50

Starting at dose level 1, three patients will be treated. De-escalation to the next lowest dose level will occur if 2 or more patients experience dose-limiting toxicities (DLTs) attributable to abemaciclib. Dose de-escalation will not occur until all patients in the cohort have completed the first cycle of therapy and the Principal Investigator has been able to review all toxicities. If 1 or fewer patients experience a DLT within a dose level, that dose level will be considered the RP2D of abemaciclib given with nivolumab.

5.1.2 Definition of RP2D and DLT

5.1.2.1 Definition of RP2D of Abemaciclib

The RP2D of abemaciclib is defined as the highest dose level at which fewer than 2 patients of a cohort of three patients experience a DLT during the first cycle. Dose de-escalations will proceed until the RP2D has been reached. If no more than one DLT in three patients is experienced in dose level 1, this will be considered the RP2D and there will be no dose de-escalation.

5.1.2.2 Dose Limiting Toxicities (DLTs)

DLTs will only be assessed during Cycle 1 of the phase I portion of the study.

Hematologic DLT is defined as neutropenia (grade 4) or thrombocytopenia (grades 4). Hematologic toxicity is not a known AE of nivolumab.

Non-hematologic DLT is defined as any possibly, probably, or definitely abemaciclib-related grade 3 or grade 4 toxicity occurring during the first cycle except:

- Grade 3 or 4 nausea, vomiting or diarrhea that occurs without maximal antiemetic/antidiarrheal prophylaxis
- Grade 3 or 4 hypertension that is adequately controlled by medication
- Grade 3 or 4 venous thromboembolism (they can receive anticoagulation)
- Any grade: anorexia, fatigue, alopecia, or lymphopenia

5.2 Phase II

5.2.1 Lead In: Abemaciclib Monotherapy

Patients will be treated with abemaciclib monotherapy at the RP2D on Day -7 through Day -1 prior to starting Cycle 1 with the combination of abemaciclib and nivolumab. Patients will proceed directly from Day -1 to Cycle 1 Day 1 of combination abemaciclib + nivolumab, there is not a Day 0.

5.2.2 Abemaciclib + Nivolumab

Patients will be treated with abemaciclib at the RP2D (Days 1 through 28) + nivolumab (480 mg, Day 1) of each 4-week cycle. Tumor response assessment will be performed after every three cycles (12 weeks). If either drug is stopped for reasons other than disease progression, the other drug will continue and the patient will remain on the protocol. Patients will remain on study therapy until disease progression, intolerance, or patient decision to stop therapy. Study treatment will be stopped when disease progression is documented, after which patients will be followed for OS.

5.2.3 Toxicity and Tumor Response Evaluations

All patients who receive any study treatment are evaluable for toxicity. Patients are evaluated from first receiving study treatment until a 30-day follow up after the conclusion of treatment or death.

All patients who have received at least one dose of abemaciclib will be evaluable for disease response (including patients who discontinue abemaciclib early but continue to receive nivolumab), unless they come off study entirely due to treatment related adverse events(s) prior to completion of Cycle 1 and have not had any disease assessment. CT scans of the neck and chest will be performed at baseline and after every 12 weeks (3 cycles) of therapy.

5.3 Definitions of Evaluability

All patients who receive any study treatment are evaluable for toxicity. Patients

are evaluated from first receiving study treatment until a 28-day follow up after the conclusion of treatment or death.

All patients who received at least one dose of abemaciclib will be evaluable for disease response (including patients who discontinue abemaciclib early but continue to receive nivolumab), unless they come off study entirely and have not had any disease assessment. CT scans of the neck and chest will be performed at baseline and after every 12 weeks (three cycles) of therapy.

A patient is evaluable for DLT assessment only during Cycle 1 of treatment, and only if enrolled in Phase I of the study. If the patient is not able to be treated on Day 1 of Cycle 2, then s/he is still considered in Cycle 1 active treatment and can experience a DLT. Once the patient has been treated in Cycle 2, s/he will no longer be evaluated for DLTs in subsequent cycles.

5.4 Concomitant Medications

5.4.1 CYP3A inhibitors

Abemaciclib is predominantly cleared by oxidative metabolism via CYP3A4. Clinical drug interaction studies with a CYP3A inhibitor and CYP3A inducer significantly altered the PK of abemaciclib and its circulating major metabolites. Therefore, drugs that are strong and moderate inducers of CYP3A and/or strong inhibitors of CYP3A should be avoided or substituted if necessary.

If concomitant use cannot be avoided, abemaciclib dose adjustments may be required:

- Patients who must take CYP3A inhibitors such as clarithromycin, diltiazem, or verapamil should reduce the abemaciclib dose to 100 mg twice daily.
- Patients who must take itraconazole should reduce the abemaciclib dose to 50 mg twice daily.
- Patients who must take ketoconazole should reduce the abemaciclib dose to 50 mg twice daily.
- Patients should avoid grapefruit or grapefruit juice.

