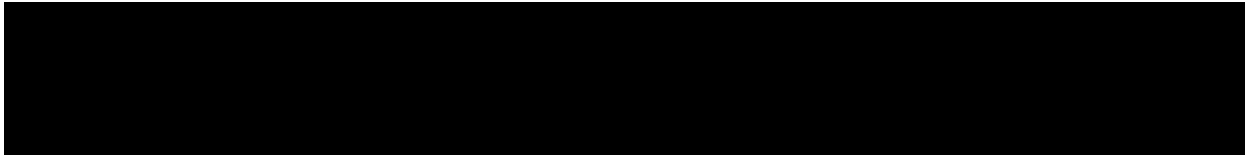




**A RANDOMIZED, MULTICENTER, DOUBLE-BLIND PHASE 2 STUDY OF
PALBOCICLIB PLUS CETUXIMAB VERSUS CETUXIMAB FOR THE
TREATMENT OF HUMAN PAPILLOMAVIRUS-NEGATIVE,
CETUXIMAB-NAÏVE PATIENTS WITH RECURRENT/METASTATIC
SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK AFTER FAILURE
OF ONE PRIOR PLATINUM-CONTAINING CHEMOTHERAPY REGIMEN**

Compound:	PD-0332991
Compound Name:	Palbociclib
US IND Number:	122168
European Clinical Trial Database (EudraCT) Number:	2015-000515-41
Protocol Number:	A5481044
Phase:	2



Document History

Document	Version Date	Summary of Changes
Amendment 2	31 March 2016	<ol style="list-style-type: none"> 1. Schedule of Activities/Tumor Assessment Requirements Flowchart: 29Jul2015 PCL removal of the phrase “on Day 1 of even cycles” for Disease Assessment to align with Sections 7.1.1, Tumor Assessments. 2. Schedule of Activities, footnote c/Section 6.2, Active Treatment Phase: Add vital signs for any new cycle Day 1 procedures. 3. Schedule of Activities, footnote l/Section 6.3, End of Treatment Visit/Section 7.3.1, Laboratory Safety Assessments: included patients starting post-study anticancer therapy for 8 week chemistry panel analysis. 4. Schedule of Activities, footnote n /Abbreviations/Section 7.3.1, Laboratory Safety Assessments: 21Oct2015 PCL added aPTT as acceptable coagulation parameter. 5. Schedule of Activities, footnote y/Section 5.8, Concomitant Treatments: Added further clarification for patients beginning new therapy before the 28-day time period is complete. 6. Schedule of Activities, footnote z/Section 7.7, Patient Reported Outcomes: Added further clarification for patients starting post-study anticancer therapy. 7. Tumor Assessment Requirments Flowchart, footnote d/Section 7.1.1 Tumor Assessment: Removed the phrase “and pelvis”. 8. Section 4.2 Exclusion Criteria: Removed the phrase “or requirement for a feeding tube” and clarified inability to swallow capsules for Exclusion Criterion # 5. 9. Section 4.4 Lifestyle Guidelines: Added phrase to template language referencing inclusion criterion # 8. 10. Section 5.4.2.2, Cetuximab: 23April2015 PCL update to align with Section5.4.1.3 verbiage.

Document	Version Date	Summary of Changes
		<p>11. Section 5.5.1, Palbociclib/Placebo/Section 5.5.2, Cetuximab: 16Oct2015 PCL added verbiage to align with Single Reference Safety Documents for monitoring the patient during study drug administration.</p> <p>12. Section 5.5.2, Cetuximab/Section 5.8.2, Medications not Recommended: 14Jan2016 PCL added instruction to administer corticosteroid premedication to align with Single Reference Safety Document, Summary of Product Characteristics for cetuximab.</p> <p>13. Section 5.5.3.1.3 Cetuximab Dermatological Toxicities: Removed the phrase “topical corticosteroids are not recommended”.</p> <p>14. Section 5.5.3.4, Palbociclib/Placebo Dose Reductions: Clarified patients requiring more than 2 dose reductions will be discontinued from palbociclib/placebo treatment.</p> <p>15. Section 7.1.1, Tumor Assessments: Corrected statement to state “secondary endpoint of PFS” in fourth sentence.</p> <p>16. Section 7.4.1, Palbociclib/Placebo PK Assessments/Section 7.5, Biomarker Assessments: Added one day for the accepted range to make-up a missed PK draw. Provided further instruction for makeup PK sampling [REDACTED].</p> <p>17. Typos and grammatical errors corrected throughout the protocol.</p>
Amendment 1	09 April 2015	<p>1. Protocol Summary/Study Design/ Tumor Assessment Requirements Flowchart/Sections 3 Study Design, 7.1.1.2 Post-Baseline Tumor Assessments: Removed statement concerning continuous treatment beyond RECIST-defined disease progression (agreement between Sponsor and FDA).</p> <p>2. Protocol Summary, Study Design/Section 3 Study Design/Section 4.3 Randomization Criteria/Section 5.1 Allocation to Treatment/9.2.1</p>

Document	Version Date	Summary of Changes
		<p>Analysis of Primary Endpoint: Clarified stratification terminology from checkpoint inhibitors to immunotherapy.</p> <ol style="list-style-type: none"> 3. Schedule of Activities/Tumor Assessment Requirements Flowchart/Sections 7.1.1.1 Screening/Baseline Tumor Assessments and 7.1.1.2 Post-Baseline Tumor Assessments: Added CT or MRI scan of the chest and abdomen (including the liver) to support PFS secondary endpoint. 4. Clarification of Inclusion Criteria # 9 for patients aged 20 years old or greater as applicable by local country regulations. 5. Section 5.5.3.1.1 Cetuximab Hypersensitivity Reactions: Simplified wording for cetuximab retreatment after Grade 2 hypersensitivity reactions. 6. Section 5.5.3.1.4 Cetuximab Gastrointestinal Adverse Events: Added “Patients experiencing treatment-related Grade 4 vomiting or diarrhea should have their cetuximab and palbociclib/placebo treatments permanently discontinued.” 7. Section 5.5.3.2.1 Palbociclib/Placebo Dosing Interruptions/Delays: Added “Patients experiencing treatment-related Grade 4 vomiting, diarrhea, or hypertension should have their palbociclib/placebo and cetuximab treatments permanently discontinued.” Removed “≥” from Grade 3 non-hematologic bullet point (5th bullet point). Added bullet point “Grade 4 non-hematologic toxicities (see exceptions of vomiting, diarrhea, or hypertension above).” 8. Section 5.5.3.3 Palbociclib/Placebo Retreatment: Added “Patients experiencing treatment-related Grade 4 vomiting, diarrhea, or hypertension should have their palbociclib/placebo and cetuximab treatments permanently discontinued.” Removed “≥” from Grade 3 non-hematologic bullet point (3rd bullet point). Added bullet point, “Grade 4 treatment-related non-hematologic AEs

Document	Version Date	Summary of Changes
		<p>with the exception of alopecia, have recovered to Grade ≤ 1 or baseline (or, at the investigator's discretion, Grade ≤ 2 if not considered a safety risk for the patient). Patients experiencing treatment-related Grade 4 vomiting, diarrhea, or hypertension should have their palbociclib/placebo and cetuximab treatments permanently discontinued.”</p> <p>9. Section 5.5.3.4 Palbociclib/Placebo Dose Reductions: Removed “\geq” from Grade 3 non-hematologic statement in Table 5 (fifth row). Added Grade 4 non-hematological toxicity row clarification.</p> <p>10. Section 7.4.1 Palbociclib PK Assessments: Removed duplicate statement “...efforts should be made to coordinate biomarker and PK blood draws within a 30 minute window.”</p> <p>11. Section 7.4.2 Cetuximab PK Assessment: Added “Blood samples for post-dose PK assessments of cetuximab should not be collected from the same arm that the cetuximab IV infusion was administered.”</p> <p>12. Section 9.3.3 Patient-Reported Outcomes (PROs): Corrected tumor type to squamous cell carcinoma of the head and neck.</p> <p>13. Typos and grammatical errors corrected throughout the protocol.</p> <p>14. Required Protocol Template updates in Adverse Event Reporting section and Communication of Results by Pfizer section.</p>
Original protocol	06 March 2015	N/A

This amendment incorporates all revisions to date, including amendments made at the request of the United States Food and Drug Administration (USFDA).

ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
bid	Bis in Die (twice a day)
CAG	Clinical Assay Group
CCND1	Cyclin D1
CDK	Cyclin-Dependent Kinase
CDKN2A, p16 ^{Ink4A}	Cyclin-Dependent Kinase Inhibitor 2A
cf	Circulating-Free
CI	Confidence Interval
CCI	
C _{max}	Maximum Plasma Concentration
CMH	Cochran-Mantel-Haenszel
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CSA	Clinical Study Agreement
CT	Computed Tomography
CTA	Clinical Trial Application
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CxDy	Cycle x, Day y (refer to Schedule of Activities)
CYP	Cytochrome P-450
d	Day
DDI	Drug-Drug Interaction
dL	Deciliter
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
DR	Duration of Response
DU	Dispensable Unit
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
E-DMC	External Data Monitoring Committee
EDP	Exposure During Pregnancy
EDTA	Ethylenediaminetetraacetic acid
EGFR	Epidermal Growth Factor Receptor

EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EORTC-QLQ-H&N35	European Organisation for Research and Treatment of Cancer Head and Neck Module 35
ER	Estrogen Receptor
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FFPE	Formalin-Fixed Paraffin Embedded
FSH	Follicle-Stimulating Hormone
g	gram
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
H1	Histamine Antagonist of the H1 Receptor
Hb	Hemoglobin
HDPE	High Density Polyethylene
HER2	Human Epidermal Growth Factor Receptor 2
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HR	Hormone Receptor or Hazard Ratio (depending on context)
HRQL	Health-Related Quality of Life
HSR	Hypersensitivity Reaction
IB	Investigator's Brochure
IC ₅₀	Concentration of 50% Inhibition
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	Identification
IHC	Immunohistochemistry
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Randomization Technology or Interactive Response Technology (depending on context)
IUD	Intrauterine Device
IV	Intravenous
IVR	Interactive Voice Response
IWR	Interactive Web Response
L	Liter
LFT	Liver Function Test
LPLV	Last Patient Last Visit
m ²	Square meter, also sqm
MedDRA	Medical Dictionary for Regulatory Activities

mg	Milligram
MID	Minimally Important Difference
mIU	Milli-International Unit
mL	milliliter
mm ³	Cubic millimeter
MRI	Magnetic Resonance Imaging
msec	millisecond
MTD	Maximum Tolerated Dose
N/A	Not Applicable
NABSA	Nucleic Acid Sequence Based Amplification
NCI	National Cancer Institute
NGS	Next-Generation Sequencing
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PCD	Primary Completion Date
PCR	Polymerase Chain Reaction
PD	Progressive Disease, Progression of Disease, or Pharmacodynamic (depending on context)
PFS	Progression-Free Survival
PK	Pharmacokinetic
PPI	Proton-Pump Inhibitor
PR	Partial Response or PR interval is measured from the beginning of the P wave to the beginning of the QRS complex (depending on context)
PRO	Patient-Reported Outcome
PS	Performance Status
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QD	Quaque Die (once daily)
QOL	Quality of Life
QRS	The QRS complex is a name for the combination of three of the graphical deflections seen on a typical electrocardiogram. The QRS complex reflects the rapid depolarization of the right and left ventricles
QT	Time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QT _c	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using Bazett's fomula
QTcF	QT interval corrected for heart rate using Fridericia's fomula
RB/Rb	Retinoblastoma
RECIST	Response Evaluation Criteria in Solid Tumors
R/M	Recurrent/Metastatic
RNA	Ribonucleic Acid

RP2D	Recommended Phase 2 Dose
RR	The interval between an R wave and the next R wave
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCCHN	Squamous Cell Carcinoma of the Head and Neck
SCL	Supply Chain Lead
SD	Stable Disease or Standard Deviation (depending on context)
SOA	Schedule of Activities
SOC	System Organ Class
SPC	Summary of Product Characteristics
Sqm	Square meter, also m ²
SRSD	Single Reference Safety Document
t _{1/2}	Terminal Elimination Half-life
TdP	Torsade de Pointes
CC	
T _{max}	Time for C _{max}
CCI	
ULN	Upper Limit of Normal
US	United States
V	version
WBC	White Blood Cells

PROTOCOL SUMMARY

Indication:

Human papillomavirus (HPV)-negative, cetuximab-naïve, recurrent/metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) after failure of one platinum-based chemotherapy regimen.

Background and Rationale:

SCCHN is the sixth most common cancer. Globally, approximately 600,000 new cases occur yearly. In the United States (US), it is estimated that about 55,000 new cases of oral cavity, pharyngeal, and laryngeal cancers will occur in 2014, which account for about 3% of new cancer cases.

Epidermal growth factor receptor (EGFR) overexpression is found in approximately 90% of SCCHN cases, and it is associated with decreased progression-free survival (PFS) and overall survival (OS). EGFR-directed drugs include antibodies that prevent ligand-binding and/or receptor dimerization (eg, cetuximab) and small molecule adenosine triphosphate-competitive inhibitors of the intrinsic catalytic activity of ErbB receptors (eg, erlotinib and gefitinib).

Important regulatory proteins involved in the cell cycle transition from G1 to the S-Phase are cyclin D1 (*CCND1*), p16^{INK4A} (thereafter referred to as p16) and cyclin-dependent kinases (CDKs). Deregulation of aspects of the cell-cycle, including CDKs, have been shown to contribute to the development of cancer. Overexpression of cyclin D1 and inactivation of p16 occur in the vast majority of cases of HPV-negative SCCHN. Genomic characterization of oral SCCHN identified amplification of *CCND1* and/or loss of *CDKN2A* (encoding p16 protein) were found in 94% of tumors, supporting the observation that cell cycle alterations were a nearly universal feature.

Palbociclib is a highly selective, reversible oral inhibitor of cyclin-dependent kinases 4 and 6 (CDK 4/6). The compound prevents cellular deoxyribonucleic acid (DNA) synthesis by prohibiting progression of the cell cycle from G1 into S phase. In clinical trials, palbociclib enhanced tumor response to letrozole in women with HR-positive, HER2-negative metastatic breast cancer. Palbociclib also has efficacy in cyclin D1 overexpressing mantle cell lymphoma and has activity in a broad range of other solid tumors.

Combinatorial efficacy was observed following treatment with palbociclib and inhibitors of the EGFR pathway, including cetuximab, in preclinical models. In a panel of 24 SCCHN cell lines the palbociclib combination with cetuximab produced synergistic growth inhibition in 50 % of models. The combination of palbociclib and cetuximab in a subset of these cell lines demonstrated increased inhibition of retinoblastoma protein and downstream transcription factor E2F signaling, leading to greater inhibition of new DNA synthesis and increased hallmarks of cellular senescence than with each agent alone. In vivo studies in patient-derived xenografts demonstrated the ability of either single agent to produce >90% tumor growth inhibition in distinct models, and in a model that failed to show significant response to either single agent, the combination of palbociclib and cetuximab yielded synergistic tumor growth inhibition.

In an ongoing Phase 1 clinical trial of escalating doses of palbociclib added to fixed-dose cetuximab, one partial tumor response was observed in a patient with SCCHN resistant to cetuximab and cisplatin. Disease control (partial response [PR] or stable disease [SD]) occurred in 6 of the 7 evaluable patients. Of the 6 patients with cetuximab-resistant SCCHN, 5 experienced disease control with combined palbociclib + cetuximab treatment. Of the 4 patients with cisplatin-resistant SCCHN, 3 experienced disease control with palbociclib + cetuximab.

The current Phase 2 study provides the opportunity to test the hypothesis that the addition of palbociclib to cetuximab will improve outcomes in patients with platinum-resistant, incurable SCCHN in a direct, double-blind comparison to cetuximab.

Objectives:

Primary Objective:

- To demonstrate that the combination of palbociclib with cetuximab is superior to cetuximab in prolonging OS in HPV-negative, cetuximab-naïve patients with R/M SCCHN in whom one prior platinum-containing chemotherapy has failed.

Secondary Objectives:

- To compare secondary measure of efficacy between the treatment arms;
- To compare safety and tolerability between the treatment arms;
- To compare Patient-Reported Outcome (PRO) measures between the treatment arms;
- To characterize the correlations between baseline biomarker (eg, p16, Rb) expression in tumor tissue and clinical efficacy in both treatment arms;
- To characterize steady state trough concentrations for palbociclib, and trough and maximum concentrations for cetuximab in patients with R/M SCCHN.

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- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

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Endpoints:

Primary Endpoint:

- Overall Survival.

Secondary Endpoints:

- Progression-Free Survival (PFS), Objective Response (OR), Duration of Response (DR), per RECIST v1.1, as assessed by investigator;
- Type, incidence, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 4.03), seriousness and relationship to study medications of adverse events (AEs) and any laboratory abnormalities;
- PRO endpoints: European Organisation for Research and Treatment of Cancer Quality of Life Instrument (EORTC-QLQ-C30); European Organisation for Research and Treatment of Cancer Head and Neck Module 35 (EORTC-QLQ-H&N35);
- Tumor tissue biomarkers by immunohistochemistry (IHC; p16 and Rb);
- Trough concentrations at steady state for palbociclib; trough and maximum concentrations for cetuximab.

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Study Design:

This is an international, multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 2 study comparing the efficacy and safety of palbociclib in combination with cetuximab versus cetuximab in HPV-negative, cetuximab-naïve patients with R/M SCCHN after failure of one platinum-containing regimen. Approximately 120 patients will be randomized 1:1 between the investigational arm (Arm A: palbociclib plus cetuximab) and the comparator arm (Arm B: placebo plus cetuximab). Crossover between treatment arms will be prohibited.

