Phase I/II Trial of the Addition of PD 0332991 to Cetuximab in Patients with Incurable SCCHN

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Study Drug: PD 0332991 (palbociclib)

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Protocol Revision History

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Principal Investigator Signature Page

Principal Investigator:	Douglas R. Adkins, M.D.	
	Signature of Investigator	Date
	Printed Name of Investigator	
	By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/HRPO procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.	

Phase I/II Trial of the Addition of PD 0332991 to Cetuximab in Patients with Incurable SCCHN

SCHEMA

Eligible Patients

- Incurable SCCHN
- Any (or no) prior therapy acceptable for phase I; prior treatment with a platin agent for Arm 1 of phase II; prior treatment with cetuximab for Arms 2 and 3 of phase II
- Prior treatment with cetuximab acceptable for phase I and for Arms 2 and 3 of phase II only
- HPV-related or -unrelated for phase I; only HPV-unrelated for Arms 1 and 2 of phase II; only HPV-related for Arm 3 of phase II

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Treatment Plan

PD 0332991 PO Days 1-21 of each 28 day cycle
Cetuximab weekly
Dosing of PD 0332991 for phase II is 125 mg (based on Phase I results)

CT scans every 2 cycles

Dose Escalation Schedule (for the Phase I portion)		
Dose Level	**PD 0332991 Dose***	**Cetuximab Dose**
Level -1	75 mg	Loading dose: 400 mg/m^2 Weekly thereafter: 250 mg/m^2 for the duration of study participation
Level 1 (Starting Dose)	100 mg	
Level 2	125 mg	

* PD 0332991 is administered on Days 1 through 21 of each 28-day cycle.

Glossary of Abbreviations

AE	Adverse event
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
AUC	Area under the curve
B-HCG	Beta human chorionic gonadotropin
CBC	Complete blood count
CDK	Cyclin dependent kinase
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DLTs	Dose Limiting Toxicities
DNA	deoxyribonucleic acid
DSM	Data and Safety Monitoring
ECG (or EKG)	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ER	Estrogen receptor
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FISH	fluorescent in situ hybridization
FWA	Federal wide assurance
GI	Gastrointestinal
HIV	Human Immunodeficiency Virus
HPV	Human papilloma virus
HRPO	Human Research Protection Office (IRB)
HSR	Hypersensitivity reaction
IHC	Immunohistochemistry
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IULN	Institutional upper limit of normal
IV	Intravenous (i.v.)
IVPB	IV push bolus
LFT	Liver function test
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute

NIH	National Institutes of Health
OHRP	Office of Human Research Protections
OPSCC	Oropharyngeal squamous cell carcinoma
OS	Overall survival
PD	Progressive disease
PDX	Patient derived xenograft
PET	Positron emission tomography
PFS	Progression-free survival
PI	Principal investigator
PK	Pharmacokinetic
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QASMC	Quality Assurance and Safety Monitoring Committee
QD	Quaque die (once a day)
QTc	Corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors (Committee)
SAE	Serious adverse event
SCC	Siteman Cancer Center
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable disease
TTP	Time to progression
UPN	Unique patient number
US	Ultrasound
WHO	World Health Organization

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1.0 BACKGROUND AND RATIONALE

1.1 Squamous Cell Carcinoma of the Head and Neck

Squamous cell carcinoma of the head and neck (SCCHN) is the sixth most common cancer. Approximately 600,000 new cases occur yearly, and most patients present with locally advanced disease. Current multimodality therapy results in 5-year overall survival (OS) of only 40-50%.

SCCHN is a heterogeneous disease which is not completely defined by clinical variables such as primary tumor stage, nodal stage, and sub-site. Smoking is the most common etiologic agent. More recently, human papillomavirus (HPV) was shown to be an important causative agent in oropharyngeal SCC (OPSCC). Assessment of p16 by immunohistochemistry (IHC) is an excellent surrogate marker of transcriptionally active HPV in OPSCC since nearly all cases of HPV-related OPSCC will demonstrate strong and diffuse staining for p16. OPSCC due to HPV carries a much better prognosis compared to OPSCC due to smoking, establishing the importance of HPV as a stratification variable in OPSCC.[1]

Gene expression profiling has highlighted the heterogeneity of SCCHN. Chung, *et al* identified four subtypes of SCCHN using expression profiling: 1) EGFR enriched, 2) mesenchymal-like, 3) normal tonsil-like, and 4) anti-oxidant enriched.[2-3] Prognosis varied amongst these subgroups. Importantly, the unique gene expression profile of each subgroup shed light on potential molecular drivers which can define tumors likely to be sensitive or resistant to selected targeted therapies.

1.2 EGFR

EGFR is overexpressed in many cases of SCCHN and is clearly important in this disease. Cetuximab, a monoclonal antibody against EGFR, is the only molecularly targeted therapy to date that has been shown to improve OS in SCCHN.[4-5] These data are proof-of-principle that defining the molecular drivers of the various subsets of SCCHN can lead to further improvements in treatment outcomes. However, the relative benefit of cetuximab in the treatment of SCCHN has been modest, suggesting that most cases of SCCHN are primarily dependent on non-EGFR molecular drivers.

1.3 CCND1 and p16 in SCCHN

CCND1, which encodes cyclin D1, is amplified in 80% or more cases of HPV-unrelated SCCHN[6] and is a marker of poor prognosis.[7-15] Internal data from this institution (J. Lewis, unpublished observations) showed that 116 of 121 (96%) cases of HPV-unrelated SCCHN had expression of cyclin D1 as assessed by IHC, and in the majority of cases, $\geq$ 20% of nuclei stained positive (range, 1-95%). These observations did not vary across subsites as nearly all cases of larynx, hypopharynx, oral cavity and HPV-unrelated oropharynx SCCHN had expression of cyclin D1 by IHC. In contrast, CCND1 is overexpressed in

only 14% of cases of HPV-related OPSCC.[16] CDKN2A, which encodes p16INK4a, is inactivated in most cases of HPV-unrelated SCCHN by mutation, methylation in combination with chromosome loss or by homozygous deletion.[17] Over expression of cyclin D1 along with decreased expression of p16 and abrogation of p53 function cause cellular immortalization of oral keratinocytes.[18] **Thus, cyclin D1 over expression in the context of decreased expression of p16 is likely to be an important driver of HPV-unrelated SCCHN.**

The consequences of cyclin D1 amplification for response to therapy are not well characterized; however, emerging data suggests that cyclin D1 amplification may adversely affect response of SCCHN tumors to the two most effective drugs used in the treatment of this disease: EGFR inhibitors and cisplatin. CCND1 is one of the many genes induced by intranuclear EGFR, linking cell cycle progression to EGFR stimulation.[19] Data from SCCHN cell lines suggest an association between resistance to EGFR inhibitors and cyclin D1 amplification and/or overexpression.[20] In EGFR-mutant lung cancer cells, cyclin D1 expression was higher in comparison to EGFR-wild type cells.[21] EGFR-mutant gefitinib-resistant lung cancer cells were sensitive to the CDK inhibitor flavopiridol, confirming the importance of the cycle D axis as a key downstream effector of mutant EGFR signaling. Cyclin D1 overexpression in SCCHN was associated with cisplatin resistance *in vitro* and *in vivo* [22, 23] and data from patients with SCCHN has emerged that supports a similar relationship of cyclin D1 expression as a predictive biomarker of cisplatin resistance.[24]

1.4 CDK4/6

Cyclin-dependent kinases (CDKs), play a key role in regulating cell cycle progression and manage cellular transitions from growth phase (G1 and G2) into phases associated with DNA replication (S) and mitosis (M).[25,26] Interaction between CDKs and cyclin proteins, such as cyclin D, has been shown to be crucial in the progression of G1 to S in the cell cycle.[27] Deregulation of aspects of the cell-cycle, including CDKs, have been shown to contribute to the development of cancer.[25,27] CDK4 and CDK6 are two closely related kinases that enable tumor cell progression during phase G1 to phase S in the cell cycle.[26] CDK 4 and 6 stimulate cell cycle progression, necessary for DNA replication and for cell division, in combination with cyclin D.[26] In preclinical studies, increased levels of cyclin D and decreased levels of p16, a naturally occurring inhibitor of CDK4, have been associated with increased sensitivity to CDK 4 and 6 inhibition.[27] Preclinical studies suggest that inhibition of cyclin D-dependent kinase activity may prevent tumor growth.[26] Inhibition of CDK 4 and 6 has been shown to prevent the deactivation of retinoblastoma (Rb), a tumor suppressor protein, and interfere with tumor cell progression.[28]