5.4.2 CYP3A inducers

Avoid concomitant use of strong CYP3A inducers. Consider alternative agents without CYP3A induction.

If a CYP3A inhibitor is discontinued, increase the abemaciclib dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor. *Communicate with the PI and receive PI approval before doing this*

5.5 Radiotherapy in Combination with Abemaciclib is NOT Permitted.

5.6 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative pregnancy test within 7 days prior to the first dose of abemaciclib.

Female and male patients (along with their female partners) are required to use two forms of acceptable contraception, including one barrier method, during participation in the study and for 3 months following the last dose of either study drug. Contraceptive methods may include an intrauterine device [IUD] or barrier method. If condoms are used as a barrier method, a spermicidal agent should be added as a double barrier protection.

If a patient is suspected to be pregnant, both study drugs should be immediately discontinued. In addition a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a female patient or female partner of a male patient becomes pregnant during therapy or within 3 months after the last dose of either study drug, the investigator must be notified in order to facilitate outcome follow-up. Data on fetal outcome and breast-feeding are to be collected for regulatory reporting and drug safety evaluation.

5.7 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue indefinitely or until one of the following criteria applies:

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

- Suspected pregnancy
- Serious noncompliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will be followed as indicated in the study calendar.

If either drug is stopped for reasons other than disease progression, the other drug will continue and the patient will remain on the protocol. Patients will remain on study therapy until one of the above criteria is met. Study treatment will be stopped when disease progression is documented, after which patients will be followed for OS.

5.8 Duration of Follow-up

Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Patients will be followed for 28 days after last dose of therapy for adverse events, and until death for OS objective.

6.0 DOSE DELAYS/DOSE MODIFICATIONS/TREATMENT OF AEs

6.1 Abemaciclib

6.1.1 Dose Levels for Abemaciclib

Starting dose for Phase II will be determined by results of Phase I. Dose escalations are not permitted. Only dose reductions are permitted.

Dose Level	Abemaciclib Dose
Starting Dose	150 mg twice daily
-1	100 mg twice daily
-2	50 mg twice daily

6.1.2 Dose Modification and Management – Hematologic Toxicities

Monitor complete blood counts prior to the start of abemaciclib therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.	
CTCAE v5.0 Grade	**Abemaciclib Dose Modifications**
Grade 1 or 2	No dose modification is required
Grade 3	Suspend dose until toxicity resolves to ≤Grade 2

	Dose reduction is not required.
Grade 3 recurrent, or Grade 4	Suspend dose until toxicity resolves to ≤Grade 2. Resume at next lower dose
Patient requires administration of a blood cell growth factor	Suspend abemaciclib dose for at least 48 hours after the last dose of blood cell growth factor and until toxicity resolves to ≤Grade 2. Resume abemaciclib at next lower dose unless the dose was already reduced for the toxicity that led to the use of the growth factor

6.1.3 Dose Modification and Management – Diarrhea

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.

At the first sign of loose stools, start treatment with antidiarrheal agents, such as loperamide, and notify the PI for further instructions and appropriate follow-up. Site personnel should assess response within 24 hours.

Patients should be encouraged to drink fluids (e.g., 8-10 glasses of clear liquids/day)

CTCAE v5.0 Grade	**Abemaciclib Dose Modifications**
Grade 1	No dose modification is required
Grade 2	If toxicity does not resolve within 24 hours to ≤Grade 1, suspend dose until resolution. Dose reduction is not required
Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures	Suspend dose until toxicity resolves to ≤Grade 1 Resume at next lower dose
Grade 3 or 4 or requires hospitalization	

Dose level reductions should be made in 50 mg increments. For example, if the starting dose of abemaciclib for the study is 150 mg q12 hours, dose reduction 1 would be 100 mg q12 hours, dose reduction 2 would be 50 mg q12 hours.

6.1.4 Dose Modification and Management – Interstitial Lung Disease (ILD)/Pneumonitis Events

Patients should be asked to report any new or worsening pulmonary symptoms such as hypoxia, cough, dyspnea, cough and fever; these symptoms should be investigated and treated as per SOC guidelines

(including corticosteroids as appropriate). Infectious, neoplastic, and other causes for such symptoms should be excluded by means of appropriate investigations. Imaging such as high resolution computer tomography (HRCT), broncheoalveolar lavage (BAL), and biopsy as clinically indicated.

CTCAE Grade	Abemaciclib Dose Modifications
Grade 1 or 2	No dose modification is required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Grade 3 or 4	Discontinue abemaciclib.

