Los Tres Paso Trial:
Step One – Neoadjuvant Palbociclib Monotherapy,
Step Two – Concurrent Chemoradiation Therapy, and
Step Three – Adjuvant Palbociclib Monotherapy
in Patients with p16^{INK4a} Negative, HPV-Unrelated Head and Neck Squamous Cell Carcinoma

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Protocol Revision History

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Amendment #2 Version	**01/24/2019**
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Glossary of Abbreviations

AE	Adverse event
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
AUC	Area under the curve
CBC	Complete blood count
CFR	Code of Federal Regulations
CMP	Comprehensive metabolic panel
CR	Complete response
CRF	Case report form
CRT	Chemoradiation
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DAI	Dosage and administration instructions
DC	Disease control
DFS	Disease-free survival
DLT	Dose limiting toxicity
DNA	deoxyribonucleic acid
DSM	Data and Safety Monitoring
ECG (or EKG)	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FOE	Fiberoptic endoscopy
HDPE	High-density polyethylene
HIV	Human Immunodeficiency Virus
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papilloma virus
HRPO	Human Research Protection Office (IRB)
HSR	Hypersensitivity reaction
IHC	Immunohistochemistry
IMRT	Intensity-modulated radiation therapy
IND	Investigational New Drug
INR	International normalized ratio
IPM	Investigational Product Manual
IRB	Institutional Review Board
ISH	In situ hybridization
IULN	Institutional upper limit of normal
IV	Intravenous

IVPB	IV piggyback
mDLx	Microlaryngoscopy
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCCN	National Cancer Center Network
NCI	National Cancer Institute
NEJM	New England Journal of Medicine
NIH	National Institutes of Health
NS	Normal saline
OHRP	Office of Human Research Protections
OPSCC	Oropharyngeal squamous cell carcinoma
OR	Overall response
OS	Overall survival
PD	Progressive disease
PEG	Percutaneous endoscopic gastrostomy
PET	Positron emission tomography
PFS	Progression-free survival
PI	Principal investigator
POACRT	Post-operative adjuvant CRT
PR	Partial response
PS	Performance status
PT	Prothrombin time
PTS	Primary tumor site
PTT	Partial thromboplastin time
QASMC	Quality Assurance and Safety Monitoring Committee
QOL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors (Committee)
RM	Recurrent/metastatic
RNA	Ribonucleic acid
RPPA	Reverse phase protein array
RT	Radiation therapy
RTOG	Radiation Therapy Oncology Group
SAE	Serious adverse event
SCC	Siteman Cancer Center
SD	Stable disease
TTP	Time to progression
UPN	Unique patient number

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1.0 BACKGROUND AND RATIONALE

1.1 Head and Neck Squamous Cell Carcinoma (HNSCC)

HNSCC is the sixth most common cancer with over 50,000 new cases diagnosed each year in the USA and 600,000 new cases each year worldwide[7]. Most patients present with stage III-IV, non-metastatic disease that is due to smoking and unrelated to the human papillomavirus (HPV). Compared to HPV-related oropharyngeal squamous cell carcinoma (OPSCC), patients with HPV-unrelated HNSCC are older, smoke more, and have a less favorable prognosis[8].

Acceptable treatment options for these patients include definitive chemoradiation therapy (CRT), surgery followed by post-operative adjuvant CRT (POA[C]RT), or induction chemotherapy followed by CRT. Although there is general agreement that all three approaches result in similar outcomes, in actual practice, most patients are treated with definitive CRT. This pattern reflects the fact that most of these patients are treated in the community setting where definitive CRT is widely practiced, but surgery and induction chemotherapy are not.

1.2 Definitive CRT Options and Efficacy Outcomes

Cisplatin or cetuximab are the two most common agents given concurrently with definitive radiation therapy (RT). Cisplatin is the gold standard systemic therapy recommended to be given concurrently with RT. Either high-dose bolus (100 mg/m^2 cisplatin on Days 1, 22, and 43 of once daily RT or 100 mg/m^2 cisplatin on Days 1 and 22 of accelerated RT) or weekly (40 mg/m^2) cisplatin regimens are recommended in the NCCN practice guidelines[9]. Cetuximab, a taxane, or 5-FU added to cisplatin and RT are no better than cisplatin monotherapy and RT[10,11.] However, cisplatin results in substantial acute toxicity (mucositis, renal dysfunction, vomiting) and can only be administered safely to patients with normal renal function, good performance status, and low comorbidity index.

Cetuximab and RT has emerged over the last decade as an alternative to cisplatin and RT, based on the results of the Bonner Trial (NEJM) which found that cetuximab and RT was more efficacious than RT alone[6]. Also, cetuximab did not increase the risk of mucositis compared with RT alone and was not associated with renal dysfunction or vomiting.

Although there have been no published head-to-head comparisons of cetuximab and RT vs cisplatin and RT, the absolute magnitude of the improvement in overall survival (OS) (10%) with cetuximab and RT was comparable to historical data with cisplatin and RT. However, controversy exists as to whether the efficacy of cetuximab and RT is as good as cisplatin and RT. Several retrospective reports showed better efficacy outcomes with cisplatin and RT.[12,13] The ongoing RTOG 1016 trial is comparing the efficacy and tolerance of these two CRT regimens in patients with HPV-related OPSCC. Similar studies are not planned or ongoing in patients with HPV-unrelated HNSCC.

Based on the controversy surrounding the comparability of these two CRT regimens, current practice at most programs is to route HNSCC patients with excellent performance status and adequate vital organ function to receive CRT with high dose bolus cisplatin. However, it is feasible to administer cetuximab but not cisplatin to a broader mix of patients, particularly those with reduced renal function, poor performance status, and a high comorbidity index. As such, cetuximab has been widely selected over cisplatin to be combined with RT for HNSCC patients with reduced performance status and/or vital organ function.

The efficacy of CRT in patients with locally advanced $p16^{INK4a}$ negative/HPV-unrelated HNSCC[1-3] is surprisingly modest with a substantial risk of disease recurrence and death. RTOG 0129 and RTOG 91-11 provide reference points for efficacy of CRT using cisplatin[1-3]. In patients with $p16^{INK4a}$ negative OPSCC, RTOG 0129 found that CRT with cisplatin resulted in three-year OS of 57%, progression-free survival (PFS) 43%, local-regional failure rate 52%, and distant metastasis rate of 16%[3]. In patients with larynx SCC, RTOG 91-11 found that CRT with cisplatin resulted in two-year OS of 74%, DFS 61%, local-regional failure rate 20%, and distant metastases rate of 8%. The poorest outcomes occur in the infrequent subset of patients with hypopharynx SCC where the 5-year OS was 38% and the local-regional and distant failure rate was 60%[4-5]. The Bonner trial provides reference points for the efficacy of CRT using cetuximab[6]. The two-year local-regional failure rate was 50%, the distant metastases rate was 16%, and the median OS varied based on sub-site: 32 months for larynx SCC, 24 months for $p16^{INK4a}$ negative OPSCC, and 13 months for hypopharynx SCC.

In the pool of patients with $p16^{INK4a}$ negative/HPV-unrelated HNSCC, larynx SCC, and hypopharynx SCC, the majority (> 90%) of relapse events occur within 18 months of completion of CRT using either cisplatin or cetuximab.

1.3 Biology of $p16^{INK4a}$ negative (HPV-unrelated) HNSCC

HNSCC is a heterogeneous disease[14,15]. Based on unique gene expression signatures, at least four subgroups have been defined, each with distinct signaling pathways[14-21]. Despite this heterogeneity, aberrant cell cycle regulation is a ubiquitous event. The mechanism underlying unrestrained proliferation varies depending on the tumor's transcriptionally-active HPV status. In HPV-related HNSCC, E7 viral protein drives unrestrained proliferation by promoting Rb degradation[22]. In HPV-unrelated HNSCC, Rb inactivation occurs through hyper-activation of the Rb inhibitory complex CDK4/cyclin D. CCND1 (encoding cyclin D1, the regulatory subunit of the complex) is amplified and/or the CDK4/6 inhibitor $p16^{INK4a}$ is inactivated in nearly all of these cancers[23-25]. Alterations of CCND1 and $p16^{INK4a}$ are rare in HPV-related HNSCC. As a result, $p16^{INK4a}$ is overexpressed in HPV-related HNSCC and under expressed in HPV-unrelated HNSCC.

The genetics of HPV-unrelated HNSCC influences the clinical course. CCND1 amplification and $p16^{INK4a}$ inactivation are poor prognostic factors in HNSCC[3,24], in part because cyclin D1 overexpression adversely affects tumor response to EGFR inhibitors and cisplatin. In HNSCC cell lines, cyclin D1 amplification and/or overexpression

correlated with resistance to these drugs[26-28]. Studies in HNSCC reveal that cyclin D1 overexpression is predictive of resistance to cisplatin[29].

1.4 Selective CDK4/6 Inhibition with Palbociclib

The essential roles of CDK4/6 and cyclin D1 in driving cell cycle progression from G1 into S phase motivated intense investigation into blocking this regulatory complex[30-32]. In pre-clinical models, CDK4/6 inhibition inhibits both Rb hyperphosphorylation and cell cycle progression[33], and the efficacy of inhibition in some models correlated with increased cyclin D1 and decreased $p16^{INK4a}$ expression[32]. Palbociclib is the first approved selective inhibitor of the CDK4/6 kinases. Palbociclib exerts potent anti-proliferative effects on Rb-positive cell lines and human breast and colon xenografts[31]. Palbociclib results in decreased Rb phosphorylation and Ki-67 expression in Rb-positive models but has no activity in Rb-negative tumor xenografts[31]. As such, phase I trials restricted the evaluation of palbociclib to patients with Rb-positive cancers[32,33]. These studies determined that the dose-limiting toxicity (DLT) of palbociclib was neutropenia and the maximum tolerated dose (MTD) was 125 mg once daily, administered for 21 days of each 28 day cycle[34,35]. The efficacy of palbociclib was demonstrated in estrogen receptor positive breast cancer[36] and in mantle cell lymphoma[37], tumors in which cyclin D contributes to their pathogenesis.

1.5 Palbociclib and Cetuximab in Recurrent/Metastatic HNSCC

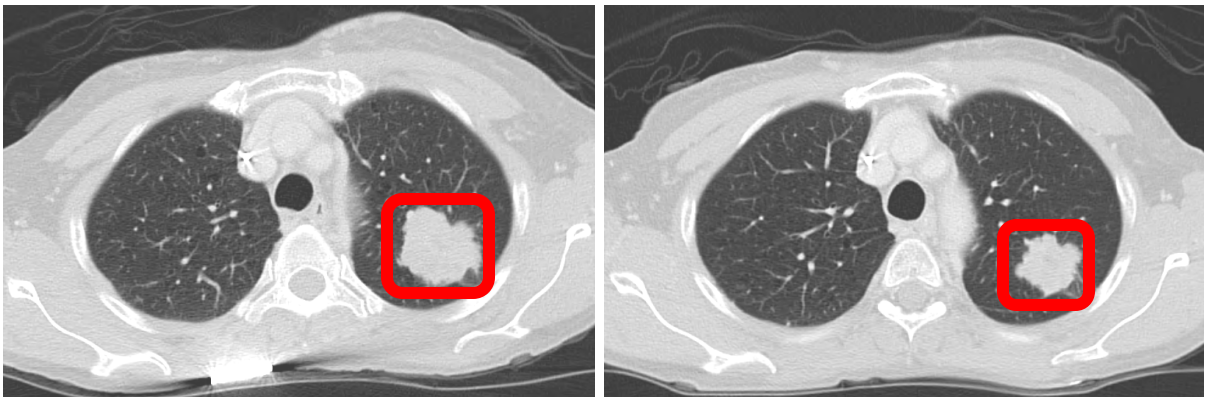
Because the genetics of HNSCC suggest a crucial role for CDK4/cyclin D in this disease, we performed a phase I trial to determine the DLT and MTD of palbociclib combined with standard weekly doses of cetuximab in patients with recurrent/metastatic (RM) HNSCC. We built upon the cetuximab platform because palbociclib targets a pathway associated with resistance to EGFR inhibitors[26].

A phase I trial using 3+3 design was performed to determine the DLT and MTD of palbociclib with standard dose weekly cetuximab.[38] Palbociclib was administered orally Days 1-21 every 28 days at dose level 1 (100 mg/d) and 2 (125 mg/d, the approved monotherapy dose). Pharmacokinetic assessments were performed on Cycle 2 Day 15. Cyclin D1, $p16^{INK4a}$, and Rb protein expression were measured on pre-treatment tumor. Tumor response was assessed using RECIST 1.1.