1.5 Investigational Agent(s)

PD 0332991 is an investigational, orally active and highly selective inhibitor of the CDK4 and CDK6 kinases[26] with low activity against a panel of 36 other protein kinases. PD 0332991 showed antiproliferative effects on Rb-positive cells in vitro and inhibition of tumor growth in several Rb-positive human breast and colon xenografts.[26] In these models,

PD 0332991 resulted in decreased Rb phosphorylation and decreased Ki-67 expression.[26] PD 0332991 showed no activity in Rb-negative tumor xenografts.[26]

Pfizer is evaluating PD 0332991 in multiple phase I, phase II, and phase III studies. Two phase I trials evaluated single agent administration of PD 0332991 to patients with Rb-positive cancers.[29,30] One of these trials determined that the dose-limiting toxicity (DLT) of PD 0332991 was neutropenia and the maximum tolerated dose (MTD) was 125 mg once daily when administered for 21 of 28 days (3/1 schedule).[29] The most common non-hematologic adverse events included fatigue, nausea, and diarrhea. The mean half-life of PD 0332991 was 25.9 hours. Patients were selected for Rb-positive cancers, based on IHC stain, defined as positive if staining intensity was 1+ or greater above background. Stable disease for ≥ 4 cycles (16 weeks) occurred in 27% of evaluable patients and in a number of tumor types (liposarcoma, testicular, renal, ovarian, breast, appendiceal, peritoneal, melanoma, thymoma and lung). Another phase I trial of PD 0332991 using an alternative dosing plan (21 day cycles; 2/1 schedule) observed a similar likelihood of disease control in a variety of tumor types.[30] These studies demonstrate that PD 0332991 has substantial activity in Rb-positive tumors.

Results of a phase I study in estrogen-receptor positive, HER2-negative advanced breast cancer not selected for cyclin D1 amplification and/or p16 loss showed that the combination of PD 0332991 and letrozole was generally well tolerated, with the recommended dose of PD 0332991 to be 125 mg once daily.[31] A second study was a randomized phase II trial initiated to determine the overall safety and efficacy of PD 0332991 (125 mg) and letrozole (2.5 mg) versus letrozole alone in post-menopausal women with ER+ HER2- advanced breast cancer.[32,33] Patients' tumors were either unselected (Part 1) or selected (Part 2) for presence of biomarkers: cyclin D1 amplification by FISH and/or p16 loss. In Part 1 of the trial, the objective response rate was 27% versus 23% with PD 0332991 plus letrozole versus letrozole alone and the clinical benefit rate was 59% versus 44%, respectively.[32] When Parts 1 and 2 of the trial were combined, the objective response rate was 45% for those women who received PD 0332991 plus letrozole versus 31% for those who received letrozole alone. The clinical benefit rate (defined as complete response plus partial response plus stable disease for ≥24 weeks) was 70% versus 44%, respectively. The differences observed in the objective response rate and clinical benefit rate were statistically significant. Importantly, the median progression-free survival (PFS) was significantly different (26.2 versus 7.5 months) favoring the combination arm. The most frequently reported treatment-related Grade 3/4 adverse events (AEs) in patients who received the combination therapy were neutropenia, leukopenia, anemia and fatigue.

PD 0332991 is also active in relapsed mantle cell lymphoma selected for cyclin D1 overexpression.[34] The objective response (CR or PR) rate was 18% and the stable disease rate was 41%. Significant reductions in phospho-Rb (89%) and Ki-67 (74%) occurred in paired biopsy samples after treatment with PD 0332991.

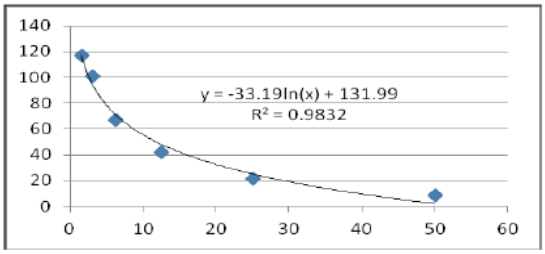
Taken together, these data provide sound evidence that inhibition of CDK4 and CDK6 kinases can be effective treatment for cancer that is selected for cyclin D1 amplification

and/or p16 loss.

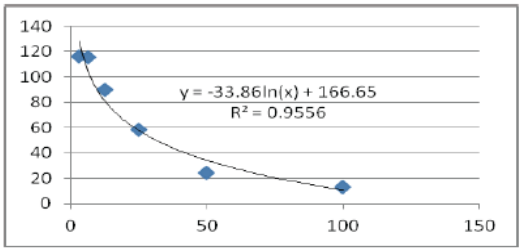
1.6 CDK4/6 Inhibition in HNSCC: Pre-Clinical Evidence of Tumor Response

Dr. Loren Michel in our group generated cisplatin-resistant derivative SCC1 cell lines from cisplatin-sensitive SCC1 by continuous exposure to cisplatin. The IC50 of cisplatin-resistant derivative SCC1 was three-fold higher than that of cisplatin-sensitive SCC1 (31.3 uM and 11.8 uM, respectively).

Generation of Cisplatin Resistant Derivative Cell Lines from Human Head and Neck Squamous Cell Cancer Lines



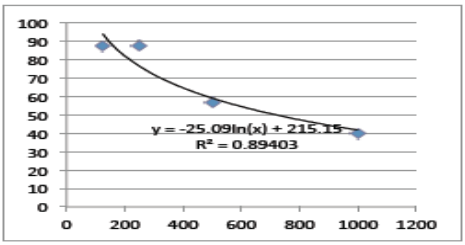
-81.99		
2.470322		
11.8	uM (SCC1)	



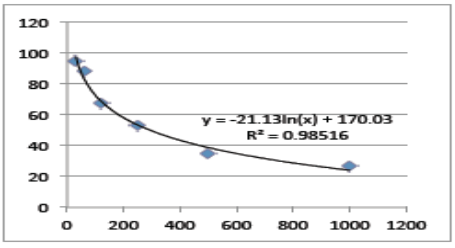
-116.65		
3.445068		
31.3	uM (Cis R. 14 uM)	

Cisplatin-resistant and cisplatin-sensitive SCC1 cell lines were then exposed to varying concentrations of PD 0332991, and the IC50 of the two cell lines to PD 0332991 were compared. As seen, the IC50 of cisplatin-resistant derivative SCC1 was 2.5 fold lower than that of cisplatin-sensitive SCC1 (293.1 nM and 722.2 nM, respectively) showing that cisplatin-resistant SCC1 is hypersensitive to PD 0332991 compared to cisplatin-sensitive SCC1.

Cisplatin-Resistant Cells are Hypersensitive to PD0332991



-165.15
6.5823037
722.2 nM (SCC1)

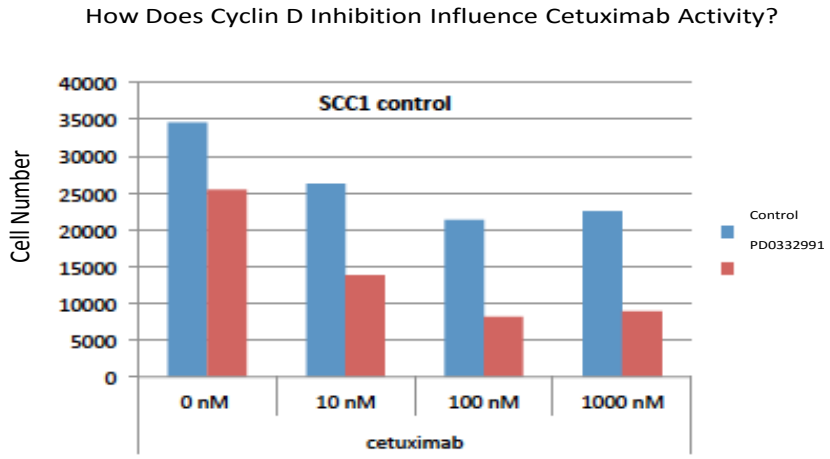


-120.03
5.680549
293.1 nM (Cis R.)