6.1.5 Dose Modification and Management – Increased ALT

Screening CMP will be used for C1D1 of abemaciclib & nivolumab treatment

CTCAE v5.0 Grade	Abemaciclib Dose Modifications
Grade 1 (>ULN-3.0 × ULN) Grade 2 (>3.0-5.0 × ULN)	No dose modification is required
Persistent or Recurrent Grade 2, or Grade 3 (>5.0-20.0 × ULN) that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Grade 3 (>5.0 x ULN) with total bilirubin > 2 x ULN, in the absence of cholestasis	Discontinue abemaciclib
Grade 4 (>20.0 × ULN)	Discontinue abemaciclib

Abbreviations: ALT = alanine aminotransferase; ULN = upper limit of normal.

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. **To ensure patient safety the investigator should collect specific recommended clinical information and follow-up laboratory tests as shown in the table below.**

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. If a study patient experiences elevated ALT 5×ULN and elevated TBL 2×ULN, or ALT 8×ULN, liver tests, including ALT, AST, TBL, direct bilirubin, gamma-glutamyl transferase (GGT), and creatine phosphokinase (CPK), should be repeated within 3 to

5 days to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator, based on the hepatic monitoring tests below.

Hepatic Monitoring Tests for a Hepatic Treatment Emergent Abnormality.

Hepatic Hematology	**Haptoglobin**
Hemoglobin	
Hematocrit	**Hepatic Coagulation**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented and bands	
Lymphocytes	**Hepatic Serologies[a]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody**
AST	**Anti-actin antibody**
GGT	**Anti-smooth muscle antibody**
CPK	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

6.1.6 Dose Modification and Management – Nonhematologic Toxicities Excluding Diarrhea, ALT Increased, and ILD/Pneumonitis

CTCAE v5.0 Grade	Abemaciclib Dose Modifications
Grade 1 or 2	No dose modification is required
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or Grade 1 Resume at next lower dose
Grade 3 or 4	

6.1.7 General Guidance for Increases in Serum Creatinine and Assessment of Renal Insufficiency

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.

6.2 Nivolumab

Guidance for dose modifications or delays and treatment of AEs attributed to nivolumab will be guided based on the package insert. If nivolumab is omitted or stopped, patients will continue to receive abemaciclib. If abemaciclib is omitted or stopped, patients will continue to receive nivolumab.

7.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outline below.

The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined in Section 7.2.

The FDA requires that all serious and unexpected adverse events be reported as outlined in Section 7.4. In addition, any fatal or life-threatening adverse experiences where there is a reasonable possibility of relationship to study intervention must be reported.

Eli Lilly requires that all events be reported as outlined in Section 7.5.

7.1 Definitions

7.1.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

7.1.2 Serious Adverse Event (SAE)

Definition: any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

All unexpected SAEs must be reported to the FDA.

7.1.3 Unexpected Adverse Experience

Definition: any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

Events that are both serious AND unexpected must be reported to the FDA.

7.1.4 Life-Threatening Adverse Experience

Definition: any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Life-threatening adverse experiences must be reported to the FDA.

7.1.5 Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.1.6 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

7.1.7 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

7.1.8 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Pre-approval of all protocol exceptions must be obtained prior to the event.

7.2 Reporting to the Human Research Protection Office (HRPO) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

7.3 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to a QASMC auditor.

7.4 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It is the responsibility of the investigator to report any unanticipated problem to the FDA as follows:

- Report any unexpected fatal or life-threatening adverse experiences (Section 7.1.4) associated with use of the drug (i.e., there is a reasonable possibility that the experience may have been caused by the drug) by telephone or fax no later than **7 calendar days** after initial receipt of the information.
- Report any serious, unexpected adverse experiences (Section 7.1.2), as well as results from animal studies that suggest significant clinical risk within

15 calendar days after initial receipt of this information.

All MedWatch forms will be sent by the investigator or investigator's team to the FDA at the following address or by fax:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products
5901-B Ammendale Rd.
Beltsville, MD 20705-1266
FAX: 1-800-FDA-0178

7.5 Reporting to Lilly Oncology

A serious adverse event is an undesirable sign, symptom or medical condition which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient definitions of a SAE
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Lilly.

All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form).

To ensure patient safety, every SAE, regardless of suspected causality, occurring

- after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment/participation
- after protocol-specified procedures begin (e.g., placebo run-in, washout period, double-blind treatment, etc.) and 30 days after the patient has

stopped study treatment

- after the start of any period in which the study protocol interferes with the standard medical treatment given to a patient (e.g., treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication) and until 30 days after the patient has stopped study treatment

All events must be reported to Lilly within 15 days of learning of its occurrence. Information about all SAEs is collected and recorded on a Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and **submit the form via the electronic SAE reporting portal within 24 hours to Lilly**.

This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 working days.

Any SAEs experienced after this 30 days period should only be reported to Lilly if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event. The end date of the first event must be provided.

The original copy of the SAE Report and the fax confirmation sheet must be kept within the Trial Master File at the study site.