Nine patients (five $p16^{INK4a}$ negative; four positive) were enrolled across dose levels 1 (n=3) and 2 (n=6) and none experienced a DLT. A MTD of palbociclib was not reached. Myelosuppression was the most common adverse event. Six of nine patients had cetuximab-resistant and four of nine had platin-resistant disease. Disease control (DC) occurred in 89%, including partial response (PR) in two (22%) and stable disease in six (67%) patients. PRs occurred in $p16^{INK4a}$ negative HNSCC. Five patients (56%) had measurable decreases in tumor target lesions. In cetuximab-resistant HNSCC, best tumor response was PR in 1 and DC in 5 and median time to progression (TTP) was 112 days (range: 28-168). In platin-resistant HNSCC, best tumor response was PR in 1, DC in 3 and median TTP was 112 days (range: 28-112). The tumor response of two patients and the waterfall plot of best overall change in tumor target lesions are shown:

CT images of partial tumor response after two cycles of palbociclib and cetuximab in patient 4 (Dose Level 2) with $p16^{INK4a}$ negative hypopharynx SCC and…

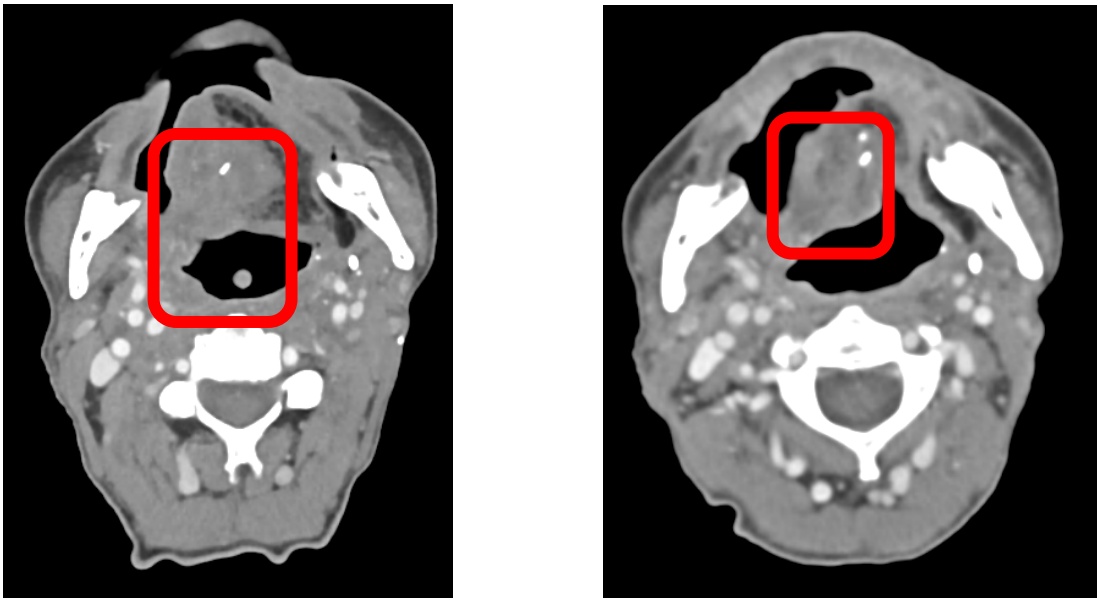
Baseline **After Cycle 2**



Target Lesion: 4.0 cm Target Lesion: 2.7 cm

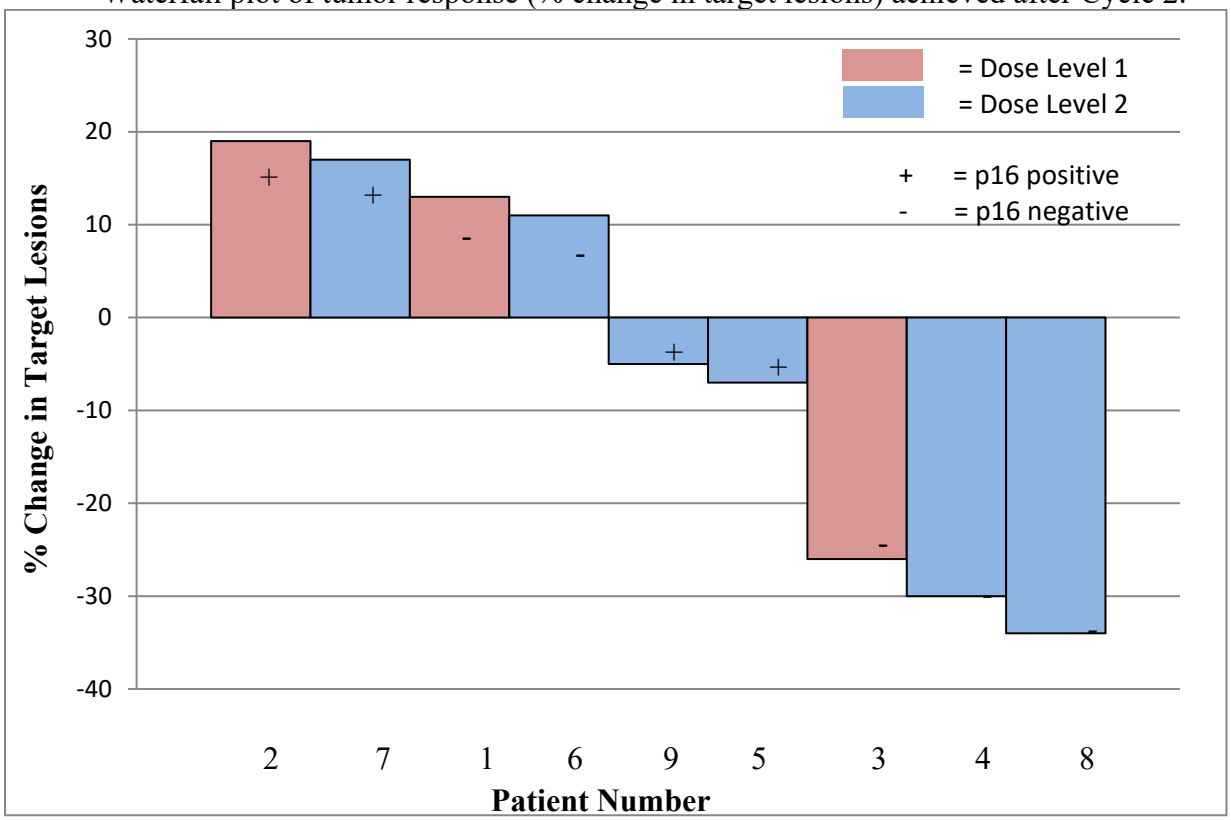
…patient 8 (Dose Level 2) with $p16^{INK4a}$ negative oral cavity SCC

Baseline **After Cycle 2**



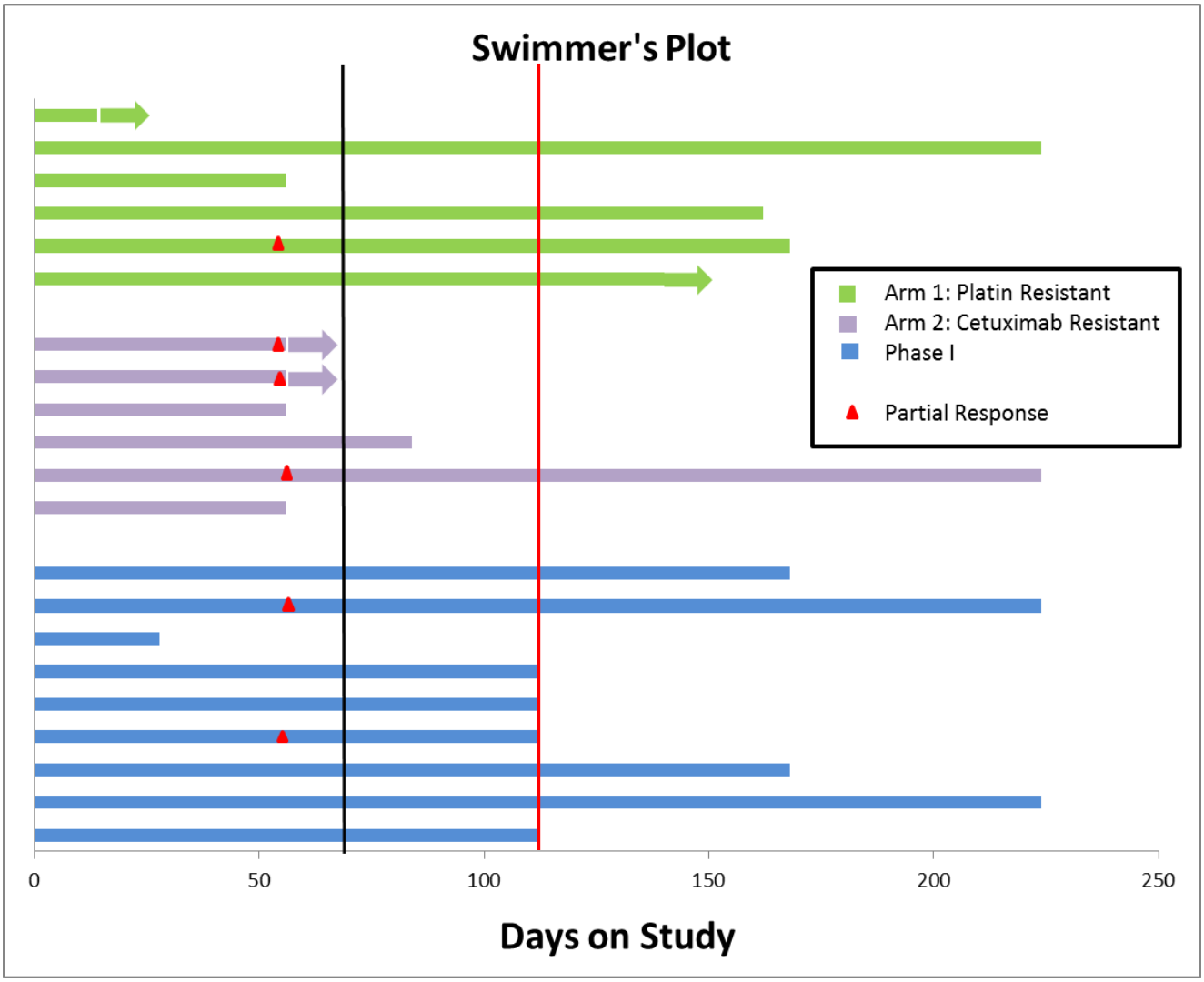
Target Lesion: 4.6 cm Target Lesion: 2.8 cm

Waterfall plot of tumor response (% change in target lesions) achieved after Cycle 2.



Time-to-best tumor response occurred by Day 56 (end of Cycle 2) in all cases.

Upon completion of the enrollment on the phase I trial, patients are currently being enrolled on the phase II component of the protocol, in which patients with platin-refractory HNSCC (Cohort 1) or cetuximab-refractory HNSCC (Cohort 2) are treated with palbociclib and cetuximab. Preliminary results of the phase II trial along with the phase I trial results are shown in the Swimmer's Plot below. As can be seen, the median TTP with palbociclib and cetuximab is longer than that of a historical cohort treated with cetuximab monotherapy.[39]



Swimmer's plot showing the TTP for each patient treated with palbociclib and cetuximab. Patients treated on phase I are colored in blue. Patients treated on phase II are divided by cohort: platin-resistant in green and cetuximab-resistant in lavender. Partial tumor responses are noted with a red triangle. The vertical black line is the historical median TTP to cetuximab monotherapy and the vertical red line is the median TTP with palbociclib and cetuximab based on the phase I data.

This trial, the first to evaluate a CDK4/6 inhibitor in HNSCC, determined that palbociclib 125 mg/day on days 1-21 every 28 days with cetuximab was safe. Tumor responses were observed, even in cetuximab- or platin-resistant disease.

2.0 OBJECTIVES

2.1 Primary Objective

Determine the tumor response rate of newly diagnosed $p16^{INK4a}$ negative, HPV-unrelated

HNSCC to neoadjuvant palbociclib monotherapy given over two cycles.

2.2 Secondary Objectives

1. Determine the combined local-regional disease relapse risk and distant metastases risk at 18 months following completion of CRT.
2. Determine the median and two-year PFS and OS (stratified by cohort) of patients treated with the three step sequence of palbociclib monotherapy, CRT, and adjuvant palbociclib monotherapy.