Patients will be stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1), and by prior use of immunotherapy (yes vs no).

Patients randomized to Arm A (investigational arm) will receive:

- Palbociclib, 125 mg, orally once daily (QD) with food on Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle;

in combination with

- Cetuximab, 400 mg/m² initial dose as a 120-minute intravenous (IV) infusion followed by 250 mg/m² weekly infused over 60 minutes.

Patients randomized to Arm B (comparator arm) will receive:

- Placebo orally QD with food on Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle;

in combination with

- Cetuximab, 400 mg/m² initial dose as a 120-minute IV infusion followed by 250 mg/m² weekly infused over 60 minutes.

Patients will continue to receive their assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurs first.

The importance of timely and complete disease assessments in this study cannot be overstated. Disease assessments will be performed every 8 weeks (± 7 days) from the date of randomization. Each assessment will be performed as scheduled according to the calendar regardless of any dosing delay to prevent the introduction of bias into the assessment of efficacy. Failure to perform any of the required disease assessments will result in the inability to determine disease status for that time point. Tumor assessments will be performed until radiographically and/or clinically (ie, for photographed or palpable lesions) documented progressive disease (PD) as per RECIST v.1.1, initiation of new anticancer therapy, or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first. Off schedule or incomplete disease assessments have the potential to weaken the conclusion of this clinical trial and must be avoided wherever possible.

Patients who discontinue study treatment for reasons other than radiographically and/or clinically (ie, for photographed or palpable lesions) documented PD as per RECIST v.1.1 will continue to have tumor assessment performed during the follow-up visits every 8 weeks (± 7 days) until RECIST-defined disease progression, initiation of new anticancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first.

Patients discontinuing the active treatment phase will enter a follow-up period during which survival and new anti-cancer therapy information will be collected every 2 months from the last dose of investigational product. The follow-up period will conclude at the time of the final OS analysis.

Efficacy analyses will be performed using the local radiologist's/investigator's tumor assessments as the primary data source.

Patients will undergo study-related safety, efficacy, and PK assessments as outlined in the [Schedule of Activities](#) section.

A key objective of the biomarker analyses that will be performed in this study is to investigate candidate biomarkers assessed in tumor tissue and blood obtained prior to treatment for their potential predictive value in identifying patients who may benefit from treatment with cetuximab in combination with palbociclib or placebo. Blood and tumor (optional) biomarkers also assessed on-treatment provide an opportunity to investigate pharmacodynamics effects, and tumor specimen (optional) and blood collected upon disease progression (end of treatment) will be analyzed to investigate potential mechanisms of resistance to treatment.

In addition, blood samples will be collected from all patients in Cycles 1 and 2 to assess steady-state trough concentrations of palbociclib and pre- and post-infusion concentrations of cetuximab to provide an opportunity to conduct an exploratory exposure/response analysis for safety and efficacy findings as well as correlative analyses between drug exposure and biomarker changes from baseline.

Examining and measuring the patient's subjective experience in this study will be accomplished using health-related quality of life questionnaires. These assessments provide the means to validly and reliably quantify subjective information, which is provided by the study patients in response to specific questions from validated instruments. Observations will be documented at specified timepoints throughout the study, plus 1 observation after treatment discontinuation (to measure the impact of progressive disease on the patient's quality of life).

An independent third party External Data Monitoring Committee (E-DMC) will monitor the the efficacy and safety of patients in the study according to the Charter. The E-DMC will make recommendation as to whether or not the trial should continue based on ongoing reviews of safety data. In addition, the E-DMC will also evaluate interim efficacy data and make a recommendation regarding study continuation based on observed results of the study. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision.

Statistical Methods:

The primary objective of this study is to demonstrate that the combination of palbociclib with cetuximab is superior to cetuximab in prolonging OS in the target population. This study is designed to test the null hypothesis of equal survival between treatment arms versus the alternative hypothesis of improved survival in the palbociclib + cetuximab arm compared with the placebo + cetuximab arm.

Assuming a median OS of 6 months in the comparator arm, approximately 79 total events (deaths) are required for 1:1 randomization to have at least 80% power to detect a true hazard ratio of 0.6 (corresponding to a median OS of 10 month in the palbociclib arm) using a one-sided, log-rank test at a significance level of 0.1. One interim analysis based on OS is planned when at least 50% of the OS events (40 deaths) have been observed. The purpose of this interim analysis is to provide an opportunity to potentially stop the study early for futility. The study may be considered for early termination if the hazard ratio estimate is greater than 0.9. The formal futility boundary will be constructed using the Gamma family of spending function with parameter = 0.05. With 40 observed events at the interim analysis, the futility boundary is p-value = 0.36 (corresponding to HR = 0.9). The boundary at final analysis is p-value = 0.1.

Approximately 120 patients will be enrolled in about 16 months and followed for about 6 months to observe the required number of events. This estimation is based on the following assumptions on the enrollment rates: 1) 5 patients per month (on average) during the first 6 months; 2) 10 patients per month (on average) thereafter.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to the Study Procedures (Section 6) and Assessments (Section 7) sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the patient.

Schedule of Activities

Visit Identifier	Screening	Active Treatment Phase ^a (One Cycle = 28 days)			End of Treatment / Withdrawal ^d	4 weeks Post-Treatment	8 weeks Post-Treatment	Post-Treatment Follow-Up ^e
		Cycles 1 and 2 ^c		Cycles ≥3				
		Day 1 ^b	Day 15	Day 1 ^c				
Study Day	Within 28 days prior to randomization unless specified otherwise	±3d	±3d	±3d		±7d	±7d	±7d
Time Window								
Baseline Documentation								
Informed Consent Process ^f	X							
Medical / Oncological History ^g	X							
Baseline Signs / Symptoms ^h		X						
Human Papillomavirus (HPV)-status analysis ⁱ	X							
Physical Examination/Vital signs ^j	X	X ^b		X	X			
Serum Pregnancy Test ^k	X	X		X	X			
ECOG Performance Status	X	X		X	X			
Laboratory Studies								
Hematology ^l	X	X ^b	X	X	X			
Blood Chemistry ^{l, m}	X	X ^{b, m}	X	X	X		X	
Coagulation ⁿ	X	X ^b	X	X	X			
Urinalysis ^l	X	X ^b	X	X	X			
12-Lead ECG (in triplicate) ^o	X	X ^b (C1 only)	X	X (C4, C7, C10)	X			

Visit Identifier	Screening	Active Treatment Phase ^a (One Cycle = 28 days)			End of Treatment / Withdrawal ^d	4 weeks Post-Treatment	8 weeks Post-Treatment	Post-Treatment Follow-Up ^e
		Cycles 1 and 2 ^c		Cycles ≥3				
Study Day	Within 28 days prior to randomization unless specified otherwise	Day 1 ^b	Day 15	Day 1 ^c				
Time Window		±3d	±3d	±3d		±7d	±7d	±7d
Special Laboratory Studies								
CCI [REDACTED]								
[REDACTED]								
Archival Tumor Tissue Specimen ^f	X							
De Novo Tumor Specimens ^g	X		X		X			
CCI [REDACTED]								
[REDACTED]								
Disease Assessment								
Computed Tomography (CT)/Magnetic Resonance Imaging (MRI) Scans of Head and Neck (oral cavity, oropharynx, hypopharynx, larynx), chest, abdomen (including the liver) and any clinically indicated sites of disease; Clinical evaluation of superficial disease ^v	X	◀--▶ Performed every 8 weeks (±7 days) from the date of randomization			X			X
Other Clinical Assessments								
Drug Compliance ^w		◀--▶						
Adverse Event (AE) Reporting ^x	X	X	X	X	X	X	X	X
Review Concomitant Medications/Treatments ^y	X	X	X	X	X			
Quality of Life Questionnaire (EORTC-QLQ-C30 and EORTC-QLQ-H&N35) ^z		X		X	X	X		
Survival Follow-up								X

Visit Identifier	Screening	Active Treatment Phase ^a (One Cycle = 28 days)			End of Treatment / Withdrawal ^d	4 weeks Post-Treatment	8 weeks Post-Treatment	Post-Treatment Follow-Up ^e
		Cycles 1 and 2 ^c		Cycles ≥3				
Study Day	Within 28 days prior to randomization unless specified otherwise	Day 1 ^b	Day 15	Day 1 ^c				
Time Window		±3d	±3d	±3d		±7d	±7d	±7d
Study Treatment								
Randomization	X							
Cetuximab (both treatment arms)		◄--► Weekly IV Infusion						
Palbociclib or Placebo		◄--► Once daily with food on Day 1 to Day 21 of each cycle followed by 7 days off						