Follow-up information is sent to the same fax number as the original SAE Report Form was sent, using a new fax cover sheet, stating that this is a follow-up to the previously reported SAE, and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the patient continued or withdrew from study participation.

7.6 Timeframe for Reporting Required Events

Adverse events will be tracked for 28 days following the last day of study treatment.

8.0 PHARMACEUTICAL INFORMATION

8.1 Abemaciclib (Verzenio)

8.1.1 Abemaciclib Description

Abemaciclib is a kinase inhibitor indicated:

- in combination with fulvestrant for the treatment of women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy
- as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting

It is a white to yellow powder with the empirical formula $C_{27}H_{32}F_2N_8$ and a molecular weight 506.59. The chemical name for abemaciclib is 2-Pyrimidinamine, *N*-[5-[(4-ethyl-1-piperazinyl)methyl]-2-pyridinyl]-5-fluoro-4-[4-fluoro-2-methyl-1-(1-methylethyl)-1*H*-benzimidazol-6-yl]-.

8.1.2 Clinical Pharmacology

Abemaciclib is an inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6). These kinases are activated upon binding to D-cyclins. In estrogen receptor-positive (ER+) breast cancer cell lines, cyclin D1 and CDK4/6 promote phosphorylation of the retinoblastoma protein (Rb), cell cycle progression, and cell proliferation. In vitro, continuous exposure to abemaciclib inhibited Rb phosphorylation and blocked progression from G1 into S phase of the cell cycle, resulting in senescence and apoptosis. In breast cancer xenograft models, abemaciclib dosed daily without interruption as a single agent or in combination with antiestrogens resulted in reduction of tumor size.

8.1.3 Pharmacokinetics and Drug Metabolism

Following single and repeated twice daily dosing of 50 mg (0.3 times the approved recommended 150 mg dosage) to 200 mg of abemaciclib, the increase in plasma exposure (AUC) and Cmax was approximately dose proportional. Steady state was achieved within 5 days following repeated twice daily dosing, and the estimated geometric mean accumulation ratio was 2.3 (50% CV) and 3.2 (59% CV) based on Cmax and AUC, respectively.

Hepatic metabolism is the main route of clearance for abemaciclib. Abemaciclib is metabolized to several metabolites primarily by cytochrome P450 (CYP) 3A4, with formation of N-desethylabemaciclib (M2) representing the major metabolism pathway. Additional metabolites include hydroxyabemaciclib (M20), hydroxy-N-desethylabemaciclib (M18), and an oxidative metabolite (M1). M2, M18, and M20 are equipotent to abemaciclib

and their AUCs accounted for 25%, 13%, and 26% of the total circulating analytes in plasma, respectively.

After a single 150 mg oral dose of radiolabeled abemaciclib, approximately 81% of the dose was recovered in feces and approximately 3% recovered in urine. The majority of the dose eliminated in feces was metabolites.

8.1.4 Supplier

Abemaciclib is an investigational agent for this trial and will be supplied by Lilly Oncology, free of charge to the patient.

8.1.5 Dosage Form and Preparation

Abemaciclib is available in 50 mg tablets.

8.1.6 Storage and Stability

Abemaciclib must be stored at room temperature. For specific storage, instructions refer to the product label.

8.1.7 Administration

Abemaciclib will be taken by mouth twice daily at the assigned dose.

8.2 Nivolumab (Opdivo)

8.2.1 Nivolumab Description

Nivolumab is a programmed death receptor-1 (PD-1) blocking antibody indicated for the treatment of patients with:

- BRAF V600 wild-type unresectable or metastatic melanoma, as a single agent
- BRAF V600 mutation positive unresectable or metastatic melanoma, as a single agent
- Unresectable or metastatic melanoma, in combination with ipilimumab
- Metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy
- Advanced renal cell carcinoma who have received prior anti-angiogenic therapy
- Classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation and post-transplantation brentuximab vedotin
- Recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy

It is a human monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Nivolumab is an IgG4 kappa immunoglobulin that has a calculated molecular mass of 146 kDa.

8.2.2 Clinical Pharmacology

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

8.2.3 Pharmacokinetics and Drug Metabolism

The pharmacokinetics (PK) of nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. Nivolumab clearance decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of approximately 24.5% (47.6%) resulting in a geometric mean steady state clearance (CLss) (CV%) of 8.2 mL/h (53.9%); the decrease in CLss is not considered clinically relevant. The geometric mean volume of distribution at steady state (Vss) (CV%) is 6.8 L (27.3%), and geometric mean elimination half-life is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks.

8.2.4 Supplier

Nivolumab is commercially available and is listed in the compendia and NCCN Practice Guidelines as indicated for the therapy of RM-HNSCC.