These data were replicated in another cell line (SCC25), in which the IC50 of cisplatin-

resistant derivative SCC25 was 4.0 fold lower than that of cisplatin-sensitive SCC25.

The effects of CDK 4/6 inhibition on cetuximab activity was then investigated in the SCC1 cell line. The data shown supports that: 1) co-exposure of PD 0332991 and cetuximab adds to the anti-proliferative effects of cetuximab alone, and 2) PD 0332991 alone has anti-proliferative effects on the SCC1 cell line.



Dr. Van Tine's laboratory is interested in: 1) validating the efficacy of PD 0332991 in patient-derived xenograft (PDX) models in the clinical context of cisplatin resistance and cetuximab synergy, and 2) identifying the mechanisms and hence the biomarkers that predict hypersensitivity to CDK 4/6 inhibition using the cisplatin-resistant cell lines his laboratory has generated as tools for this undertaking.

1.7 Study Rationale

Most patients with locally advanced HPV-unrelated SCCHN develop recurrent cancer and all patients with metastatic SCCHN ultimately die due to the disease. The EGFR inhibitor cetuximab is an important recent addition to the standard treatment options for SCCHN but has resulted in only modest improvements in clinical outcomes. New treatments are needed.

Over expression of cyclin D1 and inactivation of p16 occur in the vast majority of cases of HPV-unrelated SCCHN. Genomic characterization of oral SCCHN identified amplification of CCND1 and/or loss of CDKN2A (p16) were found in 94% of tumors, supporting that cell cycle alterations were a nearly universal feature.[35] Resistance to EGFR inhibitors and to cisplatin, the two most effective systemic agents in SCCHN, may be in part mediated by cyclin D1 overexpression which can be targeted with inhibitors of the cyclin D axis. PD 0332991 is a selective inhibitor of CDK4 and CDK6 kinases, which enhanced tumor response to letrozole in women with metastatic breast cancer selected for

the presence of cyclin D1 amplification and/or p16 loss. PD 0332991 also has efficacy in cyclin D1 overexpressing mantle cell lymphoma and has activity in a broad range of other solid tumors.

Our laboratory investigation of PD 0332991 in the SSC1 cell line demonstrated: 1) the IC50 of cisplatin-resistant derivative SCC1 to PD 0332991 was 2.5 fold lower than that of cisplatin-sensitive SCC1 (293.1 nM and 722.2 nM, respectively) showing that cisplatin-resistant SCC1 is hypersensitive to PD 0332991 compared to cisplatin-sensitive SCC1, 2) co-exposure of PD 0332991 and cetuximab adds to the anti-proliferative effects of cetuximab alone, and 3) PD 0332991 alone has anti-proliferative effects on the SCC1 cell line. These preclinical data support the conclusions that PD 0332991 has single agent activity in HNSCC, PD 0332991 is more effective against cisplatin-resistant than cisplatin-sensitive HNSCC, and PD 0332991 and cetuximab are synergistic against HNSCC.

Based on the evidence presented, we propose a phase I/II trial to test our hypotheses that the addition of PD 0332991 to cetuximab will be feasible and will improve tumor response rate and time-to-progression (TTP) in patients with platin-resistant incurable SCCHN in comparison to historical controls. In the phase II portion of the trial, patients will be required to have HPV-unrelated SCCHN tumors (which as a group are known to have nearly universal cyclin D1 overexpression or amplification and/or p16 loss) to enrich the likelihood of clinical benefit of PD 0332991. Cetuximab will be used as the platform to add PD 0332991 to since cetuximab is the current standard FDA-approved treatment indicated for patients with platin-resistant incurable SCCHN.

1.8 Amendment 6: Addition of Arm 3 to Phase II

The genomics of HPV-related SCCHN has been characterized predominantly in primary (untreated) tumor specimens. In primary HPV-related SCCHN, overexpression of p16 is a physiologic response to binding of the E7 viral oncoprotein to Rb. The normal function of p16 to inhibit the complex of CDK 4/6 and cyclin D is inconsequential due to the downstream alteration of Rb function by E7. Since palbociclib inhibits at a step upstream of pRb, palbociclib would not be expected to benefit patients with untreated HPV-related SCCHN.

However, recent work found that the genomics of recurrent/metastatic (RM) HPV-related SCCHN more closely resembles that of HPV-unrelated SCCHN.[36] In particular, the frequencies of TP53 mutations (15%), whole genome duplication (25%), and 3p deletion (55%) were significantly higher in RM tumors compared to primary tumors. Mutations in CDKN2A and amplification of 11q13 were observed in RM HPV-related SCCHN.

These data suggest that RM HPV-related SCCHN may respond to a CDK 4/6 inhibitor like palbociclib. Based on these observations, and the potential of palbociclib to inhibit one mechanism of resistance to EGFR inhibitors, we hypothesize palbociclib and cetuximab will result in tumor responses in patients with cetuximab-resistant RM HPV-related SCCHN. Arm 3 will enroll only patients with cetuximab-resistant disease, for which there are few, if any, standard treatment options.

1.9 Correlative Studies Background

The purpose of the correlative studies is to correlate overall response and TTP to cyclin D1 expression and p16 loss, both assessed by IHC, in Phase II patients with HPV-unrelated SCCHN treated with PD 0332991 and cetuximab. The methodology for assessment of cyclin D1 and p16 by IHC has been previously described.[16] At this time, a review of the literature does not clearly define the optimal methodology or cut thresholds for a positive and a negative result for cyclin D1 expression as it relates to clinical effect of PD 0332991 or other cell cycle inhibitors. IHC was chosen as the method to assess cyclin D1 expression in this study since it is a widely available methodology for assessing protein expression that is familiar to most investigators and clinical laboratories. For similar reasons, p16 will also be assessed by IHC although a generally agreed upon definition for positive p16 (>50%; 3+ or 4+) and negative p16 (Negative or <50%; 1+ or 2+) results are available.[16] However, these definitions are geared toward HPV-related OPSCC which are nearly always strongly and diffusely positive for p16 by IHC. In our experience, HPV-unrelated OPSCC and SCCHN from other subsites are nearly always p16 negative (that is, truly no staining). Thus, for the purposes of the correlative studies in this trial, we will define negative p16 to mean no staining and positive p16 to mean any staining.

Patients who participate on the Phase II portion of the trial (Arms 1 and 2 only) will be asked to consent to optional pre-Cycle 1 and post-Cycle 2 (to be collected anytime between Days 15 and 21 inclusive and at disease progression) tumor biopsies (core or excisional/incisional) to perform p16 expression, Ki-67 by IHC, total and phospho-Rb by IHC, Cyclin D1 by IHC, and TUNEL assay, and to analyze other potential biomarkers as they emerge from the scientific understanding of PD0332991 activity on formalin-fixed paraffin-embedded (FFPE) tissue. The major function of cyclin D-CDK4/6 complexes is to promote S phase entry. This can best be assayed by examining the effects of PD 0332991 on the proliferation marker Ki-67. Suppression of the activity of cyclin-CDK4/6 activity is predicted to decrease proliferation, the readout of which will be reduced percentage of cells staining positive for Ki-67 post-treatment. In addition, PD 0332991 should only be active in tumors that are Rb positive. Moreover, Rb is a substrate of cyclin D-CDK4/6. Therefore, measurement of total and phospho-Rb, which have served as pharmacodynamic markers for PD 0332991 in other clinical trials, will be evaluated. This agent should not affect total Rb, but suppress phospho-Rb. Lastly, to determine whether changes in proliferation and Rb phosphorylation are associated with an increase in apoptosis, TUNEL assay will be performed. All of these assays can be completed on FFPE tissue.

2.0 OBJECTIVES

2.1 Primary Objectives

1. Phase I: To determine the maximum tolerated dose of PD 0332991 when administered in combination with cetuximab to patients with incurable SCCHN

2. Phase II, Arm 1: To determine the efficacy of PD 0332991 in combination with cetuximab in incurable platin-resistant HPV-unrelated SCCHN. Efficacy will be measured by the overall response rate (ORR=CR+PR) defined by RECIST criteria.
3. Phase II, Arm 2: To determine the efficacy of PD 0332991 in combination with cetuximab in incurable cetuximab-resistant HPV-unrelated SCCHN. Efficacy will be measured by the overall response rate (ORR=CR+PR) defined by RECIST criteria.
4. Phase II, Arm 3: To determine the efficacy of PD 0332991 in combination with cetuximab in incurable cetuximab-resistant HPV-related SCCHN. Efficacy will be measured by the overall response rate (ORR=CR+PR) defined by RECIST criteria.