Abbreviations: ◄--► = ongoing/continuous event; AE = adverse event; CCI = [REDACTED] CT = computed tomography; CRF = case report form; CxDy = Cycle x Day y; DNA = deoxyribonucleic acid; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; FFPE = formalin-fixed paraffin embedded; HPV = Human Papillomavirus; MRI = magnetic resonance imaging; SAE = Serious Adverse Event; WBC = white blood cells

- Active Treatment Phase:** All assessments should be performed prior to dosing with study medications on the visit day unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headers. For the purposes of this trial, 1 cycle is 28 days in length. A cycle could be longer than 28 days if persistent toxicity delays the initiation of the subsequent cycle.
- Cycle 1/Day 1:** Physical examination/vital signs, blood chemistry, hematology, urinalysis, coagulation, and 12-lead ECG are not required if acceptable screening assessment is performed within 7 days prior to randomization.
- Cycle X, Day 1:** In the event that the start of a new cycle is delayed due to treatment related toxicity, procedures required on Day 1 of the given cycle will be performed when palbociclib/placebo is resumed. New cycle Day 1 procedures (ie, physical examination, vital signs, ECOG performance status, ECG, Quality of Life questionnaires, blood chemistry, hematology, urinalysis, coagulation, and serum pregnancy test) that were performed prior to knowing the need to delay the start of the cycle do not need to be repeated (1) if not required to determine whether study drug may be resumed and (2) if performed within 7 days prior to study drug resumption.
- End of Treatment/Withdrawal:** End of Treatment/Withdrawal visit will be performed as soon as possible but no later than 4 weeks (ie, 28 days) ±7 days from last dose of study treatment and prior to the initiation of any new anticancer therapy.
- Post Treatment Follow-up:** After discontinuation of study treatment, post-treatment follow-up (including survival status and post-study anticancer therapy evaluation) will be collected every 2 months (±7 days) from the last dose of study treatment. Telephone contact is acceptable.
- Informed Consent:** Informed consent may be obtained greater than 28 days from randomization; however, it must be obtained prior to any protocol required assessments being performed.
- Medical/Oncological History:** To include information on prior anticancer treatments.
- Baseline Signs/Symptoms:** Baseline tumor related signs and symptoms will be recorded at the C1D1 visit prior to initiating treatment and then reported as AEs during the trial if they worsen in severity or increase in frequency.

- i. **HPV-status:** Patients must be HPV-negative to participate in this study. Analytical method is per institutional standards.
- j. **Physical Examination/Vital signs:** A full physical examination including an examination of all major body systems (including head, ears, eyes, nose, mouth, throat, neck, thyroid, lungs, heart, breasts, abdomen, and musculoskeletal), height (at screening only), weight, blood pressure and pulse rate, which may be performed by a physician, registered nurse or other qualified health care provider, will be required at Screening and C2D1. If screening assessment is not performed within 7 days prior to randomization, a full physical examination must be performed at C1D1. Symptom-directed physical examinations, blood pressure and pulse rate assessments will be performed at subsequent visits.
- k. **Serum Pregnancy Test:** For female patients of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL, and assayed in a certified laboratory, will be performed on 2 occasions prior to starting study therapy- once at the start of screening, and once at the baseline visit, immediately before investigational product administration. A negative pregnancy result is required before the patient may receive the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected), repeated at Day 1 of each cycle, and at the end of the study to confirm the patient has not become pregnant during the study. Pregnancy tests may also be repeated as per request of institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In case of a positive confirmed pregnancy, the patient will be withdrawn from study medication and from the study. Two methods of highly effective contraception must be used throughout the study and continue for 6 months after the last dose of cetuximab. See [Section 4.4](#) for further information.
- l. **Hematology, and Blood Chemistry Panel, and Urinalysis:** Hematology includes hemoglobin, WBC, absolute neutrophils, absolute lymphocytes, and platelet count. Blood chemistry includes AST/ALT, alkaline phosphatase, sodium, potassium, magnesium, chloride, total calcium, total bilirubin, BUN (or urea), serum creatinine, uric acid, phosphorous (or phosphate), albumin, fasted glucose, and hemoglobin A1c. Additional hematology/chemistries panels may be performed as clinically indicated. Fasting glucose will be acquired at baseline C1D1, C1D15, and C2D1. For all patients, including patients starting post-study anticancer therapy, 8 weeks after the completion of therapy, blood chemistry panel consisting of magnesium, total calcium, and potassium must be checked. If abnormalities are observed, an ECG can be performed at the discretion of the investigator to check QTc. Urinalysis will be conducted via urine dipstick for urine protein: if the result is positive, further diagnostic testing will be performed as clinically indicated.
- m. **Hemoglobin A1c:** Hemoglobin A1c will be measured at C1D1, during the active treatment phase every 3 months from the date of randomization (ie, C4D1, C7D1, C10D1, etc.), and at the End of Treatment visit.
- n. **Coagulation:** Coagulation analysis includes PT or INR and PTT/aPTT.
- o. **12-Lead ECG:** All ECGs should be obtained after a fast of at least 1 hour. For the purpose of this study, triplicate ECGs are defined as three consecutive ECGs performed approximately 2 minutes apart but within 10 minutes for all 3 ECGs at the protocol-specified timepoints to determine the mean QTc interval.

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- r. **Archival Tumor Tissue Specimen:** All patients will provide a FFPE archival tumor specimen, specifically a FFPE tissue block that contain sufficient tissue to generate at least 15 unstained slides, each with tissue sections that are 5 microns thick, or at least 15 unbaked glass slides, each containing an unstained 5 micron FFPE tissue section if FFPE tissue block cannot be submitted. If an archival tumor tissue sample is not available, a de novo tumor biopsy specimen must be obtained. Specimens will be sent to the Sponsor-designated central laboratory. Details for the handling of these specimens, including processing, storage, and shipment will be provided in the Study Manual.
- s. **De Novo Tumor Specimens:** Optional de novo tumor biopsy collection at screening, C1D15 or C2D15 (pre-dose, one time point only) and at the time of progression/End of Treatment is strongly encouraged; no more than 3 timepoints should be collected in total. In all cases, these specimens will be provided in addition to the archival tumor tissue specimen that is required for enrollment. Details for handling of these specimens including processing, storage, and shipment will be provided in the Study Manual.

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- v. **Disease Assessments:** Please refer to the [Tumor Assessment Requirements Flowchart](#) for details and timing of procedures.
- w. **Drug Compliance:** Palbociclib and placebo bottle(s), including any unused capsules, will be returned to the clinic for drug accountability. Drug accountability will be performed on Day 1 of every cycle prior to dispensing drug supply for the next cycle.
- x. **AEs:** For SAEs, the active reporting period begins from the time that the patient provides informed consent through and including 28 calendar days after the last administration of the investigational product. Following the active safety reporting period, other SAEs of which the investigator becomes aware should be reported to Pfizer, unless the SAE is attributed by the investigator to complications of either the underlying malignancy or any subsequent anti-cancer therapy or to the patient’s participation in a subsequent clinical study. AEs (serious and non-serious) should be recorded on the CRF from the time the patient has taken at least one dose of study treatment through last patient visit.
- y. **Concomitant Medications/Treatments:** Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 28 days after the last dose of study treatment. If a patient begins new therapy before the 28-day time period is complete, concomitant medication information will not be recorded (from the start date of the new therapy). This includes H1 antagonists pre-medication to alleviate cetuximab infusion reactions.
- z. **EORTC-QLQ-C30 and EORTC-QLQ-H&N35 Assessments:** Patients will complete questionnaires prior to any study or medical procedure on Day 1 of Cycles 1, 2 and 3 and then Day 1 of every other cycle thereafter starting with Cycle 5 (ie, Cycle 5, 7, 9, etc.), and at the End of Treatment visit. Four weeks after discontinuation of study treatment due to progressive disease, patients, including patients starting post-study anticancer therapy, will be completing the questionnaires at the Follow-up Visit. All self-assessment questionnaires must be completed by the patients while in the clinic and cannot be taken home. Interviewer administration in clinic may be used under special circumstances, but family members are not permitted to assist with questionnaire administration.

TUMOR ASSESSMENT REQUIREMENTS FLOWCHART

	Screening ^a	Treatment Period ^b	End of Treatment Visit ^c
CT or MRI of Head and Neck (oral cavity, oropharynx, hypopharynx, larynx) ^d	Required ^e	Required	Required
CT or MRI of Chest and Abdomen (including the liver) ^d	Required ^e	Required	Required
CT or MRI of any other site of disease, as clinically indicated.	Required ^{e,1}	Required for sites of disease identified at screening.	Required for sites of disease identified at screening, unless disease progression has been confirmed elsewhere.
Photographs of all superficial lesions as applicable ^g	Required	Required for sites of disease identified at screening.	Required for sites of disease identified at screening, unless disease progression has been confirmed elsewhere.