2.3 Exploratory Objectives

1. Explore potential pharmacodynamic determinants of tumor response to palbociclib monotherapy using genomic, RNA, and protein expression methods.
2. Explore potential pharmacodynamic determinants of locoregional disease relapse risk and distant metastases risk to palbociclib-based therapy using genomic, RNA, and protein expression methods.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. Larynx SCC, hypopharynx SCC, or oral cavity SCC. HPV-unrelated OPSCC [defined as $p16^{INK4a}$ negative by IHC (staining in < 70% of cells) or HPV High Risk (Type 16 or 18) negative by ISH]. $P16^{INK4a}$ positive larynx SCC, hypopharynx SCC, and oral cavity SCC are eligible given the unknown effect of this on the biology of SCC of these subsites.
2. Overall Stage III, IVA, or IVB disease per AJCC version 7.0.
3. 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 with calipers by clinical exam.
4. At least 18 years of age.
5. Normal bone marrow function as defined below:
   a. Absolute neutrophil count ≥ 1,000/mcL
   b. Platelets ≥ 100,000/mcL
   c. Hemoglobin ≥ 9.0 g/dL
6. QTc < 500 msec by Fridericia
7. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry, for the duration of study participation, and for 90 days after completion of treatment. Should

a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

8. Ability to understand and willingness to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable).

3.1.1 Additional Cohort 1 Eligibility Criteria

Patients enrolling to Cohort 1 must meet all of the following criteria:

1. ECOG performance status 0-1 (see Appendix A).

2. Adequate organ function defined as:
   a. Serum creatinine ≤ 1.5 x IULN and creatinine clearance ≥ 75 mL/min
   b. Bilirubin ≤ 1.5 x IULN
   c. ALT and AST ≤ 2.5 x IULN

3.1.2 Additional Cohort 2 Eligibility Criteria

Patients enrolling to Cohort 2 must meet at least one of the following criteria:

1. ECOG performance status of 2 (see Appendix A)

2. Reduced organ function defined as:
   a. Creatinine clearance 30-75 mL/min; or
   b. Bilirubin 1.5-2 x IULN; or
   c. ALT and AST 2.5-5 x IULN

3.2 Exclusion Criteria

1. Diagnosis of cutaneous, paranasal sinus, salivary, or nasopharynx SCC, or diagnosis of neck nodes with unknown primary.

2. Diagnosis of P16/HPV-ISH positive OPSCC.

3. Presence of distant metastatic disease.

4. Prior systemic therapy for current diagnosis of HNSCC.

5. A history of other malignancy ≤ 2 years previous with the exception of basal cell or squamous cell carcinoma of the skin which were treated with local resection only or low risk/curatively treated prostate, thyroid, and cervical cancers.

6. Currently receiving any other investigational agents.

7. Treated within the last 7 days prior to Day 1 of protocol therapy with:

a. Food or drugs that are known to be STRONG CYP3A4 inhibitors (e.g. grapefruit juice, verapamil, ketoconazole, miconazole, itraconazole, erythromycin, clarithromycin, telithromycin, indinavir, ritonavir, nelfinavir, atazanavir, amprenavir, nefazodone, diltiazem, and delavirdine) or inducers (e.g. glucocorticoids, progesterone, rifampin, phenobarbital, St. John's wort) [moderate CYP3A4 inhibitors/inducers are okay]
b. Drugs that are known to prolong the QT interval
c. Drugs that are proton pump inhibitors

8. A history of allergic reactions attributed to compounds of similar chemical or biologic composition to palbociclib, cisplatin (for Cohort 1), or cetuximab (for Cohort 2).

9. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or uncontrolled electrolyte disorders that can compound the effects of a QTc-prolonging drug (e.g. hypocalcemia, hypokalemia, hypomagnesemia).

10. History of cirrhosis.

11. History of renal or liver transplant.

12. Pregnant and/or breastfeeding. Women of childbearing potential must have a negative serum pregnancy test within 28 days of study entry. Female patients must be surgically sterile or be postmenopausal, or must agree to use effective contraception during the period of the trial and for at least 90 days after completion of treatment.

13. Known HIV-positivity and on combination antiretroviral therapy because of the potential for pharmacokinetic interactions with palbociclib. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

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 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

"The three step" trial is a two cohort, non-randomized phase II trial in which palbociclib will be integrated into the standard CRT regimen with either cisplatin (cohort 1) or cetuximab (cohort 2). Patients with stage III-IV (non-metastatic) $p16^{INK4a}$ negative, HPV-unrelated HNSCC will be enrolled, to enrich the fraction of patients most likely to benefit from a CDK4/6 inhibitor.

During step one, patients in both cohorts will be treated with neoadjuvant palbociclib monotherapy (125 mg/day, Days 1-21 of a 28-day cycle for two cycles). A CT scan of the neck to assess tumor response and a tumor biopsy for pharmacodynamics assessment will be performed before and after palbociclib (CT scan – Cycle 2 post-treatment Day 21 through Day 25; Tumor biopsy Cycle 2 Day 21). Data will be pooled from the two cohorts to address the primary aim. The primary aim of the trial is to determine the tumor response rate (using RECIST 1.1) of newly diagnosed $p16^{INK4a}$ negative, HPV-unrelated HNSCC to palbociclib monotherapy given over two cycles, and to explore potential pharmacodynamic determinants of tumor response to palbociclib monotherapy using data derived from genomic, RNA, and protein expression methods performed on pre- and post-treatment tumor tissue.

During step two (CRT), Cohort 1 patients will be treated with cisplatin 100 mg/m^2 given on Days 1 and 22 with RT. Cohort 2 patients will be treated with cetuximab given one week before RT and then weekly during RT. Cohorts 1 and 2 will receive accelerated IMRT 70 Gy to be administered over 6 weeks in once daily fractions Monday through Friday, with one additional fraction of RT administered on (preferably) Fridays. The two fractions administered on one day will be at least 6 hours apart. Palbociclib, an oral agent, will not be given during step two due to the severe difficulty with swallowing that occurs in all patients treated with CRT and due to the lack of feasibility

studies for this combination therapy. To assess overall tumor response (stratified by cohort), a CT scan of the neck will be performed 8-10 weeks following completion of CRT, and FDG-PET/CT will be performed 14-18 weeks following completion of CRT.

During step three, patients in both cohorts will be treated with adjuvant palbociclib 125 mg/day, days 1-21 of each 28-day cycle for six cycles. Adjuvant palbociclib will begin 16 to 22 weeks following completion of CRT.

5.1 Premedication Administration

No premedications are required for palbociclib.

Recommended premedications for cisplatin are: palonosetron 0.25 mg IVPB, dexamethasone 20 mg IVPB, and fosaprepitant 150 mg IVPB. In addition, hydration consisting of 1L IVF NS (also recommended: 10 meq KCl/L + 8 meq MgSO4/L) over 60 minutes before and after cisplatin on the day of dosing is recommended, and 2L IVF NS over 60 minutes on the 2 days following cisplatin dosing is recommended.

Recommended premedications for cetuximab are: diphenhydramine hydrochloride 50 mg (or an equivalent antihistamine) IVPB given at least 30 minutes prior to cetuximab, 1L IVF NS, hydrocortisone 100 mg IVPB, and/or albuterol inhalation (by nebulizer or inhaler) according to standard of care procedures.

5.2 Agent Administration

5.2.1 Steps One and Three (Both Cohorts)

Neoadjuvant palbociclib monotherapy will be given at a dose of 125 mg/day on Days 1-21 of two 28-day cycles during Step One. Adjuvant palbociclib monotherapy will be given at a dose of 125 mg/day on Days 1-21 of six 28-day cycles during Step Three.

Palbociclib is an oral drug available as capsules (or as liquid suspension). **The capsules should be taken with food.** Patients will be required to keep a drug diary (see Appendix B).

If a patient misses a day's dose entirely, s/he must be instructed not to make it up the next day but to just take his/her regular dose the following day. If a patient vomits any time after taking a dose, s/he must be instructed not to make it up but to resume subsequent dosing the next day as prescribed. If a patient inadvertently takes an extra dose during a day, s/he must be instructed to not take the next day's dose.

For patients who cannot swallow the palbociclib capsules, an oral solution will be available. Patients who begin the study receiving the oral solution will remain on the oral solution for the duration of their time on treatment in the study. Patients,

who begin the study receiving capsules but develop difficulty swallowing the capsules and did not have disease progression will be allowed to switch to the palbociclib oral solution. These patients will then remain on the oral solution for the duration of their time on treatment in the study. Each clinical site will be provided the oral solution Investigational Product Manual (IPM) containing the dosage and administration instructions (DAI) for preparation of the palbociclib oral solution. **Patients can take palbociclib oral solution with or without food.**

5.2.2 Step Two, Cohort 1

Cohort 1 patients will receive accelerated IMRT for a total dose of 70 Gy. It will be given over 6 weeks in once daily fractions Monday through Friday, with one additional fraction given on (preferably) Fridays (total of 35 fractions). The second fraction will be given at least 6 hours after the first. Cohort 1 patients will receive cisplatin at a dose of 100 mg/m^2 IVPB over 60 minutes on Days 1 and 22 of RT.

5.2.3 Step Two, Cohort 2

Cohort 2 patients will receive accelerated IMRT for a total dose of 70 Gy. It will be given over 6 weeks in once daily fractions Monday through Friday, with one additional fraction given on (preferably) Fridays (total of 35 fractions). The second fraction will be given at least 6 hours after the first. Cohort 2 patients will receive 7 weekly doses of cetuximab starting one week before RT and then weekly during RT. The cetuximab loading dose is 400 mg/m^2 IVPB and the remaining 6 weekly doses are 250 mg/m^2 IVPB. There is a +/- 2-day window for cetuximab dosing.

5.3 Study Procedures

5.3.1 Baseline Assessment

1. Office fiberoptic endoscopy (FOE) or operative room (OR) microlaryngoscopy (mDLx) to document the size and extent of the primary tumor site (PTS) along with research and routine biopsies of the PTS. Core or excisional biopsies of the involved neck nodes is an alternative approach to obtain tumor tissue.
2. p16^{INK4a} IHC stain on all patients. HPV-HR (16,18) ISH will be required on all patients with p16^{INK4a} positive oral cavity, larynx, and hypopharynx SCC.
3. Clinical examination with ECOG PS.
4. Weight.
5. Documentation of presence of PEG tube or tracheostomy tube
6. QOL assessment
7. CBC, CMP, Mg, PT/INR, PTT, pregnancy test (if woman of childbearing potential)
8. EKG
9. CT neck with IV contrast
10. FDG-PET/CT
11. Blood for genome sequencing

12. Primary disease site photographs

5.3.2 Step One Assessments

1. Between Cycle 2 post-treatment Day 21 – Day 27, tumor response assessment will be performed by radiologic assessment with CT neck (with IV contrast).
2. Between Cycle 2 Days 18-22, office FOE or OR mDLx to document the size and extent of the PTS along with biopsy of the PTS. Core or excisional biopsies of the involved neck nodes is an alternative approach to obtain tumor tissue.
3. Between Cycle 2 Days 18-22 primary disease site photographs.
4. Clinical examination Cycle 1 Days 1, 15, and 22, and Cycle 2 Day 1 and 22.
5. CBC Days 1, 8, 15, and 22 of each cycle.
6. EKG Cycle 2: Day 1.
7. AE assessments weekly for two cycles.
8. Study Lab collection of 3 green top tubes for PBMC at C1D22 and C2D22.

5.3.3 Step Two Cohort 1 Assessments

Step Two will start the day after Cycle 2 Day 28 of neoadjuvant palbociclib monotherapy.

1. Clinical exam on Days 1, 8, 22, 29, and 36 then biweekly until adequate recovery from CRT toxicities per physician discretion.
2. CBC Days 1, 8, 22, and 29.
3. CMP, Mg Days 1 and 22. BMP, Mg on Days 8 and 29.
4. QOL assessment Days 1 and 36.
5. EKG Day 1.
6. AE assessments on Days 1, 8, 22, 29, and 36 during CRT.
7. Office FOE between 8-10 weeks after completion of CRT.
8. CT neck with IV contrast between 8-10 weeks after completion of CRT.
9. Primary disease site photographs between 8-10 weeks after completion of CRT.
10. FDG-PET/CT between 14-18 weeks after completion of CRT.

5.3.4 Step Two Cohort 2 Assessments

Step Two will start the day after Cycle 2 Day 28 of neoadjuvant palbociclib monotherapy.