2.2 Secondary Objectives

1. Phases I and II, Arms 1, 2, and 3: To assess the adverse events of PD 0332991 in combination with cetuximab
2. Phase II, Arms 1, 2, and 3: To assess the progression-free survival (PFS) of patients with incurable SCCHN treated with PD 0332991 in combination with cetuximab
3. Phase II, Arms 1, 2, and 3: To assess the overall survival (OS) of patients with incurable SCCHN treated with PD 0332991 in combination with cetuximab
4. Phase II, Arms 1, 2, and 3: To assess duration of response/stable disease of patients with incurable HPV-unrelated SCCHN treated with PD 0332991 in combination with cetuximab

2.3 Exploratory Objectives

1. Phase II, Arms 1 and 2: To document changes in p16 expression, Ki-67 (IHC), phospho-Rb (IHC), Cyclin D1 (IHC), and apoptosis (TUNEL assay) after cetuximab and PD 0332991. Exploratory analysis will be performed to correlate these molecular changes with clinical endpoints (OR, TTP, PFS, and OS). RNA sequencing will also be performed.
2. Phase II, Arms 1, 2, and 3: To monitor quality of life as documented by QOL measurements from the FACT H&N and EORTC QLQ-C30.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. Histologically or cytologically confirmed diagnosis of squamous cell carcinoma of the head and neck.

2. Disease must be considered incurable. Incurable is defined as metastatic disease or a local or regional recurrence in a previously irradiated site that is unresectable (or patient declines resection).

3. Measurable disease defined as lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$10 mm with CT scan, as $\geq$20 mm by

chest x-ray, or ≥10 mm with calipers by clinical exam. (Phase I only: patients without measurable disease by RECIST 1.1 criteria but with evaluable disease by imaging or physical exam will be eligible as well.)

4. Phase I only: any (or no) prior therapy for metastatic disease is allowed, including cetuximab. If a patient has not received prior standard therapy, s/he must have been offered and refused prior standard therapy.

5. Phase II only:
   Arm 1: disease progression after at least one cycle of prior treatment with cisplatin or carboplatin for incurable disease. Prior treatment with cetuximab for incurable disease is not permitted.
   Arms 2 and 3: disease progression after at least one cycle of treatment with cetuximab for incurable disease.

6. Phase II only: at least one line of prior therapy for incurable disease.

7. Phase II only:
   Arms 1 and 2: disease must be determined to be HPV-unrelated. HPV-unrelated SCCHN is defined as either p16-negative OPSCC or non-OPSCC (larynx, hypopharynx, oral cavity) or p16-negative unknown primary SCC presenting with a level 2 or 3 neck node. p16 will be assessed by IHC; a specimen showing any staining will be considered p16-positive.
   Arm 3: disease must be HPV-related SCCHN (defined as OPSCC or unknown primary presenting with a neck mass that is either p16 positive or HPV ISH or PCR positive).

8. Minimum of 14 days elapsed since the end of any prior therapy.

9. At least 18 years of age.

10. Resolution of all acute toxic effects of prior anti-cancer therapy or surgical procedures to NCI CTCAE version 4.0 Grade ≤ 1 (except alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion)

11. ECOG performance status ≤ 2 (see Appendix A).

12. Adequate bone marrow and organ function as defined below:
    a. Absolute neutrophil count ≥ 1,500 mm^3
    b. Platelets ≥ 100,000 mm^3
    c. Hemoglobin > 9 g/dL
    d. Total bilirubin ≤ 1.5 x IULN except in the case of patients with Gilbert's disease
    e. AST (SGOT) and ALT (SGPT) ≤ 2.5 x IULN for patients without liver metastases and ≤ 5.0 x IULN for patients with liver metastases
    f. Alkaline phosphatase ≤ 2.5 x IULN for patients without bone metastases and ≤ 5.0 x IULN for patients with bone metastases

g. Serum creatinine ≤ 1.5 x IULN OR calculated creatinine clearance ≥ 50 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal

13. Baseline corrected QT interval (QTc) < 480 ms.

14. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

15. Available archival tumor tissue for the proposed correlative studies.

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

3.2 Exclusion Criteria

1. Phase II, Arm 1 only: prior treatment with cetuximab.

2. A history of other malignancy ≤ 1 year previous with the exception of basal cell or squamous cell carcinoma of the skin which were treated with local resection only, carcinoma *in situ* of the cervix, or synchronous H&N primaries.

3. Currently receiving any other investigational agents.

4. Patient must not have a history of or clinical evidence of central nervous system metastases or leptomeningeal carcinomatosis, except for individuals who have had previously-treated CNS metastases, are asymptomatic, and have had no requirement for steroids or anti-seizure medications (with the exception of Keppra) for 1 month prior to first dose of PD 0332991.

5. A history of allergic reactions attributed to compounds of similar chemical or biologic composition to PD 0332991, cetuximab, or other agents used in the study.

6. Treated within the last 7 days prior to Day 1 of protocol therapy with:
   a. Food or drugs that are known to be CYP3A4 inhibitors (e.g. grapefruit juice, verapamil, ketoconazole, miconazole, itraconazole, erythromycin, clarithromycin, telithromycin, indinavir, ritonavir, nelfinavir, atazanavir, amprenavir, nefazodone, diltiazem, and delavirdine) or inducers (i.e. dexamethasone, glucocorticoids, progesterone, rifampin, phenobarbital, St. John's wort). (See Appendix D)
   b. Drugs that are known to prolong the QT interval.
   c. Drugs that are proton pump inhibitors.

7. Uncontrolled electrolyte disorders that can compound the effects of a QTc-prolonging drug (e.g., hypocalcemia, hypokalemia, hypomagnesemia)

8. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

9. 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 contraceptive during the period of the trial and for at least 90 days after completion of treatment. The decision of effective contraception will be based on the judgment of the principal investigator or a designated associate.

10. Phase I and Arm 1 of Phase II: Known HIV-positivity and on combination antiretroviral therapy because of the potential for pharmacokinetic interactions with PD 0332991. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.
    Arms 2 and 3 of Phase II: patients with HIV infection and antiretroviral therapy are not excluded, as there are no pharmacokinetic tests being performed.

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 by Washington University
2. Registration of patient in the Siteman Cancer Center OnCore database
3. Assignment of unique patient number (UPN)

Once the patient has been entered in the Siteman Cancer Center OnCore database, the WUSM coordinator will forward verification of enrollment and the UPN via email.

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below and scanning and emailing it to the research coordinator listed in the *Siteman Cancer Center Clinical Trials Core Protocol Procedures for Secondary Sites* packet at least one business day prior to registering patient:

1. Your name and contact information (telephone number, fax number, and email address)
2. Your site's PI's name, the registering MD's name, and your institution name
3. Patient's race, sex, and DOB
4. Three letters (or two letters and a dash) for the patient's initials
5. Currently approved protocol version date
6. Copy of signed consent form (patient name may be blacked out)
7. Planned date of enrollment
8. Completed eligibility checklist, signed and dated by a member of the study team
9. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

Registrations may be submitted Monday through Friday between 8am and 5pm CT. Urgent late afternoon or early morning enrollments should be planned in advance and coordinated with the Washington University research coordinator. Registration will be confirmed by the research coordinator or his/her delegate by email within one business day. Verification of eligibility and registration should be kept in the patient chart.

All patients at all sites must be registered through the Siteman Cancer Center OnCore database at Washington University.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. Patients will also be identified by first, middle, and last initials. If the patient has no middle initial, a dash will be used on the case report forms (CRFs). All data will be recorded with this identification number on the appropriate CRFs.

5.0 TREATMENT PLAN

5.1 Premedication for Cetuximab

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 cetuximab. Premedication may also include one liter of normal saline, hydrocortisone 100 mg IVPB, and/or albuterol inhalation (by nebulizer or inhaler) according to standard of care procedures.

5.2 Agent Administration

PD 0332991 should be taken by mouth on Days 1 through 21 of each 28-day cycle. **Patients should take PD 0332991 capsules with food.** Patients will be required to keep

a drug diary (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.