- a. Screening scans must occur within 4 weeks (ie, 28 days) prior to randomization unless otherwise specified.
- b. Tumor assessment must be done during the treatment period, every 8 weeks (± 7 days) until radiographically and/or clinically (ie, for photographed or palpable lesions) documented PD as per RECIST v.1.1, initiation of new anticancer therapy, or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow up), whichever occurs first. The schedule of assessments should be fixed according to the calendar, regardless of treatment delays/interruptions. Imaging assessments are to be scheduled using the randomization date as the reference date for all time-points and are NOT to be scheduled based on the date of the previous imaging time-point. Imaging assessment delay to conform to treatment delay is not permitted. The same tumor assessment technique MUST be used throughout the study for a given lesion/patient.
- c. Patients who have already demonstrated objective disease progression as per RECIST v.1.1 do not need to have scans repeated at the end of treatment visit or during the post-treatment follow-up. For patients who do not have documented objective disease progression at time of study treatment discontinuation, tumor assessment will continue to be performed every 8 weeks (± 7 days) until radiographically and/or clinically confirmed objective disease progression, initiation of new anticancer therapy, or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up).
- d. The CT scans, including brain CT scan if applicable, should be performed with contrast agents unless contraindicated for medical reasons. If IV contrast is medically contraindicated, the imaging modality to be used to follow the disease (either CT without contrast or MRI) should be the modality which best evaluates the disease, and the choice should be determined by the investigator in conjunction with the local radiologist. MRI of the abdomen can be substituted for CT if MRI adequately depicts the disease. However, MRI of the chest should not be substituted for CT of chest even if IV contrast is contraindicated. In such case CT will be performed without contrast. If MRI is used to follow-up bone lesion(s) it must be performed a few days before any treatment that may affect bone-marrow cellularity (eg, G-CSF).
- e. Radiographic assessments obtained per the patient's standard of care prior to randomization into the study do not need to be repeated and are acceptable to use as baseline evaluations, if (1) obtained within 28 days before randomization, (2) they were performed using the method requirements outlined in RECIST v.1.1 (3) the same technique/modality can be used to follow identified lesions throughout the trial for a given patient, and (4) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes.
- f. Baseline brain scans are required in patients with a history of metastatic brain disease. Brain scans performed before the signing of informed consent as routine procedures (but within 6 weeks before randomization) do not need to be repeated and may be used as baseline assessments as long as (1) tests were performed using the method requirements outlined in RECIST v.1.1 (2) the same technique/modality can be used to follow identified lesions throughout the trial for a given patient (3) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes. Post-baseline repeat brain scans will be required only if new metastases are suspected.

- g. Clinical assessment of superficial disease must be carried out on the same date as the imaging studies and will include photographs of all superficial metastatic lesions. All lesion measurements must be recorded in the CRF.

Notes:

- Radiographic tumor assessments may be done at any time if there is clinical suspicion of disease progression at the discretion of the investigator. If progressive disease is confirmed per RECIST v.1.1, patients are expected to discontinue study therapy and begin the follow-up phase of the trial

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1. INTRODUCTION

Squamous cell carcinoma of the head and neck (SCCHN) is the sixth most common cancer. Globally, approximately 600,000 new cases occur yearly. In the United States, it is estimated that about 55,000 new cases of oral cavity, pharyngeal, and laryngeal cancers will occur in 2014, which account for about 3% of new cancer cases. Data from a non-age-specific meta-analysis of 17,346 patients from 93 randomized trials presented oropharyngeal cancer as the most frequently observed (36%) SCCHN tumor type, followed by laryngeal and oral cavity cancers (21% each).¹

An estimated 12,000 deaths from SCCHN will occur during 2014 in the United States (US).² In the European Union (EU) an estimated 21,000 deaths from oral and hypopharyngeal cancers occurred each year between 2005 and 2009.³

Squamous cell carcinoma accounts for 90% of the head and neck tumors and the main risk factors include tobacco use, and alcohol use.⁴ Even though SCCHN is considered a predominantly male disease, several studies have reported a higher women proportion in the elderly SCCHN population, with a sex ratio close to 1. Tobacco and alcohol consumption were the major risk factors identified in 50% of the male population, whereas chronic oral trauma, leukoplakia and lichen planus were the predominant risk factors found in half of the female population.⁶ The oncogenic human papillomavirus (HPV) infection is a risk factor for oropharyngeal SCCHN.⁵ Patients with HPV infection tend to be younger than HPV-unrelated SCCHN patients. HPV seems to have minor effect in the pathogenesis of SCCHN in the elderly population. Advanced age itself is considered to be a risk factor for poor outcome.

Local treatment of SCCHN often incorporates multimodality therapy and can be associated with significant functional sequelae. Multimodality treatment including surgery and/or, radiation and/or chemotherapy is considered the best therapeutic options for patients with SCCHN. Unfortunately, development of recurrent or even metastatic disease after therapy is common, and occurs in 40-60% of patients with locally advanced disease despite initially aggressive multimodal therapy. R/M disease is associated with poor outcomes and a median overall survival (OS) of 10-11 months in the first-line treatment setting, and about 6 months in the second-line treatment setting. Chemoradiotherapy regimens have reached their upper limit of tolerability so that the investigation of new rational targets, based on the biology of the disease, is of major importance, thus highlighting the current need for more efficacious and better tolerated therapy.⁷

1.1. Mechanism of Action/Indication

Palbociclib is a highly selective, reversible oral inhibitor of cyclin-dependent kinases 4 and 6 (CDK 4/6). The compound prevents cellular deoxyribonucleic acid (DNA) synthesis by prohibiting progression of the cell cycle from G1 into S phase. Palbociclib is being developed in combination with cetuximab (Erbix[®]), an epidermal growth factor receptor (EGFR) antagonist, for the treatment of HPV-negative, cetuximab-naïve, R/M SCCHN after failure of one platinum-based chemotherapy regimen.

1.2. Background and Rationale

1.2.1. Role of EGFR in SCCHN

Epidermal growth factor receptor (EGFR) overexpression is found in approximately 90% of SCCHN cases⁸ and it is associated with decreased progression-free survival (PFS) and OS.⁹ The ErbB family of proteins contain four receptor tyrosine kinases, structurally related to EGFR, includes HER1 (EGFR, ErbB1), HER2 (EGFR, ErbB2), HER3 (ErbB3), and HER4 (ErbB4). EGFR-directed drugs include antibodies that prevent ligand-binding and/or receptor dimerization (eg, cetuximab) and small molecule adenosine triphosphate-competitive inhibitors of the intrinsic catalytic activity of ErbB receptors (eg, erlotinib and gefitinib).

1.2.2. Deregulation of Cell Cycle Related Genes and Proteins in SCCHN

Important regulatory proteins involved in the cell cycle transition from G1 to the S-Phase are cyclin D1 (*CCND1*), p16^{INK4A} (thereafter referred to as p16) and CDK4. Deregulation of aspects of the cell-cycle, including CDKs, have been shown to contribute to the development of cancer.^{10,11}

CCND1, encoded by cyclin D1 is a well characterized member of the cyclin D family and is a positive regulator of the cell cycle (in complex with CDK4, see below) and is amplified in 80% or more cases of HPV-negative SCCHN.¹² Cyclin D1 has been recognized as a marker of poor prognosis.^{13,14,15,16,17,18} With platinum as important component of first line therapy of SCCHN it is noteworthy that Cyclin D1 overexpression in SCCHN was associated with cisplatin resistance in vitro, in vivo,^{19,20} and clinically.²¹

CDK4 and CDK6 are two closely related kinases that are regulated by the cyclin D family members.²² In preclinical studies, increased levels of cyclin D and decreased levels of p16 (see below), have been associated with increased sensitivity to CDK 4 and 6 inhibition.²³ Preclinical studies suggest that inhibition of cyclin D-dependent kinase activity may prevent tumor growth.²²

CDKN2A, which encodes p16, is considered a negative regulator of the cell cycle. It is inactivated in most cases of HPV-negative SCCHN by mutation, methylation in combination with chromosome loss or by homozygous deletion.²⁴ Over-expression of cyclin D1, along with decreased expression of p16 and abrogation of p53 function, can cause cellular immortalization of oral keratinocytes.²⁵ Thus, cyclin D1 overexpression in the context of decreased expression of p16 is likely to be an important driver of HPV-negative SCCHN.

1.2.3. Interaction of EGFR and CDK4/6 in SCCHN

CCND1 is one of the many genes induced by intranuclear EGFR, linking cell cycle progression to EGFR stimulation.²⁶ Data from SCCHN cell lines suggest an association between resistance to EGFR inhibitors and cyclin D1 amplification and/or overexpression.²⁷

1.2.4. Investigational Agents: Cetuximab

Cetuximab (Erbix[®]) is a chimeric monoclonal antibody directed against EGFR. In the US, EU, and Japan, cetuximab is approved in combination with radiation therapy for the treatment of locally advanced SCCHN and in combination with platinum-based chemotherapy for the treatment of recurrent and/or metastatic SCCHN. In the US it is also approved as a single agent for the treatment of patients with recurrent or metastatic SCCHN for whom prior platinum-based chemotherapy has failed.