1. Clinical exam on day of loading dose of cetuximab, then on RT Days 1, 8, 22, 29, and 36, then biweekly until adequate recovery from CRT toxicities per physician discretion.
2. CBC day of loading dose of cetuximab, then on RT Days 1, 8, 22, and 29.
3. CMP, Mg on day of loading dose of cetuximab, then on RT Days 1 and 22. BMP, Mg on Days 8 and 29.
4. QOL assessment RT Days 1 and 36.
5. EKG on RT Day 1 (Week 2 of cetuximab).

6. AE assessments on day of loading dose of cetuximab, then on RT Days 1, 8, 22, 29, and 36.
7. Office FOE between 8-10 weeks after completion of CRT.
8. CT neck with IV contrast between 8-10 weeks after completion of CRT.
9. Primary disease site photographs between 8-10 weeks after completion of CRT.
10. FDG-PET/CT between 14-18 weeks after completion of CRT.

5.3.5 Step Three Assessments

Step Three will start 16 to 22 weeks after the completion of CRT.

1. Clinical examination Day 1 of each cycle.
2. CBC Day 1 of each cycle.
3. CMP, Mg Day 1 of each cycle.
4. EKG Day 1 of Cycles 1 and 4, and Day 29 of Cycle 6 (EOT).
5. QOL assessment at Cycle 1 Day 1, Cycle 4 Day 1, and Cycle 6 Day 29 (EOT).
6. AE assessments Day 1 of each cycle.
7. Study Lab collection of 3 green top tubes for PBMC at C1D22.
8. Thirty to 45 days after final cycle of adjuvant palbociclib, there will be a clinical examination, CBC, CMP, EKG, and AE assessment.

5.3.6 Assessments after Completion of CRT

1. Office FOE and CT neck (with IV contrast) and CT chest (or CXR) at 8, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months (+/- 1 month) after completion of CRT [FOE will be conducted as standard of care after 12 months of follow-up, so they will occur at some, but not all, of the long-term follow-up visits]
2. Documentation of presence of PEG tube or tracheostomy tube at the same monitoring intervals.
3. Documentation of weight (Kg) at the same monitoring intervals.
4. QOL assessments at the same monitoring intervals.
5. Study Lab collection of 3 green top tubes for PBMC at 4 months (+/- 1 month) after completion of adjuvant treatment (4 months post step 3).

5.4 Toxicity and 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 are evaluable for disease response unless they discontinue treatment due to adverse event(s), patient withdrawal, or early death prior to completion of the disease

assessment at the end of Step 1(neoadjuvant treatment) and have not had any disease assessment.

5.5 General Concomitant Medication and Supportive Care Guidelines

While taking palbociclib, patients should be instructed to avoid food or drugs that are known strong CYP3A4 inhibitors or inducers (moderate CYP3A4 inhibitors or inducers are okay). Patients should also refrain from the use of proton pump inhibitors; if needed, alternative antacid therapies may be used including H2-receptor antagonists, and locally acting antacids. H2-receptor antagonists should be administered with a staggered dosing regimen (twice daily). The dosing of palbociclib should occur at least 10 hours after the H2-receptor antagonist dose and 2 hours before the H2-receptor antagonist morning dose. Local antacid should be given at least 2 hours before or 2 hours after palbociclib administration.

Patients should receive full supportive care during the study, including transfusion of blood and blood products and treatment with antibiotics, analgesics, erythropoietin, or bisphosphonates when appropriate.

Anti-emetics (such as prochlorperazine, lorazepam, ondansetron, or other 5-HT3 antagonists) may be administered prophylactically in the event of nausea. Anti-diarrheals, such as loperamide, may be administered as needed in the event of diarrhea.

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 serum pregnancy test within 28 days prior to the first dose of palbociclib.

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 palbociclib.

If a patient is suspected to be pregnant, all 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 28 days after the last dose of palbociclib, the investigator must be notified in order to facilitate outcome follow-up.

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 for 2 cycles of neoadjuvant palbociclib, 6 weeks of CRT, and 6 cycles of adjuvant palbociclib or until one of the following criteria applies:

- Documented and confirmed disease progression after Step 2. Patients with disease progression after Step 1 should proceed to Step 2.
- 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 unable to receive further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious non-compliance 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.

5.8 Duration of Follow-up

Patients will have follow-up visits after the end of treatment at 30-45 days, and will also have visits at 8 months after end of CRT, 12 months after end of CRT, and every 6 months thereafter until 5 years have elapsed since the end of treatment. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

6.0 DOSE DELAYS/DOSE MODIFICATIONS

6.1 Dose Modifications for Palbociclib (Steps One and Three)

Patients will be monitored for toxicity and the dose of palbociclib may be adjusted as indicated in the table below. Dose reduction by 1, and if possible, 2 dose levels will be allowed depending on the type and severity of toxicity encountered. Patients requiring more than 2 dose reductions will be discontinued from the study.

Recommended dose reductions for palbociclib are to decrease the current dose by 25 mg. The lowest dose available is 75 mg. Doses may be held as needed for toxicity resolution during a cycle. Doses omitted for toxicity are not replaced or restored within the same cycle (meaning that the cycle remains 28 days regardless of the number of doses of taken).

If a patient experiences toxicity which has not resolved to grade 2 or lower within two weeks (inclusive of the scheduled off-week), treatment with palbociclib should be permanently discontinued.

Palbociclib Dose Modifications Based on Worst Treatment-Related Toxicity in the Previous Cycle

Worst Toxicity During Previous Cycle	New Dose Level
Grade 4 neutropenia	- Withhold Palbociclib until recover to Grade ≤ 2. Resume at the next lower dose.
Grade 4 thrombocytopenia	- Withhold Palbociclib until recover to Grade ≤ 2. Resume at the next lower dose.
Grade 3 neutropenia associated with a documented infection or fever ≥ 38.5 ºC	Withhold Palbociclib until recover to Grade ≤ 2. Resume at the next lower dose.
Grade ≥ 3 non-hematologic toxicity (includes nausea, vomiting, diarrhea, and hypertension only if persisting despite maximal medical treatment)	Withhold Palbociclib until symptoms resolve to • Grade ≤ 1: • Grade ≤ 2 (if not considered a safety risk for the patient Resume at the next lower dose.
Delay by > 1 week in receiving the next scheduled dose due to persisting treatment-related toxicities	If recovery to Grade ≤ 2 occurs within 2 weeks, continue and decrease by one dose level
Inability to deliver at least 80% of the planned dose of palbociclib due to adverse events possibly related to study treatment	Withhold Palbociclib until recovery to Grade ≤ 2. Decrease by one dose level.

6.1.1 Dose Adjustments Due to QTc Prolongation

Any patients who develops new grade 2 or greater ECG QT corrected interval prolonged at any time during the study will need to have the ECG repeated immediately for confirmation.

Grade 2: no adjustments; continue at same dose level
Grade 3 (reversible cause identified and corrected): withhold treatment until QTc ≤ 470 msec, then resume treatment at the same dose level
Grade 3 (no reversible cause identified): withhold treatment until QTc ≤ 470 msec, then decrease palbociclib by one dose level
Grade 4: permanently discontinue palbociclib

6.1.2 Dose Adjustments Due to Interstitial Lung Disease (ILD)/Pneumonitis

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis (e.g. hypoxia, cough, dyspnea). In patients who have new or worsening respiratory symptoms and are suspected to have developed ILD/pneumonitis, interrupt palbociclib immediately and evaluate the patient. Permanently discontinue palbociclib in patients with severe ILD or pneumonitis.

6.2 Step Two, Cohort 1: Dose Modifications for Cisplatin

6.2.1 Peripheral Neuropathy

Grade 0, 1, or 2: no dose modification.

Grade 3 or 4: Hold cisplatin until the event resolves to < grade 3.

6.2.2 Ototoxicity

If grade 1 or 2 hearing loss occurs, the risk of additional hearing loss versus the potential benefit of continuing cisplatin chemotherapy should be made. Grade 3 and 4 hearing loss is an indication to discontinue the drug.

6.2.3 Kidney Impairment

<table>
<tr><th>Calculated Creatinine Clearance</th><th colspan="2">Percent Dose to Give</th></tr>
<tr><td>≥ 60 mL/min</td><td colspan="2">100%</td></tr>
<tr><td rowspan="4">< 60 mL/min</td><td colspan="2">0% (withhold treatment for this cycle and repeat serum creatinine weekly after additional hydration), then for next chemotherapy cycle:</td></tr>
<tr><td>If CrCl was already < 60 mL/min and is now:</td><td>The percent dose to give is:</td></tr>
<tr><td>> 50 but < 60</td><td>80%</td></tr>
<tr><td>≥ 40 but ≤ 50</td><td>50%</td></tr>
<tr><td>< 40</td><td>0%</td></tr>
</table>

Please note that dose reduction percentage is calculated by taking off from the original dose and not the previous dose. Creatinine clearance is to be calculated using Cockcroft-Gault.

6.2.4 Thrombocytopenia

<table>
<tr><th rowspan="2">Nadir of last course</th><th colspan="2">Platelets (Day 1 of each cycle)</th></tr>
<tr><td>< 100,000</td><td>≥ 100,000</td></tr>
</table>

between 50,000 and 100,000	Hold cisplatin	Cisplatin = 100%
< 50,000 (1st occurrence)	Hold cisplatin	Cisplatin = 80%
<50,000 (2nd occurrence)	Hold cisplatin	Cisplatin = 60%

6.3 Step Two, Cohort 2: Dose Modifications or Delays for Cetuximab

6.3.1 Dermatologic Adverse Effects

Patients developing dermatologic toxicities while receiving cetuximab should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. Dose modifications of any future cetuximab infusions should be instituted in case of severe (grade 3) acneiform rash. Treatment with topical and/or oral antibiotics (minocycline 100 mg bid) should be considered; topical corticosteroids are not recommended.

If a patient experiences severe acneiform rash, cetuximab treatment adjustments should be made according to the following table. In patients with mild and moderate skin toxicity, treatment should continue without dose modification.

Cetuximab Dose Modification Guidelines

Grade 3 Acneiform Rash	Cetuximab	Outcome	Cetuximab Dose Modification
1st occurrence	Delay infusion 1-2 weeks	Improvement	Continue at 250 mg/m^2
		No Improvement	Discontinue cetuximab
2nd occurrence	Delay infusion 1-2 weeks	Improvement	Reduce Dose Level -1
		No Improvement	Discontinue cetuximab
3rd occurrence	Delay infusion 1-2 weeks	Improvement	Reduce to Dose Level -2
		No Improvement	Discontinue cetuximab
4th occurrence	Discontinue cetuximab		

Cetuximab Dose Levels*	
Starting dose	250 mg/m^2
Dose Level –1	200 mg/m^2
Dose Level –2	150 mg/m^2

*There will be no dose level reductions below a weekly dose of 150 mg/m^2.

6.3.2 Gastrointestinal Adverse Effects

Antiemetic agents may be administered prior to the administration of cetuximab. Diarrhea will be treated symptomatically with antidiarrheal agents. Should GI toxicity become severe enough to require hospitalization or outpatient IV fluid replacement, all treatment should be discontinued temporarily until the patient's condition improves.

6.3.3 Management of Hypersensitivity Reactions

Mild (grade 1) hypersensitivity reactions (HSRs) characterized by mild pruritus, flushing, rhinitis, rash, and fever are treated with symptom-directed management, including cessation of infusion, administration of diphenhydramine 25 mg IVP (may repeat x2). Vital signs should be monitored every 15 minutes until symptoms resolve. Treatment may be restarted at the same rate at resolution of symptoms.

Moderate (grade 2) HSRs consist of generalized pruritus, flushing, rash, back pain, dyspnea, hypotension, and rigors. The infusion should be stopped, and oxygen should be administered if the patient is experiencing dyspnea. Normal saline 500 mL bolus may be given if the patient is hypotensive (may repeat as needed). Diphenhydramine 50 mg IVP should be administered, followed by hydrocortisone 100 mg IVP followed by meperidine 25 mg IV (for rigors). Vital signs should be monitored every 2 minutes until stable, then every 15 minutes until symptoms resolve. Treatment may be restarted at resolution of symptoms as follows: 8 hour rate for 5 minutes, then 4 hour rate for 5 minutes, the 2 hour rate for 5 minutes until the original rate of infusion is reached.