8.2.5 Dosage Form and Preparation

Nivolumab will be provided as a 100 mg/10 mL (10 mg/mL) solution in a single-use vial.

- Withdraw the required volume of nivolumab and transfer into an intravenous container.

- Dilute nivolumab with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP, to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials of nivolumab.

8.2.6 Storage and Stability

The product does not contain a preservative.

After preparation, store the nivolumab infusion either:

- at room temperature for no more than 8 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or
- under refrigeration at 2°C to 8°C (36°F-46°F) for no more than 24 hours from the time of infusion preparation.

Do not freeze.

8.2.7 Administration

Administer the infusion over 30 minutes through an intravenous line containing a sterile, nonpyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer).

Do not coadminister other drugs through the same intravenous line.

Flush the intravenous line at end of infusion.

9.0 CORRELATIVE STUDIES

9.1 Tumor Tissue (Phase II patients only)

9.1.1 Collection of Specimens

Archived tumor tissue (10 to 15 slides; preferably from the relapsed setting) will be collected at baseline.

If the patient consents, fresh tumor tissue will be collected at baseline and then during Cycle 2 (between days 8-22) of abemaciclib and nivolumab. Tumor tissue should be preferentially collected from the primary tumor site or regional neck nodes if possible, but a distant metastatic deposit is an alternative. If possible, the same site should be biopsied at baseline and during cycle 2. The biopsy should consist of a minimum of 4 needle cores (14-18 gauge is preferred) or 2 (each 4 x 4 x4 mm) pieces of tumor.

9.1.2 Storage of Specimens

Fresh tumor tissue will be transported immediately to the Puram Lab, Monday-Friday, 8AM-6PM. Please notify the Puram lab, the Fehniger lab and Dr. Miriam Jacobs prior to submission. Sample collections that are outside those hours should be directly discussed with Dr. Jacobs at least 72 hours in advance.

Attention: Puram Lab / Ashley Reeb Schappe
WU-Genetics 6th floor, Couch Research Building
4515 McKinley Ave
St. Louis, MO 63110
Lab PI: (617) 721-6744

For some assays, cells will be isolated and used immediately for single cell or single nuclei isolation and preparation, with library generation using the droplet-based 10X genomics platform. Tissues will be de-identified with no PHI included on sample vials. Single cell preparations will then undergo library preparation and sequencing at the McGovern Genome Institute, with analysis by investigators at MGI. These single cell preparations may also be stored for future research as new scientific methods arise in the field.
In other assays, samples will be isolated, cryopreserved and stored in the Fehniger Lab (6th floor southwest tower building) in liquid nitrogen or -70^{o}C freezers for future batch analysis. Serum cytokine measurements, NK and T cell function (degranulation, cytotoxicity, cytokine-production, proliferation, survival) are planned. These cryopreserved samples may also be stored for future research as new scientific findings arise in the field.

9.1.3 Analysis of Specimens

Tumor biopsies (core or excisional/incisional) will be used to perform whole exome sequencing (WES), RNAseq, $p16^{INK4a}$ expression, Ki-67 by IHC, total and phospho-Rb by IHC, Cyclin D1 by IHC, Cyclin E by IHC, Cyclin A by IHC, cdk2 by IHC, p53 by IHC, p21 by IHC, p27 by IHC, and TUNEL assay. Deep phenotyping of tumor immune microenvironment with mass spectrometry (CyTOF) and IHC to determine potential markers to predict response to therapy and/or resistance mechanisms. Reverse phase protein array (RPPA) will be performed. RPPA is a high-throughput antibody-based technique developed for Functional Proteomics studies to evaluate protein activities in signaling networks. Additional analyses of other potential biomarkers may be performed as they emerge from the scientific understanding of abemaciclib and nivolumab activity.

9.2 Peripheral Blood (Phase II patients only)

9.2.1 Collection of Specimens

Peripheral blood will be collected at baseline, at the end of the Lead In (Cycle 1 Day 1 prior to treatment),during cycle 2 (between days 8-22), and during cycle 3 (between days 21-28), on all patients. If patient does not have progression after cycle 3, patient will also have peripheral blood collected at time of progression. Peripheral blood will be collected by standard venous phlebotomy. At each timepoint mentioned above, sixty mL of anti-coagulated blood will be collected in 3 sodium heparin green top tubes (45mL), one red top tube (5mL) and 1 streck (tiger top) tube (10 mL).

9.2.2 Storage and Processing of Specimens

Peripheral blood will be transported immediately to the Fehniger Lab, Monday-Friday, 8AM-6PM. Please notify the Fehninger lab and Dr. Miriam Jacobs prior to submission. Sample collections that are outside those hours should be directly discussed with Dr. Jacobs at least 72 hours in advance.