In a randomized Phase 3 trial conducted on 424 patients with locoregionally advanced (stage III or IV) SCCHN in which patients received either radiotherapy alone or radiation plus weekly cetuximab, cetuximab combined with radiotherapy improved median survival from 29.3 to 49.0 months (p-value = 0.03) and locoregional control from 14.9 to 24.4 months (p-value = 0.05).^{28,29}

In randomized, open-label, multinational, Phase 3 clinical trials, cetuximab plus first-line platinum-based chemotherapy significantly improved OS (primary endpoint) compared with first-line platinum-based chemotherapy in patients with recurrent and/or metastatic SCCHN.⁷ This study demonstrated a significant benefit of cetuximab with an improvement in median OS from 7.4 months to 10.1 months (p-value = 0.04).

Three Phase 2 trials have investigated the role of cetuximab in patients with advanced SCCHN who had progressed on platinum-based chemotherapy. In such trials, cetuximab administered as a single-agent in the second-line setting, was associated with response rates between 10 and 13%, a median PFS of about 3 months, and a median OS of 6 months.^{30,31,32} Vermorken and colleagues conducted a pooled analysis of these trials.³³ The analysis compared the outcome of these patients to that of patients who received a range of common second-line treatment approaches including best supportive care, palliative chemotherapy, radiotherapy and chemoradiotherapy in a retrospective study. The median OS for patients in the retrospective study was 3.4 months.

Cetuximab-related adverse events (AEs), which include skin rash, hypomagnesaemia and infusion-related reactions, are mostly mild to moderate in severity and manageable. The most serious AEs associated with cetuximab are infusion reactions, cardiopulmonary arrest, dermatologic toxicity and radiation dermatitis, sepsis, renal failure, interstitial lung disease, and pulmonary embolus. The current boxed warning includes infusion reactions and cardiopulmonary arrest.

1.2.5. Investigational Agents: Palbociclib

1.2.5.1. Pre-Clinical Data

1.2.5.1.1. Evidence of Palbociclib Single Agent Activity in SCCHN Tumor Models

Palbociclib (Molecular Weight: 447.53) is a highly selective inhibitor of CDK4/cyclinD₁ kinase activity (IC₅₀ = 11 nM; K_i = 2 nM). Palbociclib has selectivity for CDK4/6, with little or no activity against a large panel of 274 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 palbociclib inhibits CDK6 with equivalent potency to CDK4. Palbociclib showed anti-proliferative effects on Rb-positive cells *in vitro* and inhibition of tumor growth in several Rb-positive human breast and colon xenografts. In these models, palbociclib resulted in decreased Rb phosphorylation and decreased Ki-67 expression, but did not show activity in Rb-negative tumor xenografts.²² Additional information may be found in the Investigator's Brochure (IB) for palbociclib.

To assess the significance of CDK4/6 signaling in SCCHN, a breadth of efficacy studies were conducted across a panel of molecularly annotated cell lines and tumor explants. In SCCHN cell lines palbociclib treatment produced growth arrest in the majority of models tested. Palbociclib treated cells showed reduced phosphorylation of Rb, inhibition of E2F signaling, and loss of CDK4/6 substrate FOXM1. Treated cell lines displayed inhibition of new DNA synthesis, measured through incorporation of EdU, and showed no signs of apoptosis when assessed through measurement of active caspases. To evaluate the efficacy of palbociclib in SCCHN models *in vivo*, tumor growth inhibition studies were run in a panel of three patient-derived xenografts. Single agent palbociclib displayed equivalent or superior efficacy to single agent cetuximab treatment in these studies, with demonstration of >90% inhibition in one model and partial inhibition (>60% TGI) in one model (unpublished data, data on file at Pfizer).

1.2.5.1.2. Evidence for Additive/Synergistic Activity for the Combination of Palbociclib and Cetuximab

Combinatorial efficacy was observed following treatment with palbociclib and inhibitors of the EGFR pathway, including cetuximab, in preclinical models. In a panel of 24 SCCHN cell lines the palbociclib combination with cetuximab produced synergistic growth inhibition in 50% of models. The combination of palbociclib and cetuximab in a subset of these cell lines demonstrated increased inhibition of pRb and downstream E2F signaling, leading to greater inhibition of new DNA synthesis and increased hallmarks of cellular senescence than with each agent alone. *In vivo* studies in patient-derived xenografts demonstrated the ability of either single agent to produce >90% tumor growth inhibition in distinct models, and in a model that failed to show significant response to either single agent, the combination of palbociclib and cetuximab yielded synergistic tumor growth inhibition.

1.2.5.1.3. Overview of Nonclinical Safety Data

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 hemato-lymphopoietic 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 chronic progressive neuropathy), 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. Additional information may be found in the IB for palbociclib.

1.2.5.2. Clinical Data

Two Phase 1 trials evaluated single agent administration of palbociclib to patients with Rb-positive cancers.^{34,35} One of these trials determined that the dose-limiting toxicity (DLT) was neutropenia and the maximum tolerated dose (MTD) was 125 mg once daily when administered for 21 of 28 days (3/1 schedule). The most common non-hematologic AEs included fatigue, nausea, and diarrhea. The mean half-life of palbociclib was 26.9 hours. Patients were selected for Rb-positive cancers, based on immunohistochemistry (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 palbociclib using an alternative dosing plan (21 day cycles; 2/1 schedule) observed a similar likelihood of disease control in a variety of tumor types.³⁴ These studies demonstrate that palbociclib has substantial activity in Rb-positive tumors.

A randomized Phase 2 trial initiated to determine the overall safety and efficacy of palbociclib (125 mg) and letrozole (2.5 mg) versus letrozole in post-menopausal women with ER+ HER2-negative advanced breast cancer.³⁶ The overall objective response rate (ORR) was 45% for those women who received palbociclib plus letrozole versus 31% for those who received letrozole (statistically significant). Importantly, the median PFS was significantly different (26.2 versus 7.5 months) favoring the combination arm.

The most common adverse drug reactions of any grade reported in patients in the palbociclib plus letrozole arm were neutropenia, leukopenia, fatigue, anemia, upper respiratory infection, nausea, stomatitis, alopecia, diarrhea, thrombocytopenia, decreased appetite, vomiting, asthenia, peripheral neuropathy, and epistaxis. The most frequently reported serious adverse drug reaction in patients receiving palbociclib plus letrozole was diarrhea (2.4%).

Overall, neutropenia of any grade was reported in 62 (74.7%) patients in the combination arm, with Grade 3 neutropenia being reported in 40 (48.2%) patients, and Grade 4 neutropenia being reported in 5 (6.0%) patients.

In the combination arm, 56.6% of patients had a maximum grade of Grade 3 neutropenia and 4.8% of patients had a maximum grade of Grade 4 neutropenia based on laboratory data. The median time to first episode of neutropenia was 15 days for any grade, Grade ≥ 2 , and Grade 4 neutropenia, and 28 days for Grade ≥ 3 neutropenia in the palbociclib plus letrozole arm. Median duration of Grade 3 or 4 neutropenia was 7 days. Most episodes of Grade ≥ 3 neutropenia were managed by dose reduction and/or dose delay or temporary discontinuation and did not require permanent discontinuation of study treatment or addition of supportive therapy.

Palbociclib, in combination with anti-hormonal treatment, is currently being tested in large Phase 3 studies, in patients with advanced ER+ HER2-negative breast cancer.

Palbociclib has also demonstrated activity in a broad range of other solid tumors and hematological malignancies. In relapsed mantle cell lymphoma selected for cyclin D1 overexpression,³⁷ the objective response (complete response [CR] or partial response [PR]) rate was 18% and the stable disease (SD) rate was 41%. Significant reductions in phospho-Rb (89%) and Ki-67 (74%) occurred in paired biopsy samples after treatment with palbociclib.

In a study in 29 patients with well-differentiated and dedifferentiated liposarcoma, Dickson et al reported a 66% (90% CI, 51% to 100%) PFS rate at 12 weeks. The median PFS was 18 weeks, and there was one partial response. Grade 3 to 4 events included anemia, thrombocytopenia, neutropenia, and febrile neutropenia in one patient.³⁸

In an ongoing Phase 1 clinical trial of escalating doses of palbociclib added to fixed dose cetuximab in patients with SCCHN, one partial tumor response was observed in a patient with SCCHN resistant to cetuximab and cisplatin. Disease control (PR or SD) occurred in 6 of the 7 evaluable patients. Of the 6 patients with cetuximab-resistant SCCHN, 5 experienced disease control with combined palbociclib + cetuximab treatment. Of the 4 patients with cisplatin-resistant SCCHN, 3 experienced disease control with palbociclib + cetuximab. These clinical data support significant potential efficacy of palbociclib in SCCHN (Appendix 1). Further data analyses, including PK, safety, and efficacy analysis, are in progress for this study. Additional information may be found in the IB for palbociclib.