Severe (grade 3) HSRs are characterized by bronchospasm, generalized urticaria, hypotension, and angioedema. These HSRs should be managed by stopping the infusion and administering: normal saline 500 mL bolus (repeat as needed), epinephrine (1:1000) 0.3 mg IM, diphenhydramine 50 mg IVP, hydrocortisone 100 mg IVP, and albuterol 2.5 mg inhalation (for bronchospasms). Vital signs should be monitored every 2 minutes until stable, then every 15 minutes until symptoms resolve. If cetuximab is restarted, restart the infusion rate at 25% of original rate for 30 minutes, then increase to 50% of infusion rate for the remainder of the infusion. The infusion rate should be permanently reduced by 50%.

Life-threatening/disabling (grade 4) HSRs consist of anaphylaxis, airway obstruction, shock, cardiac arrest, or prolonged hypotension.

Grade 4 HSRs require the immediate interruption of cetuximab therapy and permanent discontinuation from further treatment with cetuximab. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Patients should be carefully observed until the complete resolution of all signs and symptoms.

6.3.4 Infusion Reaction Adverse Effects

Severe infusion reactions (Grade 4) require the immediate interruption of cetuximab therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Patients should be carefully observed until the complete resolution of all signs and symptoms.

In prior clinical trials, mild to moderate infusion reactions were managed by slowing the infusion rate of cetuximab and by continued use of antihistamine pre-medications (e.g., diphenhydramine) in subsequent doses. If the patient experiences a moderate (Grade 3) infusion reaction, the infusion rate should be permanently reduced by 50%. For grade 1 or 2 reactions, additional doses of diphenhydramine or corticosteroids may be administered.

6.3.5 Drug Fever Adverse Effects

If a patient experiences isolated drug fever, subsequent pre-treatment with acetaminophen or a non-steroidal anti-inflammatory agent may be considered. If a patient experiences recurrent isolated drug fever following premedication and post-dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be 50% of previous rate.

6.3.6 Pulmonary Adverse Effects

In the event of acute onset (grade ≥ 2) or worsening pulmonary symptoms which are not thought to be related to underlying cancer, cetuximab therapy should be interrupted and a prompt investigation of these symptoms should occur. Cetuximab retreatment should not occur until these symptoms have resolved to grade 1. If interstitial lung disease is confirmed, cetuximab should be discontinued and the patient should be treated appropriately.

6.3.7 Renal Adverse Effects

Hypomagnesemia has been reported with cetuximab when administered as a single agent and in combination with multiple different chemotherapeutic regimens. Patients receiving cetuximab should be monitored for hypomagnesemia. Magnesium repletion may be necessary based on clinical judgment.

7.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outline below. Please refer to Appendix F for definitions and Appendix G for a grid of reporting timelines.

Adverse events will be tracked from the start of treatment through 30 days following the last day of study treatment. All adverse events must be recorded on the toxicity tracking case report form (CRF).

Refer to the data submission schedule in Section 12 for instructions on the collection of AEs in the EDC.

Reporting requirements for Washington University study team may be found in Section 7.1.

7.1 Sponsor-Investigator Reporting Requirements

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

Reporting will be conducted in accordance with Washington University IRB Polices.

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

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

The Sponsor investigator is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (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 qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

7.1.3 Reporting to Pfizer

Within 24 hours of first awareness of the event (immediately if the event is fatal or life-threatening), the PI or designee will report to Pfizer by facsimile any serious adverse drug experience (as defined in Appendix F) that occurs during the SAE reporting period (as defined in Section 7.0) in a study subject receiving palbociclib. Such SAEs will be reported using MedWatch form and the Pfizer Reportable Event Fax Cover Sheet (Appendix C) should also be included. SAEs should be reported as soon as they are determined to meet the definition, even if complete information is not yet available.

Even though there may not be an associated SAE, exposure to palbociclib during pregnancy or lactation is reportable. In addition, occupational exposure to palbociclib is reportable, and a lack of effect of palbociclib may also be reportable.

Hy's Law Cases: Cases of potential drug-induced liver injury as assessed by laboratory test values ("Hy's Law Cases") are also reportable to Pfizer. If a study subject develops abnormal values in aspartate transaminase (AST) or alanine transaminase (ALT) or both, concurrent with abnormal elevations in total bilirubin and no other known cause of liver injury, that event would be classified as a Hy's Law Case.

7.1.4 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 Washington University principal investigator to report to the FDA as follows:

- Report any unexpected fatal or life-threatening, suspected adverse reaction (refer to Appendix F for definitions) no later than **7 calendar days** after initial receipt of the information.
- Report a suspected adverse reaction that is both serious and unexpected (SUSAR, refer to Appendix F) no later than **15 calendar days** it is determined that the information qualifies for reporting. Report an adverse event (Appendix F) as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:
    - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure
    - One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug
    - An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group
- Report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies that suggest a significant risk in humans exposed to the drug no later than 15 calendar days after it is determined that the information qualifies for reporting.
- Report any findings from animal or in vitro testing that suggest significant risk in humans exposed to the drug no later than 15 calendar days after it is determined that the information qualifies for reporting.
- Report any clinically important increase in the rate of a serious suspected adverse reaction of that listed in the protocol or IB within 15 calendar days after it is determined that the information qualifies for reporting.

Submit each report as an IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. Study teams must notify the Siteman Cancer Center Protocol Development team of each potentially reportable event within 1 business day after initial receipt of the information, and must bring the signed 1571 and FDA Form 3500A to the Siteman Cancer Center Protocol Development team no later than 1 business day prior to the due date for reporting to the FDA.

Each notification to FDA must bear prominent identification of its contents ("IND Safety Report") and must be transmitted to the review division in the Center for Drug Evaluation and Research (CDER) or in the Center for Biologics Evaluation and Research (CBER) that has responsibility for review of the IND. Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such ("Follow-up IND Safety Report").

7.2 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 7.1

- planned hospitalizations
- hospitalizations < 24 hours
- respite care
- events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.

8.0 PHARMACEUTICAL INFORMATION

8.1 PD 0332991 (Palbociclib)

8.1.1 PD 0332991 Description

Laboratory Code: PD 0332991-00
Molecular Weight: 447.54
Molecular Formula: $C_{24}H_{29}N_7O_2$

Formulations:
Capsule:
PD-0332991-00 capsules will be provided as the active ingredient with precedented excipients filled in hard gelatin capsules composed of gelatin and precedented colorants. These formulations will be packaged in appropriate packaging material and should be stored in line with labeled storage conditions.

Oral Solution:

PD-0332991-00 will be provided and/or dosed as an oral solution using precedented excipients with appropriate packaging and storage conditions.

8.1.2 Clinical Pharmacology

PD 0332991 is a highly selective inhibitor of Cdk4/cyclinD1 kinase activity (IC_{50} = 11 nM; K_i = 2 nM). PD 0332991 has selectivity for Cdk4/6, with little or no activity against a large panel of 34 other protein kinases including other Cdks and a wide variety of tyrosine and serine/threonine kinases. Cdk6, another enzyme that also complexes with cyclin-D subunits, is also commonly expressed in mammalian cells and tumors. Cdk6 is highly homologous to Cdk4 and can perform the same function by phosphorylating Rb, thus potentially creating a redundant mechanism to promote cell cycle progression. Consequently, inhibition of both enzymes is necessary to ensure complete suppression of Rb phosphorylation and the greatest possible spectrum of antitumor activity. Results indicate that PD 0332991 inhibits Cdk6 with equivalent potency to Cdk4.

8.1.3 Pharmacokinetics and Drug Metabolism

To date pharmacokinetic data have been reported for four studies (A5481001, A5481002, A5481003 and A5481004). Final PK data are available from studies A5481001 and A5481002. Pharmacokinetic parameters are available from all 74 patients enrolled in Protocol A5481001 following a single-dose (Day 1 of Cycle 1), and from 51 patients following multiple-dose administration (Day 8 of Cycle 1) of daily doses ranging from 25 to 225 mg of PD 0332991 (Table 4.). On Day 1, all patients had detectable plasma concentrations of PD 0332991 at the first measured time point (1 hour) following oral administration. The exposure ($AUC_{(0\text{-}10)}$ and C_{max}) increased in a dose-proportional manner over the dose range of 25-225 mg QD following PD 0332991 administration on Days 1 and 8 of Cycle 1, although some variability (low to moderate) around these doses was observed particularly at the 150 mg QD dose level.

Summary of PD 0332991 Mean and Median Plasma PK Parameters by Dose (Day 1 and Day 8 Data Combined)

Treatment Description (QD)	Study Day	C_{max}[1] (ng/mL)	T_{max}[2] (hour)	$AUC_{(0-10)}$[1, 3] (ng.hour/mL)
25 mg	1 (n=3)	9.6 (63)	4.0 (4.0-4.0)	58 (51)
	8 (n=3)	15.9 (32)	4.0 (2.0-7.0)	119 (32)
50 mg	1 (n=3)	20.7 (3)	4.0 (4.0-4.3)	134 (5)
	8 (n=3)	35.7 (16)	4.1 (2.0-7.0)	274 (15)
75 mg	1 (n=7)	28.7 (24)	4.0 (4.0-10.0)	199 (20)
	8 (n=6)	58.6 (24)	4.0 (4.0-9.0)	492 (27)
100 mg	1 (n=6)	45.6 (45)	4.0 (2.0-10.0)	332 (34)
	8 (n=6)	71.2 (31)	5.5 (4.0-10.0)	513 (45)
125 mg	1 (n=22)	51.6 (43)	7.0 (2.0-24.4)	299 (44)
	8 (n=13)	86.2 (34)	4.0 (1.0-10.0)	724 (38)
150 mg	1 (n=7)	83.8 (17)	4.0 (4.0-9.8)	633 (9)
	8 (n=6)	161 (44)	7.0 (7.0-10.0)	1342 (42)
200 mg	1 (n=20)	80.8 (35)	5.7 (1.0-10.2)	525 (36)
	8 (n=8)	174 (17)	4.0 (2.0-7.0)	1395 (23)
225 mg	1 (n=6)	104 (58)	4.0 (4.0-7.0)	718 (55)
	8 (n=6)	186 (64)	4.5 (1.0-7.0)	1491 (64)

[1] C_{max} and $AUC_{(0-10)}$: mean (%CV)
[2] T_{max}: Median (Range)
[3] For $AUC_{(0-10)}$, the number of patients on Day 1 for the 100 mg, 125 mg, 150 mg and 200 mg groups were 5, 21, 5 and 19 respectively and on Day 8 for the 75 mg, 100 mg and 125 mg groups were 5, 4 and 12 respectively

Steady-state PK parameters are available for nine patients on Day 14 of Cycle 1 (receiving 200 mg SC 0332991 QD for 2 weeks) and four patients on Day 21 of Cycle 1 (receiving 125 mg QD for 3 weeks). PD 0332991 was absorbed with a median Tmax of ~4 hours. The mean PD 0332991 Vz/F was 3103 L, which is significantly greater than total body water (42 L), indicating that PD 0332991 extensively penetrates into peripheral tissues. PD 0332991 was eliminated slowly; the mean elimination half-life (t½) was 26.5 hours and the mean CL/F was 86.1 L/hour. PD 0332991 accumulated following repeated dosing with a median Rac of 2.4, which is consistent with the elimination half-life.

Summary of the Steady-State Mean Plasma PK Parameters on Day 14 (200 mg) and Day 21 (125 mg) Following Oral Administration of PD 0332991 Dose Corrected to 125 mg Dose Level (N=13)

Treatment Description	C_{max}[1] (ng/mL)	T_{max}[2] (hour)	$AUC_{(0-24)}$[1] (ng.hour/mL)	$AUC_{(0-72)}$[1] (ng.hour/mL)	$t_{1/2}$[1] (hour)	CL/F[1] (L/hour)	V_z/F[1] (L)	R_{ac}[2,3]
Dose corrected 125 mg QD (n=13)	104 (48)	4.2 (2-9.8)	1863 (59)	3549 (71)	26.5 (26)	86.1 (50)	3103 (40)	2.4 (1.5-4.2)

[1] mean (%CV)
[2] Median (Range)
[3] For Rac, n=12 ($AUC_{(0-24)}$ was not estimable for Patient 10021099 on Cycle 1, Day 1 in the 200 mg group)
Note: Combined PK parameter data from Day 14 (200 mg) and Day 21 (125 mg) dose corrected to the 125 mg dose level.

Renal excretion of PD 0332991 was a minor route of elimination with ~1.7% of the drug excreted unchanged in urine over the 10-hour collection period in the 125 mg and 200 mg dose group, combined. The mean renal clearance (CLR) was 6.59 L/hour.