Attention: Fehniger Lab / Michelle Becker-Hapak or Tim Schappe
WU-Oncology 7th floor, Southwest Tower Building, Room 724
4940 Parkview Place
St. Louis, MO 63110
Lab: (314) 273-0156 / Secondary: (314) 747-1547 / Tertiary: (314) 747-1385 or (314) 510-2397 (pager)
Fax: (314) 362-9333

For some assays, cells will be isolated and used immediately. In other assays, samples will be isolated, cryopreserved and stored in the Fehniger Lab (7th floor southwest tower building) in liquid nitrogen or -70^{o}C freezers for future batch analysis. No PHI is included on the sample vials. Serum cytokine measurements, NK and T cell function (degranulation, cytotoxicity, cytokine-production, proliferation, survival) are planned. These samples may also be stored for future research as new scientific findings arise in the field.

9.3 Quality of Life (Phase II patients only)

The EORTC QLQ-30 (Appendix B) and FACT H&N (Appendix C) will be given at the following time-points:

- Screening
- Cycle 2 D1
- Cycle 4 D1
- End of treatment (EOT)

10.0 STUDY CALENDAR

Screening evaluations and baseline procedures are to be conducted within 21 days prior to date of enrollment, with the exception of scans which can be within 28 days prior to date of enrollment.

	Screening	Baseline	Lead-In	Cycle 1: Day 1 (+/- 2 days)	Cycle 1: Day 15 (+/- 2 days)	Cycle 2+: Day 1 (+/- 2 days)	EOT	F/U[i]
Physical exam	X		X	X	X	X	X	
Vitals signs	X		X	X	X	X	X	
Performance status	X		X	X	X	X	X	
AE assessment	X		X	X	X	X	X	
CBC	X		X	X	X	X[j]	X	
Chemistry panel[a], LFTs[b]	X			*	X	X	X	
Pregnancy test	X						X	
PT/INR; PTT	X							
Research blood		X		X[c]		X[c]	X	
QOLs		X				X[g]	X	
Archival tissue		X						
Biopsy		X[d]				X[d]		
Tumor assessment	X					X[h]	X	
Abemaciclib			X[e]	X[f]	X[f]	X[f]		
Nivolumab				X		X		

[*] Screening CMP will be used for C1D1 of abemaciclib & nivolumab treatment

[a] Chemistry includes Ca, Mg, K, Na, glucose, albumin, urea, and creatinine.

[b] LFTs include ALT, AST, alkaline phosphatase, and total bilirubin.

[c] Peripheral blood (5 tubes, see correlatives section) to be collected at baseline, Cycle 1 Day 1 prior to treatment, C2 D8-22, C3 D21-28, and EOT.

[d] Optional. If patient consents, collect at baseline and C2 D8-22.

[e] Lead In. Will be administered po on Day -7 through Day -1.

[f] Will be administered po on Days 1-28

[g] Cycle 2 day 1 and Cycle 4 Day 1 only.

[fh] Tumor assessments with CT will be performed at screening and every 12 weeks (3 cycles). All patients must have neck and chest CT; patients with liver metastases also require abdominal CT. Confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

[i] Patients will be followed for 28 days post treatment for AEs and until death for OS objective.

[j] CBC at Cycle 2 Day 15.

11.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form	Prior to starting treatment
Treatment Form	Every cycle
Toxicity Form	Continuous
Treatment Summary Form	Completion of treatment
Follow Up Form	28-day follow-up
Tumor Measurement Form	Baseline, end of every 4th cycle, and end of treatment
Research Specimen Form	Baseline, if patient consents – Cycle 2
QOL Form	Baseline, C2, C4 EOT
MedWatch Form	See Section 7.0 for reporting requirements

12.0 MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 12 weeks. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm by chest x-ray, as >10 mm with CT scan, or >10 mm with ruler or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using ruler or calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual

lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

12.4 Response Criteria

12.4.1 Evaluation of Target Lesions

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

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions). Please note that disease progression will be determined using CT imaging and not PET imaging. That is, if a CT scan shows progression by RECIST criteria, the patient will be determined to have progressed regardless of the results of the PET scan; however, if a PET scan shows disease progression while a CT scan does not, the patient's disease will be determined to have progressed only if there are physical examinations signs or symptoms that are consisted with disease progression as judged by the treating physician and principal investigator.

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

12.4.2 Evaluation of Non-Target Lesions

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

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or

maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once >4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

12.4.4 Definition of Modified Partial Response

In the phase I trial of pazopanib and cetuximab, 39% of patients developed cavitation of target and non-target lesions while on therapy. In these cases, FDG-PET/CT showed findings consistent with mPR or mCR by PERCIST[50]. Cavitation only occurred in pulmonary sites of disease. The cavitating lesions usually did not decrease in dimensions but clearly decreased in tumor volume. Although these cases were scored as stable disease by RECIST, they correlated with prolonged PFS as did cases of PRs by RECIST.