1.2.6. Dose Rationale for the Combination

In the aforementioned ongoing Phase 1 dose escalation study, palbociclib was administered at doses of 100 and 125 mg QD for 21 out of 28 days (3/1 schedule). Cetuximab was administered at the initial dose of 400 mg/m² as a 120-minute IV infusion, followed by 250 mg/m² weekly dose, infused over 60 minutes. The combination was well tolerated without any DLTs observed at either dose level. Uncomplicated neutropenia was the most frequent AE. Based on this study, the recommended Phase 2 dose (RP2D) was determined to be 125 mg of palbociclib administered on the 3/1 schedule in combination with the standard dose for cetuximab.

Complete information for palbociclib may be found in the Single Reference Safety Document (SRSD), which for this study is the IB. The SRSD for the active comparator agent, cetuximab (Erbix[®]), is the most recent version of the Summary of Product Characteristics (SPC).³⁹

1.2.7. Study Rationale

HPV-negative, R/M, SCCHN represents a disease with a dismal prognosis. Although the EGFR inhibitor cetuximab is an important recent addition to the treatment options for the second-line treatment of SCCHN, it has resulted in only modest improvements in clinical outcomes, and no standard of care exists. Therefore, newer treatments or treatment regimens with novel mechanisms of action are desperately needed.

Overexpression of cyclin D1 and inactivation of p16 occur in the vast majority of cases of HPV-negative SCCHN, but not in HPV-related SCCHN, in which both loss of Rb and high p16 expression levels are common. Genomic characterization of oral HPV-negative SCCHN identified amplification of *CCND1* (cyclin D1) and/or loss of *CDKN2A* (p16) in 94% of tumors, supporting that cell cycle alterations are a nearly universal feature in this patient population,³² and that a drug targeting cell cycle such as palbociclib may be appropriate to test in this disease setting.

A breadth of preclinical *in vitro* and *in vivo* efficacy studies were conducted in which palbociclib displayed equivalent or superior efficacy to single agent cetuximab treatment and combination treatment with the two agents increased efficacy and/or the DR.

Based on the evidence presented, the proposed Phase 2 study provides the opportunity to test the hypothesis that the addition of palbociclib to cetuximab will improve outcomes in patients with recurrent or metastatic SCCHN after failure of one platinum-containing regimen.

1.2.8. Summary of Benefit Risk Assessment

Current second-line treatments for HPV-negative, R/M, SCCHN have minimal effectiveness and are undesirably toxic. The result is OS in this setting is very short; therefore, there is a high unmet medical need for new and improved treatment options.

The potential benefits of the present study are based on sound preclinical and preliminary clinical evidence that inhibition of the cyclin D1/CDK4 axis by palbociclib in combination with EGFR inhibition by cetuximab can be an effective treatment for patients with incurable, cetuximab-naïve, HPV-negative SCCHN. It can be expected that patients will benefit from prolonged survival, PFS, and other health-related outcomes, such as delayed deterioration or improvement of global health status, pain and swallowing capabilities.

Potential risks associated with palbociclib include non-cumulative, reversible, uncomplicated neutropenia (about 50% Grade 3) managed by dose reduction and/or dose delay or temporary discontinuation without the requirement of permanent discontinuation of treatment or addition of supportive therapy. Other risks associated include leukopenia, fatigue, anemia, upper respiratory infection, nausea, stomatitis, alopecia, diarrhea, thrombocytopenia, decreased appetite, vomiting, asthenia, peripheral neuropathy, and epistaxis. Risks associated with cetuximab include infusion reactions, dermatologic toxicity, cardiac arrest, and hypomagnesemia. The overall toxicity profiles of palbociclib and cetuximab do not overlap.

Therefore, the potential benefits outweigh the potential risks, supporting an overall favorable benefit/risk assessment in the treatment of patients with incurable, cetuximab-naïve, HPV-negative R/M SCCHN after failure of one platinum-containing regimen.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

- To demonstrate that the combination of palbociclib with cetuximab is superior to cetuximab in prolonging OS in HPV-negative, cetuximab-naïve patients with R/M SCCHN in whom one prior platinum-containing chemotherapy has failed.

2.1.2. Secondary Objectives

- To compare secondary measure of efficacy between the treatment arms;
- To compare safety and tolerability between the treatment arms;
- To compare Patient-Reported Outcome (PRO) measures between the treatment arms;

- To characterize the correlations between baseline biomarker (eg, p16, Rb) expression in tumor tissue and clinical efficacy in both treatment arms;
- To characterize steady state trough concentrations for palbociclib, and trough and maximum concentrations for cetuximib in patients with R/M SCCHN.

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2.2. Endpoints

2.2.1. Primary Endpoint

- Overall Survival.

2.2.2. Secondary Endpoints

- PFS, Objective Response (OR), and DR, according to Response Evaluation Criteria in Solid Tumours (RECIST version [v.]1.1, see [Appendix 2](#)), as assessed by investigator;
- Type, incidence, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v. 4.03), seriousness and relationship to study medications of AEs and any laboratory abnormalities;
- PRO endpoints: European Organisation for Research and Treatment of Cancer Quality of Life Instrument (EORTC-QLQ-C30, see [Appendix 3](#)); European Organisation for Research and Treatment of Cancer Head and Neck Module 35 (EORTC-QLQ-H&N35, see [Appendix 4](#));
- Tumor tissue biomarkers by IHC (p16 and Rb);
- Trough concentrations at steady state for palbociclib; trough and maximum concentrations for cetuximib.

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3. STUDY DESIGN

This is an international, multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 2 study comparing the efficacy and safety of palbociclib in combination with cetuximab versus cetuximab in HPV-negative, cetuximab-naïve patients with R/M SCCHN after failure of one platinum-containing regimen. Approximately 120 patients will be randomized 1:1 between the investigational arm (Arm A: palbociclib plus cetuximab) and the comparator arm (Arm B: placebo plus cetuximab). Crossover between treatment arms will be prohibited.

Patients will be stratified by Eastern Cooperative Oncology Group (ECOG, see [Appendix 5](#)) performance status (0 vs 1), and by prior use of immunotherapy (yes vs no).

Patients randomized to Arm A (investigational arm) will receive:

- Palbociclib, 125 mg, orally once daily (QD) with food on Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle;

in combination with

- Cetuximab, 400 mg/m² initial dose as a 120-minute intravenous (IV) infusion followed by 250 mg/m² weekly infused over 60 minutes.

Patients randomized to Arm B (comparator arm) will receive:

- Placebo orally QD with food on Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle;

in combination with

- Cetuximab, 400 mg/m² initial dose as a 120-minute IV infusion followed by 250 mg/m² weekly infused over 60 minutes.

Patients will continue to receive their assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurs first.

The importance of timely and complete disease assessments in this study cannot be overstated. Disease assessments will be performed every 8 weeks (± 7 days) from the date of randomization. Each assessment will be performed as scheduled according to the calendar regardless of any dosing delay to prevent the introduction of bias into the assessment of efficacy. Failure to perform any of the required disease assessments will result in the inability to determine disease status for that time point. Tumor assessments will be performed until radiographically and/or clinically (ie, for photographed or palpable lesions) documented PD as per RECIST v.1.1, initiation of new anticancer therapy, or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first. Off schedule or incomplete disease assessments have the potential to weaken the conclusion of this clinical trial and must be avoided wherever possible.

Patients who discontinue study treatment for reasons other than radiographically and/or clinically (ie, for photographed or palpable lesions) documented PD as per RECIST v.1.1 will continue to have tumor assessment performed during the follow-up visits every 8 weeks (± 7 days) until RECIST-defined disease progression, initiation of new anticancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first.

Patients discontinuing the active treatment phase will enter a follow-up period during which survival and new anti-cancer therapy information will be collected every 2 months from the last dose of investigational product. The follow-up period will conclude at the time of the final OS analysis. Crossover will not be allowed in the trial.

Efficacy analyses will be performed using the local radiologist's/investigator's tumor assessments as the primary data source.

Patients will undergo study-related safety, efficacy, and PK assessments as outlined in the [Schedule of Activities](#) section.

A key objective of the biomarker analyses that will be performed in this study is to investigate candidate biomarkers assessed in tumor tissue and blood obtained prior to treatment for their potential predictive value in identifying patients who may benefit from treatment with cetuximab in combination with palbociclib or placebo. Blood and tumor (optional) biomarkers also assessed on-treatment provide an opportunity to investigate pharmacodynamics effects, and tumor specimen (optional) and blood collected upon disease progression (end of treatment) will be analyzed to investigate potential mechanisms of resistance to treatment.