An exploratory evaluation of the circulating metabolites for PD 0332991 was conducted in plasma samples obtained from patients treated with PD 0332991 200 mg QD. Preliminary assessment of the pooled plasma samples on Day 14 of Cycle 1 indicated that the glucuronide conjugate of PD 0332991 and the lactam of PD 0332991 were the main metabolites present in plasma. Other metabolites observed were the glucuronide conjugates of hydroxylated PD 0332991 and the glucuronide conjugate of reduced PD 0332991.

The preliminary results from the recently performed food-effect study ("A5481021, a Phase 1, open-label 4 sequence 4 period crossover study of palbociclib (PD-0332991) in healthy volunteers to estimate the effect of food on the bioavailability of palbociclib") has provided evidence that when a single 125 mg dose of palbociclib was administered under fed conditions (including high fat or low fat meal given together with palbociclib, or moderate fat meal given 1 hour before and 2 hours after palbociclib) as a freebase capsule formulation the palbociclib exposure levels were more uniform across the population than when taken in the fasting condition.

Drug-drug interaction between PD 0332991 and letrozole was evaluated during the Phase 1 portion of a breast cancer study (A5481003 The preliminary data indicate a lack of a potential for drug-drug interaction between PD 0332991 and letrozole when administered in combination.

In a study in healthy subjects (Study A5481079), a PD 0332991 oral solution administered under fasted conditions and fed conditions (moderate fat, standard

calorie meal) was bioequivalent to the commercial free base capsule formulation of PD 0332991 given under fed conditions. Additionally, the PD 0332991 oral solution administered under fasted conditions was bioequivalent to PD 0332991 oral solution administered under fed conditions, suggesting that the PD 0332991 oral solution formulation can be given without regards to food intake. Additional information may be found in the IB for PD 0332991.

8.1.4 Supplier(s)

Pfizer will supply the study agent. The study agent will be free of charge to the patient.

8.1.5 Dosage Form and Preparation

Palbociclib Capsules
PD 0332991 will be supplied as capsules containing 75 mg, 100 mg, or 125 mg equivalents of PD 0332991 free base. The sponsor will supply the oral drug formulation to sites in high-density polyethylene (HDPE) bottles containing 75 mg, 100 mg, or 125 mg capsules. The capsules can be differentiated by their size and color, as shown in the table below. Labeling will occur according to local regulatory requirements.

PD 0332991 Capsule Characteristics

Strength	Capsule color
75 mg	Sunset Yellow
100 mg	Caramel/Sunset Yellow
125 mg	Caramel

The patient number and the protocol number should be recorded on the bottle label in the spaces provided. Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be given a sufficient supply to last until their next study visit. Unused drug and/or empty bottles should be returned to the site at the next study visit. Returned, unused medication MUST NOT be re-dispensed to the patient.

PD 0332991 is an agent that must be handled and administered with care. Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other container. Due to possible unknown hazards associated with topical and environmental exposure to experimental agents, capsules must not be opened and/or emptied into any vehicle for oral ingestion; capsules must be swallowed intact.

Only one capsule strength will be dispensed to the patient at each dispensing visit. In the event of dose modification, request should be made of the patient to return all previously dispensed medication to the clinic and new capsules will be dispensed.

Palbociclib Oral Solution
PD 0332991 oral solution (25 mg/mL) will be supplied in HDPE packaged bottles with a PIBA (push in bottle adapter) and a reusable oral syringe for dosing. Labeling will occur according to local regulatory requirements. Each clinical site will be provided the oral solution IPM which contains the detailed dosage and administration instructions for preparation of the PD 0332991 oral solution. The oral solution should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, or pharmacist) as allowed by local, state, and institutional guidance.

The patient number should be recorded on the bottle label in the spaces provided by site personnel at the time of assignment to patient. Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be given a sufficient supply to last until their next study visit. Unused drug and/or empty bottles should be returned to the site at the next study visit. Returned, unused medication MUST NOT be re-dispensed to the patient.

PD 0332991 oral solution is an agent that must be handled and administered with care. Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other container.

8.1.6 Storage and Stability

PD 0332991 capsules should be stored at controlled room temperature (15-25°C, 59-77°F) in their original container. PD 0332991 oral solution should be stored in its original container and in accordance with the conditions described in the oral solution IPM. Medication should be kept in a secured locked area at the study site in accordance with applicable regulatory requirements. Returned medication should be stored separately from medication that needs to be dispensed.

To ensure adequate records, PD 0332991 capsules and oral solution will be accounted for as instructed by Pfizer. Unless otherwise authorized by Pfizer, at the end of the clinical trial all drug supplies unallocated or unused by the subjects must be returned to Pfizer or its designee. All containers of PD 0332991 that were sent to the investigator throughout the study must be returned to the sponsor or designee, whether they are used or unused, and whether they are empty or contain capsules/solution.

8.1.7 Administration

Patients should be encouraged to take their dose of PD 0332991 at approximately the same time each day. Patients should be instructed to record daily administration of the study drugs in a patient diary.

Patients must be instructed to withhold their daily dose of PD 0332991 on

pharmacokinetic sampling days until the pre-dose pharmacokinetic sample and safety assessments (ie, hematology, blood chemistry and ECGs) have been completed. On days the patient is in the clinic, PD 0332991 will be taken when instructed by the investigator.

Patients who miss a day's dose must be instructed NOT to "make it up" the next day. Patients who vomit any time after taking a dose must be instructed NOT to "make it up," and to resume treatment the next day as prescribed. Patients who inadvertently take 1 extra dose during a day must be instructed to skip the next day's dose

Palbociclib Capsules
Patients should be instructed to swallow PD 0332991 capsules whole and not to chew them prior to swallowing. No capsule should be ingested if it is broken, cracked, or otherwise not intact. PD 0332991 capsules will be administered once a day, orally, for 21 days followed by 7 days off treatment in 28-day cycles. **Patients should take PD 0332991 with food.**

Palbociclib Oral Solution
For patients who are unable to swallow capsules, a PD 0332991 oral solution is available as of IRB/EC approval of Amendment 5.

For patients who develop inability to swallow capsules during the study, it is allowed to switch to the PD 0332991 oral solution.

The PD 0332991 oral solution (25 mg/mL) will be administered using an oral syringe at volumes corresponding to the dose prescribed by the investigator (125 mg dose = 5mL, 100 mg dose = 4 mL, and 75 gm dose = 3 mL). Detailed instructions for administration of the oral solution can be found in the DAI.

PD 0332991 oral solution will be administered once a day, orally or via feeding tube, for 21 days followed by 7 days off treatment in 28-day cycles. The route of administration of the oral solution (oral vs via feeding tube) will be recorded in patient's dosing diary and the study CRF.

Patients can take PD 0332991 oral solution with or without food.

8.1.8 Special Handling Instructions

Females of childbearing potential should not handle or administer the study agent unless they are wearing gloves.

8.1.9 Pregnancy

The nonclinical safety profile of palbociclib has been well characterized through the conduct of single- and repeat-dose toxicity studies up to 39 weeks in duration,

and safety pharmacology, genetic toxicity, reproductive and developmental toxicity, and phototoxicity studies. Consistent with the pharmacologic activity of palbociclib (cell cycle inhibition, CDK4/6 inhibition), the primary target organ findings included hematolymphopoietic (decreased cellularity of bone marrow and lymphoid organs) and male reproductive organ (seminiferous tubule degeneration, and secondary effects on the epididymis, prostate, and seminal vesicle) effects in rats and dogs, and altered glucose metabolism that was accompanied by effects on the pancreas and secondary changes in the eye, teeth, kidney, and adipose tissue in rats only, and effects on bone in rats only that were observed following single and/or repeat dosing at clinically relevant exposures. Altered glucose metabolism (hyperglycemia/glucosuria) correlated with pancreatic islet cell vacuolation that was determined to reflect a loss of beta cells with corresponding decreases in insulin and C-peptide. The reversibility of the effects on glucose homeostasis, pancreas, eye, kidney, and bone was not established following a 12-week non-dosing period; whereas partial to full reversal of effects on the hematolymphopoietic and male reproductive systems, teeth, and adipose tissue were observed. Additionally, a potential for QTc prolongation and hemodynamic effects were identified from safety pharmacology studies, and developmental toxicity was identified from embryo-fetal development studies in the rat and rabbit. Though gastrointestinal effects would be anticipated from a cell cycle inhibitor and while effects were observed in rats and dogs following single- and repeat-dose studies up to 3 weeks in duration (emesis, fecal changes, and microscopic changes in stomach and intestines), the effects were of limited severity at clinically relevant doses. Gastrointestinal effects were not prominent in longer duration studies, limited to effects on the glandular stomach and rodent-specific effects on the non-glandular stomach in rats following 27 weeks of intermittent dosing that did not reverse during a 12-week non-dosing period. Additional palbociclib-related findings considered non-adverse at tolerated doses based on limited severity and/or absence of degenerative changes included cellular vacuolation in multiple tissues that was morphologically consistent with phospholipidosis; hepatic (increases in liver enzymes, hepatocellular hypertrophy/increased vacuolation), renal (increased CPN), adrenal (cortical cell hypertrophy), and respiratory (clinical signs, tracheal epithelial cell atrophy) effects; and prolonged coagulation times. Reversibility (partial or full) was established for these additional toxicities. Finally, palbociclib was determined to be an aneugen, for which a no effect exposure was identified

8.1.10 QT Interval

The patients enrolled in clinical studies should be closely monitored for potential cardiovascular symptoms. Appropriate monitoring should include clinical examinations, vital signs, routine ECGs, and AEs monitoring. In case of QTc prolongation, concomitant conditions such as electrolyte unbalances or use of medications affecting the QT interval should be ruled out or corrected. In case of clinically significant toxicities, PD 0332991 administration should be interrupted and the dose reduced as indicated in clinical protocols.

In Study A5481001 using QTcF, 46 of 73 patients had a maximum increase from baseline of <30 msec and no patient had a maximum on treatment value of ≥ 500 msec. Notably, one female patient who had received PD 0332991 at 75 mg QD on Schedule 3/1, had a maximum QTcF increase of 67 msec from baseline to Cycle 1. Additionally, QTcF increases ranging from 39 to 51 msec compared to baseline persisted throughout her ECG collection period of 5 subsequent cycles. After 7 cycles, the dose was increased to 100 mg QD. The patient remained on treatment for a total of 39 cycles with no cardiac related adverse events. QT data analysis for study A5481002 indicated no clinically significant mean changes with ECGs. Using Fridericia's correction in the A5481002 study, all 17 subjects in the analysis had a maximum increase from baseline of <30 msec and a maximum post-baseline value for QTc of <500 msec.

8.2 Cisplatin (CDDP, Platinol-AQ®)

8.2.1 Cisplatin Description

Molecular formula: PtCl2H6N2
Molecular weight: 300.1.

8.2.2 Clinical Pharmacology

The mechanism of action of cisplatin has not been clearly elucidated. However the most likely mechanism of antitumor action of this drug resides in its ability to inhibit DNA synthesis, and to a lesser degree, RNA and protein synthesis. It has also been shown that Cisplatin binds to DNA and produces inter-strand cross-links. Also cisplatin is not phase-sensitive and its cytotoxicity is similar in all phases of the cell cycle. Additional information can be found in the package insert.

8.2.3 Supplier

Cisplatin is commercially available as 1 mg/mL in both 50 mL multiple dose vial and 100 mL multiple dose vial.

8.2.4 Dosage Form and Preparation

The stability of cisplatin in solution is dependent upon the chloride ion concentration present in the diluent. Cisplatin should be diluted into an IV solution containing NaCL at a minimum chloride ion concentration of 0.040 mol/L (0.2% NaCL). Needles, syringes, catheters and IV administrations sets containing aluminum must be avoided during preparation and administration due to cisplatin-aluminum reaction causing precipitation and loss of potency. Mannitol 12.5 to 25 gm may be added per institutional guidelines.

8.2.5 Storage and Stability

The dry, unopened vials should be stored at room temperature (15° -25° C). The unopened container should be protected from light and stored in the carton until contents are used. Do not refrigerate. Cisplatin remaining in the amber vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light.

8.2.6 Administration

Patients will receive cisplatin via IV infusion over 60 minutes. Adequate hydration must be maintained during and after administration as described in the treatment section. It is recommended that all patients should be premedicated with antiemetics.

8.3 Cetuximab (Erbitux)

8.3.1 Cetuximab Description

Cetuximab is an anti-EGFR human-to-murine chimeric antibody.