Cetuximab will be administered intravenously on a weekly schedule. The first dose of cetuximab will be 400 mg/m^2; every week thereafter, patients will receive a dose of 250 mg/m^2. Patients will continue to receive weekly cetuximab at 250 mg/m^2 for the duration of their participation on study.

Upon IRB/EC approval of Amendment 5, a PD 0332991 oral solution will be available for patients who cannot swallow the PD 332991 capsules. 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 PD 0332991 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 PD 0332991 oral solution. **Patients can take PD 0332991 oral solution with or without food.**

5.3 Re-Treatment Criteria

A new cycle of treatment with PD 0332991 may begin only if:

- ANC ≥1,000/mcL.
- Platelets count ≥50,000/mcL.
- Non-hematologic toxicities have returned to baseline or no greater than grade 1 (or no greater than grade 2 if not considered a safety risk for the patient (at the investigator's discretion)).

If these conditions are not met, treatment with PD 0332991 must be delayed by one week. If, after a one-week delay, all toxicities have recovered within the limits described above, treatment with PD 0332991 can be resumed.

If the patient has not recovered after 2 weeks (including the scheduled 1-week off treatment period within a cycle), treatment with PD 0332991 will be permanently discontinued.

5.4 Dose Escalation Schema for Phase I

Dose Escalation Schedule (for the Phase I portion)		
Dose Level	**PD 0332991 Dose***	**Cetuximab Dose**
Level -1	75 mg	Loading dose: 400 mg/m^2 Weekly thereafter: 250 mg/m^2 for the duration of study participation
Level 1 (Starting Dose)	100 mg	
Level 2	125 mg	

* PD 0332991 is administered on Days 1 through 21 of each 28-day cycle.

Dose escalation will not occur until all patients in the cohort have completed the first cycle and the Principal Investigator has been able to review all toxicities.

5.5 Definition of MTD, DLT, Dose Escalation Criteria, and Toxicity, Response, and DLT Evaluations for Phase I

5.5.1 Definition of Maximum Tolerated Dose (MTD)

The maximum tolerated dose (MTD) is defined as the dose level immediately below the dose level at which 2 patients of a cohort (of 2 to 6 patients) experience dose-limiting toxicity during the first cycle. Dose escalations will proceed until the MTD has been reached.

5.5.2 Dose Limiting Toxicities (DLTs)

Hematologic DLT is defined as any of the following that occur during the first cycle that are attributed as possibly, probably, or definitely related to the study treatment:

- grade 4 neutropenia ≥ 7 day duration
- grade 4 infection with grade 3 or 4 neutropenia
- grade 4 thrombocytopenia associated with life-threatening bleeding
- treatment held for > 14 days due to hematologic toxicity
- febrile neutropenia of any duration with temperature ≥ 38.5 °C

Non-hematologic DLT is defined as any possibly, probably, or definitely related grade 3 or grade 4 non-hematologic toxicity that occurs during the first cycle with the following specific exceptions:

- suboptimally treated grade 3 or 4 nausea, vomiting, diarrhea, anorexia, or lymphopenia
- grade 3 metabolic abnormalities (specifically limited to potassium, magnesium and calcium)
- any hypersensitivity / infusion reaction or acneiform rash due to cetuximab
- treatment held for > 14 days due to non-hematologic toxicity

5.5.3 Dose Escalation Criteria

Dose escalations will proceed as follows after the occurrence of dose-limiting toxicity (DLT):

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. If 0 of these 3 patients experience DLT, proceed to the next dose level. If 1 or more of this group suffer DLT, then dose escalation is stopped. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

5.5.4 Toxicity, Response, and DLT 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 come off study due to treatment related adverse events(s) prior to completion of Cycle 2 and have not had any disease assessment.

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

5.6 Dosing for Phase II

Dosing for phase II will be administered as per Section 5.2. Dose of PD 0332991 will be 125 mg, which was the highest dose given in phase I (no MTD found). Thirty patients will

be enrolled to Arm 1 of phase II, 30 patients will be enrolled to Arm 2 of phase II, and 24 patients will be enrolled to Arm 3 of phase II. Enrollment for all arms may take place concurrently.

5.7 General Concomitant Medication and Supportive Care Guidelines

While taking PD 0332991, patients should be instructed to avoid food or drugs that are known strong CYP3A4 inhibitors or inducers. 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 PD 0332991 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 PD 0332991 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.

5.8 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 study treatment.

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 PD 0332991.

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 either study drug, the investigator must be notified in order to facilitate outcome follow-up.

5.9 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the

patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

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

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

5.10 Duration of Follow-up

Patients will be followed every 2 months for 5 years or until death, whichever occurs first. 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 PD 0332991

Patients will be monitored for toxicity and the dose of PD 0332991 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 PD 0332991 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 a toxicity which has not resolved to grade 2 or lower within two weeks (inclusive of the scheduled off-week), treatment with PD 0332991 should be

permanently discontinued.

PD 0332991 Dose Modifications Based on Worst Treatment-Related Toxicity in the Previous Cycle

Worst Toxicity During Previous Cycle	New Dose Level
Grade 4 neutropenia	Decrease by one dose level
Grade 4 thrombocytopenia	Decrease by one dose level
Grade 3 neutropenia associated with a documented infection or fever ≥ 38.5 ºC	Decrease by one dose level
Grade ≥ 3 non-hematologic toxicity (includes nausea, vomiting, diarrhea, and hypertension only if persisting despite maximal medical treatment)	Decrease by one dose level
Delay by > 1 week in receiving the next scheduled dose due to persisting treatment-related toxicities	If recovery occurs within 2 weeks, continue and decrease by one dose level
Inability to deliver at least 80% of the planned dose of PD 0332991 due to adverse events possibly related to study treatment	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 PD 0332991 by one dose level
Grade 4: permanently discontinue PD 0332991

6.2 Dose Modifications or Delays for Cetuximab

6.2.1 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.

6.2.2 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.

6.2.3 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.

6.2.4 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.

6.2.5 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.

6.2.6 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.

6.2.7 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 outlined below.

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

The FDA requires that all serious and unexpected adverse events be reported as outlined in Section 7.6. In addition, any fatal or life-threatening adverse experiences where there is a reasonable possibility of relationship to study intervention must be reported.

Pfizer requires that adverse events be reported as outlined in Section 7.7.

7.1 Definitions

7.1.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any

abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 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

7.1.2 Serious Adverse Event (SAE)

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

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

All unexpected SAEs must be reported to the FDA.

7.1.3 Unexpected Adverse Experience

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

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

7.1.4 Life-Threatening Adverse Experience

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

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

7.1.5 Unanticipated Problems

Definition:

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

7.1.6 Noncompliance

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

7.1.7 Serious Noncompliance

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

7.1.8 Protocol Exceptions

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

Local IRB pre-approval of all protocol exceptions must be obtained prior to the event. For secondary sites, the Washington University PI will issue approval of the exception, but it must also be submitted to the local IRB with documentation of approval forwarded to Washington University. HRPO approval is not required for protocol exceptions occurring at secondary sites.

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

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

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

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

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

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

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

7.4 Reporting Requirements for Secondary Sites

The research team at each secondary site is required to promptly notify the Washington University PI and research coordinator of all reportable events (as described in Section 7.6) within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event. This notification may take place via email if there is not yet enough information for a formal written report (using either an FDA MedWatch form if required or an institutional SAE reporting form if not). A formal written report must be sent to the Washington University PI and research coordinator within **10 working days** of the occurrence of the event or notification of the secondary site's PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event.

The research team at a secondary site is responsible for following its site's guidelines for reporting applicable events to its site's IRB according to its own institutional guidelines. The research team at Washington University is responsible for reporting all applicable events to the FDA.

7.5 Reporting to Secondary Sites

The Washington University PI (or designee) will notify the research team at each secondary

site of all reportable events that have occurred at other sites within **10 working days** of the occurrence of the event or notification of the PI of the event. This includes events that take place both at Washington University and at other secondary sites, if applicable.

7.6 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 any unanticipated problem to the FDA as follows:

- Report any unexpected fatal or life-threatening adverse experiences (Section 7.1.4) associated with use of the drug (i.e., there is a reasonable possibility that the experience may have been caused by the drug) by telephone or fax no later than **7 calendar days** after initial receipt of the information.
- Report any serious, unexpected adverse experiences (Section 7.1.2), as well as results from animal studies that suggest significant clinical risk within **15 calendar days** after initial receipt of this information.