As such, patients on this trial who develop cavitation of pulmonary metastases without decrease in measurement will be scored as modified PR and summed with other cases of PRs by RECIST as long as no new target or non-target lesions appear and as long as the cavitating lesion does not enlarge by $\geq$ 20%. A confirmatory tumor response assessment will be required, as noted earlier for PR by RECIST.

12.4.5 Duration of Response

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

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

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

13.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least five patients have been enrolled) or one year after accrual has opened (if fewer than five patients have been enrolled at the six-month mark).

During phase I, the Principal Investigator will review all patient data at least monthly (or before each dose de-escalation if occurring sooner than monthly), and provide a semi-annual report to the Quality Assurance and Safety Monitoring Committee (QASMC). During phase II, the Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date and accrual by cohort
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities separated by cohorts with the number of dose-limiting toxicities indicated
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

14.0 STATISTICAL CONSIDERATIONS

14.1 Study Design

This is an open-label, single center, one arm, Phase I/II study. The aim is to investigate the safety and efficacy of combining abemaciclib + nivolumab in patients with RM-HNSCC. In Phase I, a dose de-escalation design will be applied. In Phase 2, the one-year OS of the study group will be compared to a known historical control (i.e., null hypothesis).

14.2 Study Endpoints

Primary endpoints are (a) Phase I: safety as measured by establishment of DLT, MTD and RP2D and (b) Phase II: OS. Secondary endpoints include best tumor response, duration of tumor response, AEs, and PFS. The exploratory endpoint includes QOL scores.

14.3 Study Population

Patients with RM-HNSCC will be enrolled and will receive abemaciclib + nivolumab. The Phase I trial will enroll up to 9 patients. For the Phase II trial, a total of 23 patients with be enrolled.

14.4 Accrual

Based on historical experience at this institution, we expect to accrue 4 patients per month to phase I and 1-2 patients per month to phase II, completing accrual to phase I in 3 months, and completing accrual to phase II in 18 months.

14.5 Power Analysis

Power analysis is not applicable for the Phase I trial.

Phase II: The primary endpoint is OS and the secondary endpoints include best tumor response rate, duration of tumor response, AEs, PFS and QOL scores. The sample size calculation is based on the primary endpoint only. Prior data suggests one-year survival probability for the patients treated with nivolumab is 36%[2]. With an accrual interval of 18 months and additional follow-up of 18 months after the accrual interval, 18 patients will have 80% power to detect the survival difference if one-year survival probability for the patients treated with abemaciclib plus nivolumab is 60% using a one-sided test at the type I error of 5%[13]. An additional 5 patients will be accrued for a total of 23 patients to address patients who enroll but either do not proceed on study, complete less than one cycle of therapy due to causes other than disease progression or adverse events, or are lost to follow-up.

14.6 Data Analysis

All data will be evaluated as observed, and no imputation method for missing values will be used.

Descriptive statistics will be used to summarize the trial results, i.e., statistics for continuous variables may include means, medians, ranges and appropriate measures of variability. Qualitative variables will be summarized by counts and percentages. The uncertainty of estimates will be assessed by confidence intervals (CIs).

OS is defined as the time from the date of treatment to the date of death, censored at the last follow-up otherwise. PFS is defined as the time from treatment to the date of progression or death, whichever occurs first. The alive patients without progression is censored at the last follow-up. The Kaplan-Meier method will be used to calculate the probability of OS and PFS at specific time points, e.g. one-year. Best rumor response rate and associated 95% confidence intervals will be calculated assuming a binomial distribution. Duration of response will be summarized by dose using the minimum, 25th percentile, median, 75th percentile, and maximum values. AEs and SAEs occurring during each cycle will be summarized by patient, dose, type and grade with 95% CIs. Frequencies for the full treatment period will be summarized in the same manner. Descriptive statistics will be used to report tissue and blood specimens. In phase II, the QOL assessment tools (EORTC QLQ-C30 and FACT-H&N) will be performed at baseline and after cycle 3 of therapy. Scoring of each tool will be performed using the published guidelines established for each tool. Median scores for each item and domain will be reported at each time point. Reporting will be descriptive and will not test a specific QOL hypothesis.

14.7 Stopping Rules (Phase I)

For Phase I, using the dose de-escalation design, three patients will be initially enrolled into the highest dose cohort (i.e., abemaciclib starting dose). If there are no patients or only one patient experiencing DLTs, the RDP2 is established and enrollment to phase I stops. If two or more patients experience DLTs, de-escalation to the next lower dose level will occur. Phase I will be halted if two or more patients experience DLTs at the lowest dose level. Twelve is the maximum number of patients that could be enrolled in Phase I.