8.3.2 Clinical Pharmacology

The epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFR, HER2, HER3, and HER4. The EGFR is constitutively expressed in many normal epithelial tissues, including the skin and hair follicle. Expression of EGFR is also detected in many human cancers including those of the head and neck, colon, and rectum.

Cetuximab binds specifically to the EGFR on both normal and tumor cells, and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, such as transforming growth factor-alpha. *In vitro* assays and *in vivo* animal studies have shown that binding of cetuximab to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. Signal transduction through the EGFR results in activation of wild-type KRAS protein. However, in cells with activating *KRAS* somatic mutations, the mutant KRAS protein is continuously active and appears independent of EGFR regulation.

In vitro, cetuximab can mediate antibody-dependent cellular cytotoxicity (ADCC) against certain human tumor types. *In vitro* assays and *in vivo* animal studies have shown that cetuximab inhibits the growth and survival of tumor cells that express the EGFR. No antitumor effects of cetuximab were observed in human tumor xenografts lacking EGFR expression. The addition of cetuximab to radiation

therapy or irinotecan in human tumor xenograft models in mice resulted in an increase in anti-tumor effects compared to radiation therapy or chemotherapy alone.

8.3.3 Pharmacokinetics and Drug Metabolism

Cetuximab administered as monotherapy or in combination with concomitant chemotherapy or radiation therapy exhibits nonlinear pharmacokinetics. The area under the concentration time curve (AUC) increased in a greater than dose proportional manner while clearance of cetuximab decreased from 0.08 to 0.02 L/h/m^2 as the dose increased from 20 to 200 mg/m^2, and at doses >200 mg/m^2, it appeared to plateau. The volume of the distribution for cetuximab appeared to be independent of dose and approximated the vascular space of 2–3 L/m^2.

Following the recommended dose regimen (400 mg/m^2 initial dose; 250 mg/m^2 weekly dose), concentrations of cetuximab reached steady-state levels by the third weekly infusion with mean peak and trough concentrations across studies ranging from 168 to 235 and 41 to 85 μg/mL, respectively. The mean half-life of cetuximab was approximately 112 hours (range 63–230 hours). The pharmacokinetics of cetuximab were similar in patients with HNSCC and those with colorectal cancer. Based on a population pharmacokinetic analysis, female patients with colorectal cancer had a 25% lower intrinsic clearance of cetuximab than male patients. Qualitatively similar, but smaller gender differences in cetuximab clearance were observed in patients with HNSCC. The gender differences in clearance do not necessitate any alteration of dosing because of a similar safety profile.

8.3.4 Supplier

Cetuximab is commercially available and is listed in the compendia as indicated for the therapy of HNSCC.

8.3.5 Dosage Form

Each single-use, ready to use 50-mL vial contains 100 mg of cetuximab at a concentration of 2 mg/mL and is formulated in a preservative-free solution containing 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.42mg/mL sodium phosphate monobasic monohydrate, and Water for injection, USP.

8.3.6 Storage and Stability

Cetuximab should be stored in a secure area according to local regulations. Store vials under refrigeration at 2° C to 8° C (36° F to 46° F). DO NOT FREEZE. Increased particulate formation may occur at temperatures at or below 0°C. This product contains no preservatives. Preparations of cetuximab in infusion containers are chemically and physically stable for up to 12 hours at 2° C to 8° C (36° F to 46° F) or up to 8 hours at controlled room temperature (20° C to 25° C; 68° F to 77° F).

Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2° to 8° C. Discard any unused portion of the vial.

8.3.7 Safety Precautions

Appropriate mask, protective clothing, eye protection, gloves, and Class II vertical-laminar-airflow safety cabinets are recommended during preparation and handling. Opened vials must be disposed of at the investigational center as chemotherapy or biohazardous waste provided documented procedures for destruction are in place.

Cetuximab therapy should be used with caution in patients with known hypersensitivity to cetuximab, murine proteins, or any component of this product. It is recommended that patients wear sunscreen and hats and limit sun exposure while receiving cetuximab as sunlight can exacerbate any skin reactions that may occur.

8.3.8 Premedication

In an effort to prevent a hypersensitivity reaction, all patients should be premedicated with diphenhydramine hydrochloride 50 mg (or an equivalent antihistamine) IVPB given at least 30 minutes prior to the cetuximab. Premedication will also include 1Liter normal saline, hydrocortisone 100 mg IVPB and albuterol inhalation (by nebulizer or inhaler) according to standard of care procedures.

8.3.9 Preparation and Administration

Cetuximab must not be administered as an IV push or bolus. Cetuximab must be administered with the use of a low protein binding 0.22-micrometer in-line filter. Cetuximab is supplied as a 50-mL, single-use vial containing 100 mg of cetuximab at a concentration of 2 mg/mL in phosphate buffered saline. DO NOT SHAKE OR DILUTE.

Cetuximab can be administered via infusion pump.

Infusion Pump:

- Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike or other appropriate transfer device may be used).
- Fill cetuximab into a sterile evacuated container or bag such as glass containers, polyolefin bags (e.g., Baxter Intravia), ethylene vinyl acetate bags (e.g., Baxter Clintec), DEHP plasticized PVC bags (e.g., Abbott Lifecare), or PVC bags.
- Repeat procedure until the calculated volume has been put in to the container. Use a new needle for each vial.
- Administer through a low protein binding 0.22-micrometer in-line filter (placed as proximal to the patient as practical).

- Affix the infusion line and prime it with cetuximab before starting the infusion.
- Maximum infusion rate should not exceed 5 mL/min.
- Use 0.9% saline solution to flush line at the end of infusion.
- The infusion rate of cetuximab must never exceed 10 mg/minute (5 mL/min). The infusion time of cetuximab should not exceed 4 hours. Patients must be continuously observed during the infusion for signs of anaphylaxis.

8.3.10 Patient Monitoring

Patients should be closely monitored for treatment-related adverse events, especially hypersensitivity reactions during the infusion and for one post-infusion observation hour. Vital signs (blood pressure, heart rate, and temperature) will be monitored and recorded prior to the administration of cetuximab, 1/2 hour into the infusion, at the completion of the infusion, and 1 hour post-infusion for the initial dose. During all subsequent administrations of cetuximab, vital signs will be monitored and recorded prior to administration of cetuximab and at the end of the infusion; however, it is recommended that the patient be observed for 1-hour post infusion.

9.0 CORRELATIVE STUDIES

9.1 Tumor Biopsy

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, p53 by IHC, p21 by IHC, p27 by IHC, and TUNEL assay. 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 palbociclib activity. If a biopsy is not feasible for financial reasons or safety concerns, at the Primary Investigator's discretion, the biopsy may be foregone.

9.1.1 Collection of Specimens

Tumor tissue will be collected at baseline and then after two cycles of neoadjuvant palbociclib monotherapy (conclusion of Step One). It should be collected form the primary tumor site if possible, but involved neck nodal tumor tissue is an alternative. If possible, the same site should be biopsied at baseline and end of C2.

The biopsy should consist of a minimum of 4 needle cores (14-18 gauge is preferred) if neck nodal tissue or 2 small (each 4 x 4 x4 mm) pieces of tumor if primary tumor site tissue.

If the patient has been previously enrolled in Washington University's TAP protocol (head and neck bank, HRPO #201102323), tissue that has been banked may be accessed in lieu of fresh biopsy at baseline.

9.1.2 Handling of Specimen(s)

Tissue should be delivered on saline to the Siteman Cancer Center Tissue Procurement Core within 30 minutes of collection.

9.2 Peripheral Blood

Peripheral blood will be stored to serve as normal DNA comparisons to tumor DNA. It will also be used in an exploratory fashion to look for immunologic changes.

9.2.1 Collection of Specimen

Thirty mL of peripheral blood will be collected into 3 green top tubes at baseline, Cycle 1 D22 of neoadjuvant treatment, Cycle 2 D 22 of neoadjuvant treatment, Cycle 1 D22 of adjuvant treatment, and four months post completion of adjuvant treatment.

9.2.2 Handling of Specimen(s)

Deliver to the SCC Tissue Procurement Core within 30 minutes of collection.

9.3 QOLs

Quality of life will be assessed by administration of the EORTC QLQ-C30 (Appendix D) and the FACT H&N (Appendix E) at the following time points:

- Baseline
- Step One Cycle 2 Day 22
- Day 1 of RT
- Day 35 of RT
- 8-10 weeks after completion of CRT
- Cycle 1 Day 1 (adjuvant)
- Cycle 4 Day 1 (adjuvant)
- EOT (adjuvant)
- 8 months after completion of CRT
- 12 months after completion of CRT
- 18 months after completion of CRT
- 24 months after completion of CRT
- 30 months after completion of CRT
- 36 months after completion of CRT
- 42 months after completion of CRT
- 48 months after completion of CRT

- 54 months after completion of CRT
- 60 months after completion of CRT

10.0 STUDY CALENDAR

10.1 Induction Palbociclib Monotherapy – Step One

	Baseline[4]	Step 1 – Cycle 1				Step 1 – Cycle 2					Definitive Chemotherapy/Radiation
		D1	D8	D15	D22	D1	D8	D15	D22	Between D18 and D22	
Palbociclib administration[1]		X[1]	X[1]	X[1]		X[1]	X[1]	X[1]			
PE w/ECOG PS	X	X		X	X	X			X		
CBC	X	X	X	X	X	X	X	X	X		
CMP + magnesium	X										
PT/INR, PTT	X										
Neck CT w/contrast	X								X[5]		
FDG-PET/CT	X										
Laryngoscopy w/biopsy[2]	X									X	
EKG	X					X					
Pregnancy test[3]	X										
FACT-H&N, EORTC QLQ-C30	X								X		
Blood for genomic sequencing	X				X				X		
Rad Tx Planning						X					See Study Calendar 2
Primary Site Photographs	X									X	

1. Palbociclib po 125 mg/day, Days 1-21 of a 28 day cycle.
2. Tumor biopsy specimens (punch, incisional or core needle) will be obtained from PTS or neck nodes. P16 to be tested by IHC and/or HPV-HR ISH at baseline only. Assessment of primary tumor site will be done by laryngoscopy performed in the office or operating room. If the patient has been previously enrolled in Washington University's TAP protocol (head and neck bank, HRPO #201102323), tissue that has been banked may be accessed in lieu of fresh biopsy at baseline.
3. In women of childbearing potential only.
4. Baseline assessments must take place no more than 28 days prior to enrollment.
5. To occur anytime post treatment D21-D25 (for M, 26 for W and 27 for Th patients).

10.2 Definitive Chemoradiation (CRT) and Adjuvant Palbociclib - Steps Two and Three

	Step 2							Short Term Follow-up (weeks)[12]		Step 3						Long-Term Follow-Up										
	Definitive CRT (weeks)									Adjuvant Palbociclib[9]						Post Step 3[10]	Months post-end of CRT[11]									
	0	1	2	3	4	5	6	8-10	14-18	1	2	3	4	5	6		8	12	18	24	30	36	42	48	54	60
Cohort 1: Cisplatin[1]		X			X																					
Cohort 2: Cetuximab[7]	X	X	X	X	X	X	X																			
Accelerated IMRT[2]		X----------X																								
Palbociclib[5]										X[5]	X[5]	X[5]	X[5]	X[5]	X[5]											
PE w/palpation	X	X	X		X	X	X	X[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC	X	X	X		X	X		X		X	X	X	X	X	X	X										
CMP + magnesium	X	X			X			X		X	X	X	X	X	X	X										
BMP + magnesium			X			X																				
Neck CT w/contrast								X				X[6]			X[6]		X	X	X	X	X	X	X	X	X	X
FDG-PET/CT									X																	
Laryngoscopy								X				X[3]			X[3]		X	X	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]
EKG		X								X[8]			X[8]		X[8]	X										
FACT-H&N		X					X	X		X			X		X		X	X	X	X	X	X	X	X	X	X
EORTC QLQ-C30		X					X	X		X			X		X		X	X	X	X	X	X	X	X	X	X
Primary Site Photographs								X																		
Blood for genomic sequencing										X[13]						X[13]										

1. Cisplatin 100mg/m^2 D1, D22. IV Fluids D2-3, D23-24. Sites standard premedication(s) prior to each administration.
2. Delivered once per day M-Th with a boost of 2 treatments at least 6 hours apart on Friday
3. Assessment of primary tumor site will be done by laryngoscopy performed in the office or operating room. To occur 8 months post CRT.
4. Weekly until adequate recovery from CRT toxicities (per physician discretion)
5. Palbociclib po 125 mg/day, Days 1-21 of a 28 day cycle
6. To occur 8 months post CRT. CT of Neck AND Chest
7. Cetuximab 400mg/m^2 D-7, 250 mg/m^2 D1, 8, 15, 22, 29, 36. Sites standard premedication(s) prior to each administration. Week 0 (D -7) applies to cohort 2 only.
8. C1D1, C4D1, C6D29
9. Starting 16-22 weeks post CRT
10. 30-45 days after final cycle of adjuvant palbociclib
11. +/- 1 month
12. After completion of CRT
13. To be collected at Step 3 Cycle 1 D22 and at 4 months post Step 3 (see protocol section 9.2)

14. Laryngoscopy (FOE) will be conducted as standard of care after 12 months of follow-up, so they will occur at some, but not all, of the long-term follow-up visits

11.0 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 one patient has been enrolled) or one year after accrual has opened (if no patients have been enrolled at the six-month mark).