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

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

Secondary sites must submit a completed MedWatch form to the Washington University PI and research coordinator within **4 calendar days** (for fatal or life-threatening adverse experiences) or **11 calendar days** (for serious, unexpected adverse experiences). The Washington University PI will be responsible for submitting all MedWatch forms from secondary sites to the FDA within the timeframes specified above.

7.7 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 Section 7.7) that occurs during the SAE reporting period (as defined in Section 7.9) in a study subject receiving PD 0332991. 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 PD 0332991 during pregnancy or lactation is reportable. In addition, occupational exposure to PD 0332991 is reportable, and a lack of effect of PD 0332991 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.

7.8 Timeframe for Reporting Required Events

Adverse events will be tracked for 30 days following the last day of study treatment.

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)	$AUC_{(0\text{-}10)}$[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 $AUC_{(0\text{-}10)}$: mean (%CV)
[2] T_{max}: Median (Range)
[3] For $AUC_{(0\text{-}10)}$, 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

PD 0332991 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**Error! Reference source not found.**. 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.

PD 0332991 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

PD 0332991 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.**

PD 0332991 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 Cetuximab (Erbitux)

8.2.1 Cetuximab Description

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

8.2.2 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.

8.2.3 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.

8.2.4 Supplier

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

8.2.5 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.

8.2.6 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.

8.2.7 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.

8.2.8 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.

8.2.9 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.

8.2.10 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 Optional Tumor Biopsy

9.1.1 Collection of Specimens

Phase II patients (Arms 1 and 2 only) will be asked to consent to three optional tumor biopsies, the first at pre-treatment and the second at the end of Cycle 2 (between Days 15 and 21 inclusive) and the third at disease progression (from cetuximab and PD0332991).

Tumor tissue biopsy site will be chosen by the PI. Readily accessible sites for biopsy such as subcutaneous or dermal soft tissue masses or neck nodal masses will not likely require image guidance. In those tumor sites that are not readily accessible for biopsy such as deep neck masses or visceral organ metastases, image guidance (ultrasound or CT) will be used. The biopsy will consist of a minimum of 4 needle cores (14 gauge is preferred) or 2 small (each 4 x 4 x 4 mm) pieces of tumor. Tissue should be delivered on saline within 30 minutes of collection. Tissue

is to be stored at the Siteman Cancer Center Tissue Procurement Core Facility until analysis in the lab of Dr. Van Tine. The optional pre-treatment and Cycle 2 Day 15-21 and disease progression tumor biopsies (core or excisional/incisional) will be used to perform RNAseq, p16 expression, Ki-67 by IHC, total and phospho-Rb by IHC, Cyclin D1 by IHC, and TUNEL assay, and to analyze other potential biomarkers as they emerge from the scientific understanding of PD0332991 activity on formalin-fixed paraffin-embedded (FFPE) tissue.

9.1.2 Handling of Specimens

Tissue should be sent to the Tissue Procurement Core Facility for processing and storage until analysis.

9.2 Archival Tumor Tissue

Fifteen slides are needed (minimum of 4 accepted).

9.2.1 Phase I

Eight additional slides will be collected for each patient.

p16 by IHC will be performed on all patients if not already available for review.

Analysis of cyclin D1 expression as well as total and phospho-Rb by IHC will be performed on all archived specimens.

9.2.2 Phase II

p16 by IHC will be performed on all patients to determine eligibility and arm assignment.

Analysis of cyclin D1 expression as well as total and phospho-Rb by IHC will be performed on all archived specimens.

9.3 Blood for Pharmacokinetic Analysis

Blood for pharmacokinetic analysis will be drawn from all Phase I and Phase II Arm 1 patients only. Blood will be drawn at the following time points:

- Cycle 1 Day 15 pre-cetuximab
- Cycle 1 Day 15 post-cetuximab
- Cycle 1 Day 22 pre-cetuximab
- Cycle 1 Day 22 post-cetuximab
- Cycle 2 Day 15 pre-PD 0332991
- Cycle 2 Day 15 immediately post-PD 0332991
- Cycle 2 Day 15 pre-cetuximab
- Cycle 2 Day 15 immediately post-cetuximab

- Cycle 2 Day 15 1 hour post-PD 0332991
- Cycle 2 Day 15 2 hours post-PD 0332991
- Cycle 2 Day 15 4 hours post-PD 0332991
- Cycle 2 Day 15 8 hours post-PD 0332991
- Cycle 2 Day 22 pre-cetuximab
- Cycle 2 Day 22 post-cetuximab

9.3.1 PD 0332991 PK Collection and Processing

For each time point, collect 3 mL of venous blood into K_2EDTA tubes. Upon collection of the blood PK samples, keep them on wet ice at all times prior to processing the plasma. Samples will be centrifuged at approximately 1700 x g for about 10 minutes at 4°C. The plasma will be stored in an appropriately labeled amber screw-capped polypropylene tube at approximately -70°C within 1 hour of collection. Specimens will be batch shipped to a lab designated by Pfizer at a later date.

9.3.2 Cetuximab PK Collection and Processing

For each time point, collect 3 mL of venous blood into a red top glass tube containing no additive. Upon collection of the blood PK samples, keep them on wet ice to allow blood to clot prior to processing to serum. Samples will be centrifuged at approximately 1700 x g for about 10 minutes in a refrigerated centrifuge at 4°C to harvest serum. Rapidly transfer a minimum of 1 mL serum into the pre-labeled 2 mL clear polypropylene storage cryovial. The samples will be stored in a freezer at approximately -20°C within 1 hour of collection. Ship frozen samples to CRO on dry ice.

9.4 Quality of Life

The EORTC QLQ-C30 (Appendix E) and FACT H&N (Appendix F) will be given at baseline and on Day 1 of Cycles 2, 3, 4, and 6 for patients in Phase II (all 3 arms) only.

10.0 STUDY CALENDAR

Screening evaluations are to be conducted within 28 days prior to start of protocol therapy.

	Screening	Weekly during Cycle 1	Prior to Day 1 of each cycle (every 4 weeks Cycle 2 and beyond)[p]	EOT	F/U[j]
Physical exam	X	X	X	X	
Vitals signs	X	X	X[a]	X	
Performance status	X	X	X	X	
Adverse event assessment	X ----------				X[k]
CBC	X	X	X[b]	X	
Chemistry panel, LFTs[f]	X	X	X	X	
Pregnancy test	X			X	
EKG	X	X[c]	X[c]		
CT neck and chest	X[d]		X[d]		
Archival tissue	X[m]				
Optional tumor biopsy	X[e]		X[e]	X	
QOLs (Phase II only)	X		X[n]		
Blood for PKs[o]		Refer to Section 9.3			
PD0332991[g]		X ----------		X[g]	
Cetuximab[h]		X ----------		X[h]	

[a]Vital signs should be taken weekly, even if treatment is held for toxicity. This can occur at chemotherapy visits when not having physical exams.
[b]CBC to be performed weekly throughout all cycles, even if treatment is held for toxicity
[c]EKG: Day 22 of each cycle
[d]Tumor assessments with CT of neck and chest will be performed at screening and at subsequent 8 week intervals (every 2 cycles).
[e]Tumor biopsies will be encouraged at baseline and at Cycle 2 Day 15-21 and at disease progression in patients in for Phase II patients (Arms 1 and 2 only). Cyclin D1, p16 by IHC, Ki-67, RNAseq, total and phospho-Rb and TUNEL assays will be performed on all three tissue sets.
[f]Chemistry includes Ca, Mg, K, Na, glucose, albumin, urea, creatinine; LFTs include ALT, AST, alkaline phosphatase, total bilirubin; please refer to Section 7.8 for special LFT AE reporting guidance.
[g]PD0332991 will be taken orally on Days 1-21 of a 28 day cycle.
[h]Cetuximab will be administered weekly
[j]Follow-up will consist of checks every 2 months (+/- 2 weeks) for recurrence and survival for 5 years; this may be done over the phone or as a review of the medical record.
[k]Adverse events should be collected for 30 days after the last dose of study treatment.
[m]p16, cyclin D1, and total and phospho-Rb will be assessed from FFPE tissue (15 slides, minimum of 4 accepted) on all patients (p16 to be done at screening; other testing to be performed at a later date)
[n]Administer QOLs at C2D1, C3D1, C4D1, and C6D1.
[o]Phase I and Phase II Arm 1 only
[p]+/- 2 day window for visits

11.0 DATA SUBMISSION SCHEDULE

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

Electronic data management systems will be used in this trial in collaboration with the Institute for Informatics at Washington University.