15.0 REFERENCES

1. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus Cetuximab in head and neck cancer. N Engl J Med. 2008;359:1116-27.
2. Ferris RL, Blumenschein Jr. G, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2016;375:1856-67.
3. Network CGA. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature.* 2015;517(7536):576-582.
4. Michel L, Ley J, Wildes TM, et al. Phase I trial of Palbociclib, a selective cyclin dependent kKinase 4/6 inhibitor, in combination with Cetuximab in patients with recurrent/metastatic head and neck squamous cell carcinoma. Oral Oncol. 2016;58:41-8.
5. Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH1: Results from a phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as monotherapy, in patients with HR+/HER2- breast cancer, after chemotherapy for advanced disease. J Clin Oncol. 2016;34:supplement abstract 510.
6. Patnaik A, Rosen LS, Tolaney SM, et al. Efficacy and safety of abemaciclib, an inhibitor of CDK4 and CDK6, for patients with breast cancer, non–small cell lung cancer, and other solid tumors. Cancer Discov. 2016;6:740-53.
7. Gelbert LM, Cai S, Lin X, et al. Preclinical characterization of the CDK4/6 inhibitor LY2835219: In-vivo cell cycle-dependent/independent anti-tumor activities alone/in combination with gemcitabine. Invest New Drugs. 2014;32:825-37.
8. Lallena MJ, Boehnke K, Torres R, et al. In-vitro characterization of abemaciclib pharmacology in ER+ breast cancer cell lines. Cancer Res. 2015;75:suppl abstract nr3101.
9. Pfizer: Ibrance package insert. http://labeling.pfizer.com/ShowLabeling.aspx?id=2191
10. Novartis Pharmaceuticals: Kisquali package insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209092s000lbl.pdf
11. Sledge Jr. GW, Toi M, Neven P, Sohn J, et al. MONARCH2: Abemaciclib in combination with fulvestrant in women with HR+/HER2- Advanced breast cancer who had progressed while receiving endocrine therapy. J Clin Oncol. 2017;35(25):2875-84.
12. Goel S, DeCristo MJ, Watt AC, et al. CDK4/6 inhibition triggers anti-tumor immunity. Nature. 2017;548(7668):471-5.
13. Lawless, JF. Statistical Models and Methods for Lifetime Data. 2nd ed. John Wiley & Sons, 2003.

APPENDIX A: ECOG Performance Status Scale

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

APPENDIX B: EORTC QLQ-C30

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

	Not at All	A Little	Quite a bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4

25. Have you had difficulty remembering things?	**1**	**2**	**3**	**4**
26. Has your physical condition or medical treatment interfered with your family life?	**1**	**2**	**3**	**4**
27. Has your physical condition or medical treatment interfered with your social activities?	**1**	**2**	**3**	**4**
28. Has your physical condition or medical treatment caused you financial difficulties?	**1**	**2**	**3**	**4**

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	**2**	**3**	**4**	**5**	**6**	**7**
Very Poor						**Excellent**

30. How would you rate your overall quality of life during the past week?

1	**2**	**3**	**4**	**5**	**6**	**7**
Very Poor						**Excellent**

APPENDIX C: FACT-H&N

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
H&N1	I am able to eat the foods that I like	0	1	2	3	4
H&N2	My mouth is dry	0	1	2	3	4
H&N3	I have trouble breathing	0	1	2	3	4
H&N4	My voice has its usual quality and strength	0	1	2	3	4
H&N5	I am able to eat as much food as I want	0	1	2	3	4
H&N6	I am unhappy with how my face and neck look	0	1	2	3	4
H&N7	I can swallow naturally and easily	0	1	2	3	4
H&N8	I smoke cigarettes or other tobacco products	0	1	2	3	4
H&N9	I drink alcohol (e.g. beer, wine, etc.)	0	1	2	3	4
H&N 10	I am able to communicate with others	0	1	2	3	4
H&N 11	I can eat solid foods	0	1	2	3	4
H&N 12	I have pain in my mouth, throat or neck	0	1	2	3	4

APPENDIX D: Medication Diary (for Lead In week, block out Days 8-28)

Today's Date: _____ Agent: abemaciclib Cycle: _____ Study ID#: _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each month. Take _____mg of abemaciclib at approximately the same times each day with or without food. Swallow the capsules whole and do not chew them.
2. Record the date, the number of capsules taken, and when you took them.
3. If you have any questions or notice any side effects, please record them in the comments section. Record the time if you should vomit.
4. Please return the forms to your physician or your study coordinator when you go to your next appointment. Please bring your unused study medications and/or empty bottles with you to each clinic visit so that a pill count can be done.
5. Avoid St. John's Wort, Seville oranges, grapefruit, grapefruit juice, grapefruit hybrids, pummelos, and exotic citrus fruits from 7 days before you start taking abemaciclib and throughout the entire study.

Day	Date	What time was dose taken?		# of capsules taken, if applicable		Comments
		AM dose	PM dose	AM dose	PM dose	
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						