For phase I dose escalation studies, the Principal Investigator will review all patient data at least monthly (or before each dose-escalation if occurring sooner than monthly), and provide a semi-annual report to the Quality Assurance and Safety Monitoring Committee (QASMC). For phase II or dose expansion cohorts of a phase I study, 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 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 (phase I studies only if efficacy is objective of the protocol)
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Power analysis and/or interim analysis (if described in the protocol)
- 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.

12.0 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 Cohort Assignment Form Research Blood Form	Baseline
PEG Tube Tracker Trach Tube Tracker Weight Form Toxicity Form	Continuous
Step 1 Treatment Form	End of each cycle during Step 1
Step 2 Treatment Form	End of Step 2
Step 3 Treatment Form	End of each cycle during Step 3
MEDWATCH Form	Refer to Section 7.0
Visual Response Form	As needed
FOE or mDLx Form	Baseline Between Day 18 & 22 of Step One Cycle 2 8-10 Week Follow-up 8, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months after completion of CRT
FACT-H&N Form and QLQ-C30 Form	Baseline Step One Cycle 2 Day 22 Day 1 and 36 of RT 8-10 week Follow-up Cycle 1 Day 1 and Cycle 4 Day 1 (adjuvant) EOT (adjuvant) 8, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months after completion of CRT
RECIST Form	Baseline Step One Cycle 2 Day 22 8-10 Week Follow-up 8, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months after completion of CRT
Follow Up Form	8, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months after completion of CRT
Death Form	Time of death

12.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment must be captured in the Toxicity Form.

Participant death due to disease progression should be reported on the Toxicity Form as grade 5 disease progression. If death is due to an AE (e.g. cardiac disorders: cardiac arrest),

report as a grade 5 event under that AE. Participant death must also be recorded on the Death Form.

13.0 MEASUREMENT OF EFFECT

13.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 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.

13.2 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 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.

13.3 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 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.

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

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

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

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.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

13.4 Response Criteria

13.4.1 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).

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.

13.4.2 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).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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).

13.4.3 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

13.4.4 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.

13.4.5 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

13.4.6 Overall Survival

Overall survival is measured from time of diagnosis to time of death.

13.4.7 Response Review

All responses will be reviewed by an expert independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

14.0 STATISTICAL CONSIDERATIONS

14.1 Study Design

This three-step, non-randomized, open-label, phase II trial is designed to explore the efficacy effect of palbociclib in addition to the standard CRT regimen with either cisplatin or cetuximab in patients with $p16^{INK4a}$ negative, HPV-unrelated HNSCC (OP, Larynx, Hypopharynx, and Oral Cavity), Stage III-IV disease. In step one, all patients will be treated with neoadjuvant palbociclib monotherapy for two cycles (28 days per cycle). In step two (CRT), based upon performance status and organ function at enrollment, patients will be assigned to two cohorts: one will be treated with cisplatin and RT over 6 weeks, and the second will be treated with cetuximab and RT over 7 weeks. In step three, all patients in the trial (both cohorts) will be treated with adjuvant palbociclib for six cycles (28 days per cycle) following the completion of CRT.

14.2 Primary Endpoint

Overall tumor response to neoadjuvant palbociclib monotherapy at the end of step one, a categorical variable (CR, PR, SD, or Progression). Overall tumor response rate is defined as the proportion of subjects who achieve a CR or PR based on RECIST criteria.

14.3 Secondary Endpoints

- Local-regional disease relapse, a binary variable (Yes vs. No). Local-regional disease relapse rate is defined as the proportion of subjects alive who have local-regional progressed disease at 18 months following completion of CRT.
- Distant metastases, a binary variable (Yes vs. No). Distant metastases rate is defined as the proportion of subjects alive who have distant metastases at 18 months following completion of CRT.
- Progression-free survival (PFS), defined as the days from the start of Step 2 (CRT) to the first documentation of disease progression or death from any cause or the end of follow-up.

- Overall survival (OS), defined as the days from the time of diagnosis to death from any cause or the end of follow-up.

14.4 Study Population

Twenty-four eligible patients with $p16^{INK4a}$ negative/HPV-unrelated OPSCC, larynx SCC, hypopharynx SCC, and oral cavity SCC will be enrolled into the trial to receive 2 months of neoadjuvant palbociclib monotherapy at Step One, 6-7 weeks CRT (either cisplatin or cetuximab) at Step Two, and 6 months of adjuvant palbociclib at Step Three. The sampling method is non-random. Patients with excellent performance status and adequate vital organ function at enrollment will be assigned to the cisplatin cohort. Patients with reduced performance status and/or vital organ function will be assigned to the cetuximab cohort.

14.5 Power Analysis and Sample Size

Power analysis is conducted based upon the primary endpoint. The results of a small phase I trial of palbociclib and cetuximab in RM-HNSCC (Michel, et al., 2016) showed a tumor response rate of 22% (2 of 9 pts). In the phase I trial, the tumor response rate was 17% (1 of 6 pts) in cetuximab-resistant disease, supporting an independent effect of palbociclib in this disease. Assuming the true tumor response rate with palbociclib monotherapy in patients with $p16^{INK4a}$ negative untreated HNSCC could be substantially higher than 17%, a sample size of 24 patients yields a >80% power if the true tumor response rate is at least 38%, using a one-sided exact test at the significance level of 0.05 and null response rate of 17%. PASS 15.0 was used for sample size calculation. The results of this exploratory study are considered hypothesis-generating, and will provide critical baseline information to develop future confirmatory trials.

14.6 Data Analysis

All data will be evaluated as observed, and no imputation method for missing values will be used. All data will be presented in a descriptive manner. All analyses are considered as exploratory, even if statistical tests are 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.

14.6.1 Primary Endpoint Analyses

The tumor response rate to neoadjuvant palbociclib monotherapy at the end of step one and the corresponding 95% confidence interval will be calculated for the whole sample. Exact binomial one sample proportion test will be conducted to compare the estimated tumor response rate to a null response rate of 17%.

14.6.2 Secondary Endpoints Analyses

Local-regional disease relapse rate and distant metastases rate and their corresponding 95% confidence intervals will be calculated in each cohort, separately. PFS and OS at two-year will be presented in subject listings. PFS and OS will be analyzed by Kaplan-Meier method in each cohort, separately. Paired t-test or paired-sample Wilcoxon Signed Rank test will be used to compare the genomic, RNA, and protein expression data derived at baseline and then after two cycles of neoadjuvant palbociclib monotherapy. The association between the genomic, RNA, and protein expression data derived after 2 cycles of palbociclib monotherapy and local-regional disease relapse/distant metastases will be explored through independent t-test, Fisher's Exact test, or Kruskal-Wallis test as appropriate.

14.7 Interim Efficacy Assessment and Interim Analyses

An interim efficacy assessment will be performed after the first 14 patients are enrolled and have completed step one. Progression events will be the primary concern for the interim efficacy analysis. Progression, as used for this purpose, will be defined as disease progression on CT scan of the neck (assessed by RECIST criteria) occurring at the completion of step one. The occurrence of three or more progression events during step one will be cause to stop trial accrual to assess if the trial should be amended, closed, or continued as planned. The interim analysis will be prepared for preliminary (abstract) presentation at cancer meeting(s). Trial accrual will not be stopped while the interim efficacy analysis is ongoing. The stopping rule will not be considered in this interim efficacy analysis given the small sample size.

A safety assessment will be performed for the first 14 patients enrolled using a continuous method. The safety endpoint of interest is delays in starting potentially curative chemoradiation therapy defined as failure to start chemoradiation within three weeks of cycle 2 day 28 (of Step One) due to adverse events considered to be definitely, probably, or possibly related to palbociclib. Trial accrual should be stopped to assess if the trial should be amended, closed, or continued as planned, using the following thresholds for continuous assessment:

# of patients delayed in starting chemoradiation	In first # of patients
2	4
2	5
2	6
3	7
3	8
3	9
4	10
4	11
4	12
4	13
5	14

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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: Medication Diary

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

Formulation: ___ Liquid ___ Capsules Route (if liquid): ___ By mouth ___ Feeding tube

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle. Take _____mg of palbociclib at approximately the same time each day with food (if capsules) or with or without food (if liquid). 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 forget to take your dose before 6:00PM, then do not take a dose that day. Restart taking it the next day.
4. If you have any questions or notice any side effects, please record them in the comments section. Record the time if you should vomit.
5. Please return the forms 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.
6. Avoid St. John's Wort, Seville oranges, grapefruit, grapefruit juice, grapefruit hybrids, pummelos, and exotic citrus fruits from 7 days before you start taking palbociclib and throughout the entire study.

Day	Date	What time was dose taken?	# of capsules taken, if applicable	Comments
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				

APPENDIX C: Pfizer Reportable Event Cover Sheet

Investigator-Initiated Research
Reportable Event Fax Cover Sheet

Use this fax cover sheet to fax a Reportable Event for Investigator-Initiated Research studies.

Include with this form the completed Pfizer Investigator-Initiated Research Serious Adverse Event (IIR SAE) form, MedWatch Form FDA 3500A-Mandatory Reporting, which can be obtained from the FDA website: www.fda.gov/medwatch/getforms.htm, or other Pfizer agreed-upon form for SAE reporting.

If you are using the MedWatch Form to report, the following information should be included in block 5 of the Adverse Events section:

- **The complete clinical course of the patient receiving Pfizer drug**
- **The causality assessment for each Reportable Event**
- **The action taken for each study drug and for each Reportable Event**
- **The outcome for each Reportable Event**

This cover sheet MUST be provided with each completed SAE form. Do not substitute forms/reports or submit additional documentation other than what is required.

Do not fax these forms to any additional fax numbers other than the one listed below.

TO:	*Pfizer U.S. Clinical Trial Department*		
FAX:	*1-866-997-8322*		
FROM:		DATE:	
TELEPHONE:		FAX:	
NUMBER OF PAGES (INCLUDING COVER SHEET):			
PRODUCT	PRODUCT NAME		
PFIZER REFERENCE NUMBER	TRACKING NUMBER	EXTERNAL REFERENCE NUMBER	EXTERNAL REFERENCE
STUDY TITLE	*STUDY TITLE*		
PATIENT NUMBER			
INVESTIGATOR	INVESTIGATOR NAME, DEGREE		

FormCT26-USA01-10 Reportable Event Fax Cover Sheet: US_eff 19-DEC-2008

APPENDIX D: 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?				
18. Were you tired?				
19. Did pain interfere with your daily activities?				
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?				
21. Did you feel tense?				
22. Did you worry?				
23. Did you feel irritable?				
24. Did you feel depressed?				

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

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 E: 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 F: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 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

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

D. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse event

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

E. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

F. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

APPENDIX G: Reporting Timelines

Expedited Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Drug/Device Manufacturer**
Serious AND unexpected suspected adverse reaction			Report no later than 15 calendar days after it is determined that the information qualifies for reporting	Within 24 hours of first awareness of the event
Unexpected fatal or life-threatening suspected adverse reaction			Report no later than 7 calendar days after initial receipt of the information	Immediately if the event is fatal or life-threatening
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment		
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.			
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.			
Protocol exception	Approval must be obtained prior to implementing the change			
Clinically important increase in the rate of a serious suspected adverse			Report no later than 15 calendar days after it is determined that the	

Event	HRPO	QASMC	FDA	Drug/Device Manufacturer
reaction of that list in the protocol or IB			information qualifies for reporting	
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.			
Breach of confidentiality	Within 10 working days.			
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.			

Routine Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Drug/Device Manufacturer**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report which is typically due every 6 months.	The most current toxicity table from the DSM report is provided to the FDA with the IND's annual report.	
Minor deviation	Report summary information at the time of continuing review.			
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.			
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and			

the patient will be withdrawn, report at continuing review.