REDCap is a web-based clinical studies data management system that will be used for capture of clinical data from this trial. An electronic study calendar will drive the study's data collection workflow. Each participating center has access only to data from its own participants by creation of Data Access Groups. Washington University, as the data coordinating center, has access to data from all sites.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
Demographics Form On Study Form On Study Prior Therapy Form Treatment Assignment Form	Prior to starting treatment
Treatment Form EKG Form	Every cycle
Adverse Event Form	Continuous
Tumor Biopsy Form PKs Form	Baseline and end of Cycle 2
QOLs Form	Baseline and at C2D1, C3D1, C4D1, and C6D1
Treatment Summary Form	Completion of treatment
Follow Up Form	Every 2 months for 5 years
Tumor Measurement Form	Baseline, end of every even numbered cycles, and end of treatment
MedWatch Form	See Section 7.0 for reporting requirements

Any queries generated by Washington University must be responded to within 28 days of receipt by the participating site. The Washington University research team will conduct a regular review of data status at all secondary sites, with appropriate corrective action to be requested as needed.

12.0 MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

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

12.2 Disease Parameters

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

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

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

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

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

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

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

12.3 Methods for Evaluation of Measurable Disease

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

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using 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.

12.4 Response Criteria

12.4.1 Evaluation of Target Lesions

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

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

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

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

12.4.2 Evaluation of Non-Target Lesions

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

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).

12.4.3 Evaluation of Best Overall Response

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

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

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

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

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

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

12.4.4 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 disease control (CR, PR, stable disease): Disease control 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.

12.4.5 Efficacy

Efficacy will be measured by the overall response rate (CR+PR) defined by RECIST criteria and by time to progression.

12.4.6 Progression-Free Survival

Progression-free survival is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

12.4.7 Overall Survival

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

12.4.8 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.

13.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, an independent Data and Safety Monitoring Committee (DSMC) will be specifically convened for this trial to review toxicity data at least every 6 months following the activation of the first secondary site. A DSMC will consist of no fewer than 3 members including 2 clinical investigators and a biostatistician. Like investigators, DSMC members are subject to the Washington University School of Medicine policies regarding standards of conduct. Individuals invited to serve on the DSMC will disclose any potential conflicts of interest to the trial principal investigator and/or appropriate university officials, in accordance with institution policies. Potential conflicts that develop during a trial or a member's tenure on a DSMC must also be disclosed.

The DSM report will be prepared by the study statistician with assistance from the study team, will be reviewed by the DSMC, and will be submitted to the Quality Assurance and Safety Monitoring Committee (QASMC).

Note that during the phase I dose escalation, 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 QASMC. The report provided to QASMC will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual including numbers from participating sites
- Protocol activation date at each participating site
- Average rate of accrual observed in year 1, year 2, and subsequent years at each participating site
- Expected accrual end date, accrual by cohort, and accrual by site
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities at all participating sites 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

Further DSMC responsibilities are described in the DSMC charter.

Until such a time as the first secondary site activates this protocol, a semi-annual DSM report to be prepared by the study team will be submitted to the QASMC beginning 6 months after study activation at Washington University.

The study principal investigator and coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines (please refer to Section 7.0).

Refer to the Washington University Quality Assurance and Data Safety Monitoring Committee Policies and Procedures for full details on the responsibilities of the DSMC at https://siteman.wustl.edu/wp-content/uploads/2015/10/QASMC-Policies-and-Procedures-03.31.2015.pdf

14.0 AUDITING

As coordinating center of this trial, Washington University (via the Quality Assurance and Safety Monitoring Committee (QASMC) will monitor each participating site to ensure that all protocol requirements are being met; that applicable federal regulations are being followed; and that best practices for patient safety and data collection are being followed per protocol. Participating sites will be asked to send copies of all audit materials, including source documentation. The audit notification will be sent to the Washington University Research Patient Coordinator, who will obtain the audit materials from the participating institution.

Notification of an upcoming audit will be sent to the research team one month ahead of the audit. Once accrual numbers are confirmed, and approximately 30 days prior to the audit, a list of the cases selected for review (up to 10 for each site) will be sent to the research team. However, if during the audit the need arises to review cases not initially selected, the research team will be asked to provide the additional charts within two working days.

Items to be evaluated include:

- Subject screening and enrollment
- Reporting of adverse events
- Maintenance of HIPAA compliance
- Completeness of regulatory documentation
- Completeness of participant documentation
- Acquisition of informed consent
- IRB documentation
- Issues of protocol adherence

Additional details regarding the auditing policies and procedures can be found at https://siteman.wustl.edu/wp-content/uploads/2015/QASMC-Policies-and-Procedures-03.31.2015.pdf

15.0 STATISTICAL CONSIDERATIONS

This trial consists of an open-label phase I study, where the MTD and DLT of the combination of PD 0332991 will be determined, followed by a phase II study where patients with incurable HPV-unrelated SCCHN will be treated with PD 0332991 and cetuximab. The phase I portion of the study will adopt a 3 + 3 design and at most 12 patients will be needed in this group.

Dose escalations and de-escalations will proceed as follows after the occurrence of dose-limiting toxicity (DLT):

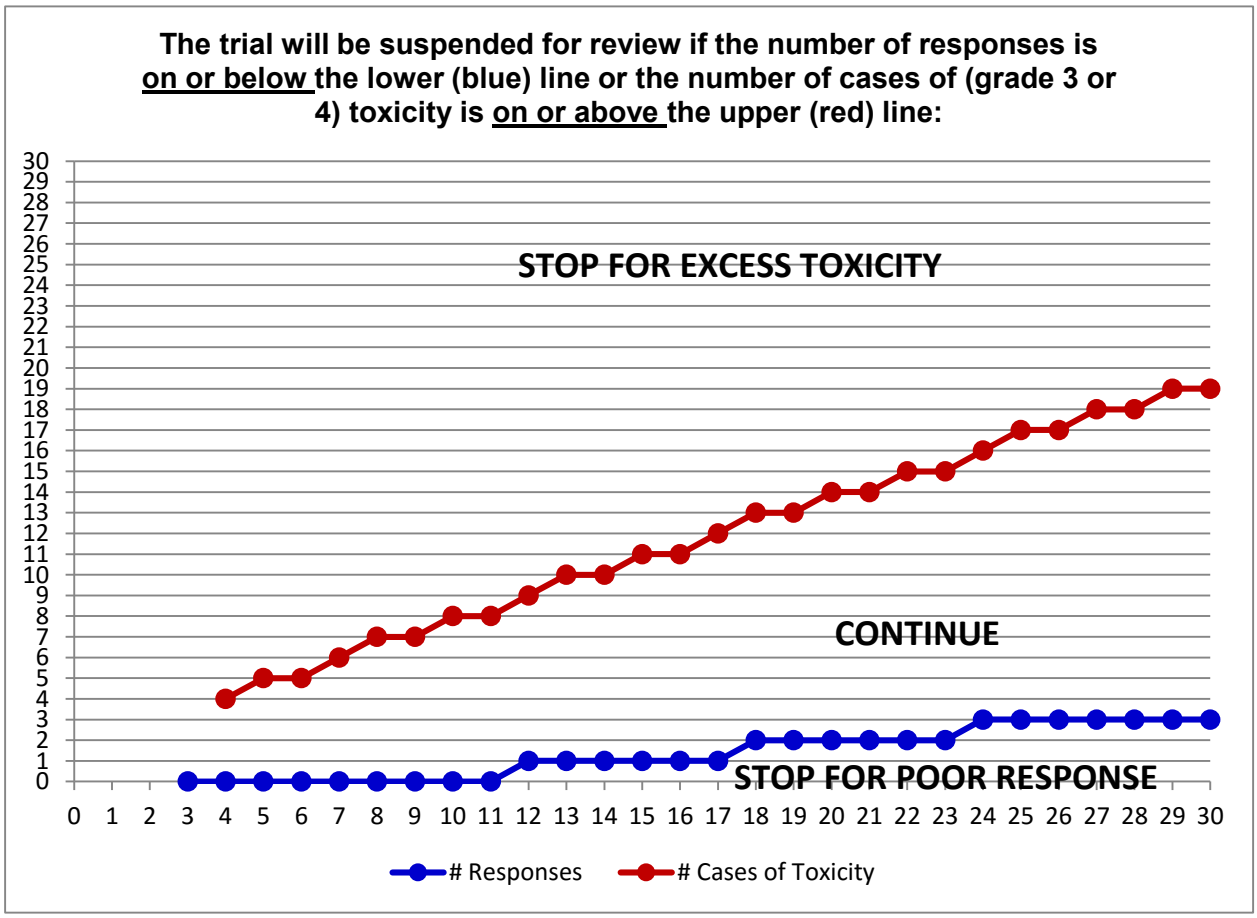
Cohort	# DLTs	Escalation Decision Rule
1	0	Escalate to dose 2.
	1	Enter 3 additional patients at dose 1.
	2	De-escalate to dose -1.
2	0	Conclude that the MTD has not yet been reached.
	1	Enter 3 additional patients at dose 2 if 0 in cohorts 1 and 2. Identify dose 2 as the MTD if 1 in cohorts 1 and 2.
	2	Conclude that dose 1 is the MTD.

For the phase II Arm 1 portion, based upon currently available data for cetuximab alone in platin-resistant incurable SCCHN[37], an overall tumor response rate (CR + PR) of 13% or lower would be unacceptable and an overall tumor response rate of 26% or higher of clinical interest. A total of 30 eligible and evaluable patients will be accrued to the phase II portion of the study, and if 4 or more patients' tumors respond, the therapy will be accepted for further investigation. The design is based on Thall P and Sung H-G[38].

Assumes 13% response with standard treatment, response rate increase of 13% (26% response rate with experimental treatment), expected (grade 3 or 4) toxicity rate of 46% with standard, 0% allowable increase with experimental treatment.

Stop for poor response if:		Stop for excess (grade 3 or 4) toxicity if:	
# Patients is:	# Responses is ≤:	# cases of toxicity is ≥:	In 1st # patients
3	0		
4	0	4	4
5	0	5	5
6	0	5	6
7	0	6	7
8	0	7	8
9	0	7	9
10	0	8	10
11	0	8	11
12	1	9	12
13	1	10	13

14	1	10	14
15	1	11	15
16	1	11	16
17	1	12	17
18	2	13	18
19	2	13	19
20	2	14	20
21	2	14	21
22	2	15	22
23	2	15	23
24	3	16	24
25	3	17	25
26	3	17	26
27	3	18	27
28	3	18	28
29	3	19	29
30	3	19	30



For the phase II arm 2 portion, the tumor response rate to any agent in patients with cetuximab-resistant incurable SCCHN is unknown but it is expected to be < 13%. An overall tumor response

rate (CR+PR) of 13% or lower would be unacceptable and an overall tumor response rate of 26% or higher would be of clinical interest. A total of 30 eligible and evaluable patients will be accrued to the phase II arm 2 portion of the study, and if 4 or more patients' tumors respond, the therapy will be accepted for further investigation. The design is based on Thall P and Sung H-G[38]. The table and figure above also apply to phase II Arm 2.

For phase II Arm 3 portion, an overall tumor response rate (CR + PR) of 5% or lower would be unacceptable and an overall tumor response rate of 20% or higher of clinical interest. A total of 24 eligible and evaluable patients will be accrued to this arm. One or more tumor responses in the first 18 patients are required to continue enrollment. Two or more tumor responses in the first 24 patients are required to accept the alternative hypothesis. The design has probability = .74 of early stopping after the first cohort of 18 patients if the true response rate is 5% or less. The cumulative probability of completing the study (enrolling 24 patients) is 0.70 if the true response rate is 20% or greater. The design is based on Thall P and Sung H-G[38].

Number of patients	Cumulative probability of early stopping if response rate = 5% (null hypothesis)	Cumulative probability of early stopping if response rate = 20% (minimum alternative hypothesis)	Cumulative probability of continuing to end of study if response rate = 20% (minimum alternative hypothesis)
1	0	0	0
18	0.7436	0.2858	.7142
24	0.8335	0.2953	.7047

15.1 Correlative Studies

Standard statistical methods will be used to describe cyclin D1 and p16 results by IHC, which will then be correlated to overall tumor response and TTP in Phase II patients. Similarly, RNAseq, Ki-67, total and phospho-Rb, and TUNEL assay performed on paired pre-Cycle 1 and post-Cycle 2 FFPE tumor tissue will be described and compared using standard statistical methods.

16.0 MULTICENTER REGULATORY REQUIREMENTS

Washington University requires that each participating site sends its informed consent document to be reviewed and approved by the Washington University Regulatory Coordinator (or designee) prior to IRB/IEC submission.

Site activation is defined as when the secondary site has received official written documentation from the coordinating center that the site has been approved to begin enrollment. At a minimum, each participating institution must have the following documents on file at Washington University prior to study activation:

- Documentation of IRB approval of the study in the form of a letter or other official document from the participating institution's IRB. This documentation must show which version of the protocol was approved by the IRB.

- Documentation of IRB approval of an informed consent form. The consent must include a statement that data will be shared with Washington University, including the Quality Assurance and Safety Monitoring Committee (QASMC), the DSMC (if applicable), and the Washington University study team.
- Documentation of FWA, signed FDA Form 1572 (if applicable), and the CVs of all participating investigators.
- Protocol signature page signed and dated by the investigator at each participating site.

The coordinating center Principal Investigator (or designee) is responsible for disseminating to the participating sites all study updates, amendments, reportable adverse events, etc. Protocol/consent modifications and IB updates will be forwarded electronically to the secondary sites within 4 weeks of obtaining Washington University IRB approval. Activated secondary sites are expected to submit protocol/consent/IB modifications to their local IRBs within 4 weeks of receipt, unless otherwise noted. Upon the secondary sites obtaining local IRB approval, documentation of such shall be sent to the Washington University study team within 2 weeks of receipt of approval.

Documentation of participating sites' IRB approval of annual continuing reviews, protocol amendments or revisions, all SAE reports, and all protocol violations/deviations/exceptions must be kept on file at Washington University.

The investigator or a designee from each institution must participate in a regular conference call to update and inform regarding the progress of the trial.

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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: PD 0332991 Cycle: _____ Study ID#: _____

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

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each month. Take _____mg of PD 0332991 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 to your physician or your study coordinator when you go to your next appointment. Please bring your unused study medications and/or empty bottles with you to each clinic visit so that a pill count can be done.
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 PD 0332991 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				

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		

FormCT25-USA01-10 Reportable Event Fax Cover Sheet: US_eff 19-DEC-2006

APPENDIX D: CYP3A4 Inhibitors, Inducers, and Substrates

(*Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). "http://medicine.iupui.edu/clinpharm/ddis/clinical-table/" Accessed 01/22/14.)*

CYP3A4 Inhibitors - Avoid
Indinavir
Nelfinavir
Ritonavir
Clarithromycin
Itraconazole
Ketoconazole
Nefazodone
Erythromycin
Grapefruit juice
Verapamil
Diltiazem
Cimetidine
Amiodarone
Fluvoxamine
Mibefradil
Toleandomycin

CYP3A4 Inducers – Avoid and Consider an Alternate Medication
Carbamazepine
Phenobarbital
Phenytoin
Pioglitazone
Rifabutin
Rifampin
St. John's wort
Troglitazone

CYP3A4 Substrates – Not Recommended, Consult PI before Use
Clarithromycin
Erythromycin
Telithromycin
Quinidine → 3-OH
Alprazolam
Diazepam → 3-OH
Midazolam
Triazolam
Cyclosporine
Tacrolimus
Indinavir
Ritonavir

Saquinavir
Cisapride
Astemizole
Chlorpheniramine
Amlodipine
Diltiazem
Felodipine
Nifedipine
Nisoldipine
Nitrendipine
Verapamil
Atorvastatin
Lovastatin
Simvastatin
Aripiprazole
Boceprevir
Buspirone
Gleevec
Haloperidol
Methadone
Pimozide
Quinine
Sildenafil
Tamoxifen
Telaprevir
Trazodone
Vincristine

APPENDIX E: 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 F: 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