In addition, blood samples will be collected from all patients in Cycles 1 and 2 to assess steady-state trough concentrations of palbociclib and pre- and post-infusion concentrations of cetuximab to provide an opportunity to conduct an exploratory exposure/response analysis for safety and efficacy findings as well as correlative analyses between drug exposure and biomarker changes from baseline.

Examining and measuring the patient's subjective experience in this study will be accomplished using health-related quality of life questionnaires. These assessments provide the means to validly and reliably quantify subjective information, which is provided by the study patients in response to specific questions from validated instruments. Observations will be documented at specified timepoints throughout the study, plus 1 observation after treatment discontinuation (to measure the impact of progressive disease on the patient's quality of life).

An independent third party E-DMC will monitor the the efficacy and safety of patients in the study according to the Charter. The E-DMC will make recommendation as to whether or not the trial should continue based on ongoing reviews of safety data. In addition, the E-DMC will also evaluate interim efficacy data and make a recommendation regarding study continuation based on observed results of the study. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision.

4. PATIENT SELECTION

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient.

4.1. Inclusion Criteria

Patient eligibility should be reviewed and documented by an appropriate member of the investigator's study team before patients are included in the study.

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Histologically or cytologically confirmed squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx, not amenable for salvage surgery or radiotherapy.
2. Measurable disease as defined per RECIST v. 1.1. Tumor lesions previously irradiated or subjected to other locoregional therapy will only be deemed measurable if disease progression at the treated site after completion of therapy is clearly documented.
3. HPV- negative SCCHN tumor as determined per institutional standard (eg, p16 IHC; multiplex nucleic acid sequence based amplification [NASBA] or other polymerase chain reaction [PCR]-based assays).
4. Documented progressive disease according to RECIST v1.1 ([Appendix 2](#)) following receipt of at least 2 cycles of one platinum-containing chemotherapy regimen administered for R/M disease (min. 50 mg/m² for cisplatin, minimum area under the curve [AUC] >4 for carboplatin).

5. Availability of a tumor tissue specimen (ie, archived formalin fixed paraffin embedded tissue [block preferred, or 15 unstained slides]), which will be used for centralized, retrospective biomarker analysis. If archived tumor tissue is not available, then a de novo biopsy will be required for patient participation.
6. ECOG performance status (PS) 0 or 1 ([Appendix 5](#)).
7. Adequate organ and marrow function defined as follows:
 - Leukocytes $>3,000/\text{mm}^3$ ($3.0 \times 10^9 /\text{L}$);
 - Absolute Neutrophil count (ANC) $\geq 1,200/\text{mm}^3$ ($1.2 \times 10^9 /\text{L}$);
 - Platelets $\geq 75,000/\text{mm}^3$ ($75 \times 10^9 /\text{L}$);
 - Hemoglobin (Hb) ≥ 9 g/dL (90 g/L);
 - Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or estimated creatinine clearance ≥ 40 mL/min as calculated using the method standard for the institution;
 - Total serum bilirubin ≤ 1.5 x ULN (≤ 3.0 x ULN if Gilbert's disease);
 - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤ 2 x ULN (≤ 5.0 x ULN if liver metastases present);
 - Alkaline phosphatase ≤ 2.5 x ULN (≤ 5.0 x ULN if bone or liver metastases present).
8. Male and female patients of childbearing potential and at risk for pregnancy must agree to use two highly effective methods of contraception throughout the study and for 6 months after the last dose of cetuximab.

Female subjects who are not of childbearing potential (ie, meet at least 1 of the following criteria):

- Have undergone a documented hysterectomy and/or bilateral oophorectomy;
 - Have medically confirmed ovarian failure; or
 - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women.
9. Age ≥ 18 years (or ≥ 20 years as applicable by local country regulations).
 10. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

11. Patients who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

4.2. Exclusion Criteria

Patients presenting with any of the following will not be included in the study:

1. Prior nasopharyngeal cancer, salivary gland or sinus tumors.
2. More than one chemotherapeutic regimen given for R/M disease. Prior treatment with immunotherapy is allowed.
3. Known active uncontrolled or symptomatic central nervous system (CNS) metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral edema, and/or progressive growth. Patients with a history of CNS metastases or cord compression are eligible if they have been definitively treated with local therapy (eg, radiotherapy, stereotactic surgery) and are clinically stable off anticonvulsants and steroids for at least 4 weeks before randomization.
4. Progressive disease within 3 months after completion of curatively intended treatment for locoregionally advanced SCCHN.
5. Inability to swallow capsules.
6. Prior use of cetuximab in the R/M disease treatment setting.
7. Prior treatment with any CDK4/6 or EGFR inhibitor (except cetuximab during curative radiotherapy).
8. Patients treated within the last 7 days prior to randomization with:
 - Food or drugs that are known to be strong CYP (cytochrome P-450) 3A4 inhibitors (ie, amprenavir, atazanavir, boceprevir, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, voriconazole, and grapefruit or grapefruit juice);
 - Drugs that are known to be strong CYP3A4 inducers (ie, carbamazepine, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentin, and St. John's wort);
 - Drugs that are known to prolong the QT interval ([Appendix 6](#)).
9. Major surgery, chemotherapy, radiotherapy, any investigational agents, or other anti-cancer therapy within 2 weeks before randomization. Patients who received prior radiotherapy to $\geq 25\%$ of bone marrow ([Appendix 7](#)) are not eligible independent of when it was received.

10. Diagnosis of any other malignancy within 3 years prior to randomization, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix.
11. QTc >480 msec (based on the mean value of the triplicate electrocardiograms (ECGs), family or personal history of long or short QT syndrome, Brugada syndrome or known history of QTc prolongation, or Torsade de Pointes).
12. Uncontrolled electrolyte disorders that can compound the effects of a QTc-prolonging drug (eg, hypocalcemia, hypokalemia, hypomagnesemia).
13. Any of the following within 6 months of randomization: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of NCI CTCAE version 4.03 Grade ≥ 2 , atrial fibrillation of any grade, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident including transient ischemic attack, or symptomatic pulmonary embolism.
14. Active inflammatory bowel disease or chronic diarrhea, short bowel syndrome, or any upper gastrointestinal surgery including gastric resection that could impair drug absorption.
15. Known human immunodeficiency virus infection.
16. Other severe acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.
17. History of allergic reactions attributed to compounds of similar chemical or biologic composition to cetuximab.
18. Pregnant female subjects; breastfeeding female subjects; male and female subjects of childbearing potential who are unwilling or unable to use two highly effective methods of contraception as outlined in this protocol for the duration of the study and for 6 months after the last dose of cetuximab.
19. Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees directly involved in the conduct of the study.
20. Participation in other studies involving investigational drug(s) (Phases 1-4) within 4 weeks before the current study begins and/or during study participation.

4.3. Randomization Criteria

Patients will be randomized into the study provided they have satisfied all patient selection criteria.

The investigators or their pre-specified designee will randomize eligible patients by interactive randomization technology (IRT) as described in the Study Reference Manual.

At the time of randomization, information about patient demographics and stratification factors (ie, ECOG PS [0 vs 1] and prior use of immunotherapy [yes vs no]) will be requested.

The central computerized system will provide the randomization number and treatment assignment.

4.4. Lifestyle Guidelines

In this study, all male and female patients of childbearing potential, as defined in Inclusion Criterion 8, must agree to use 2 methods of highly effective contraception throughout the study and continue for 6 months after the last dose of cetuximab. The investigator or his/her designee, in consultation with the patient, will confirm the patient has selected 2 appropriate methods of contraception for the individual patient (and his female partner as warranted) from the list of permitted contraception methods (see below) and confirm that the patient has been instructed in their consistent and correct use. Patients need to affirm that they meet at least 2 of the selected methods of contraception. The investigator or his/her designee will discuss with the patient the need to use highly effective contraception consistently and correctly according to the [Schedule of Activities](#) and document such conversation in the patient's chart. In addition, the investigator or his/her designee will instruct the patient to call immediately if a selected contraception method is discontinued or if pregnancy is known or suspected.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include:

1. Established use of oral, inserted, injected, or implanted hormonal methods of contraception are allowed provided the patient plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.
2. Correctly placed copper-containing intrauterine device (IUD).
3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.
4. Male sterilization with absence of sperm in the post-vasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

All sexually active male subjects must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for 6 months after the last dose of cetuximab.

4.5. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list, located in the coordinator's manual.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study numbers, contact information for the investigational site, and contact details for a help desk in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patient's participation in the study. The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should only be used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The help desk number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

If the patient is found to be eligible for the study, he/she should be randomized using a centralized internet/telephone registration system no more than 4 calendar days before administration of the first dose of investigational product.

Allocation of patients to treatment groups will proceed through the use of an Interactive Reponse Technology (IRT) system (Interactive Web Response (IWR)/Interactive Voice Response (IVR) System). The site personnel (study coordinator or specified designee) will be required to enter or select information including, but not limited to, the user's identification (ID) and password, protocol number, the patient number and date of birth of the patient. The site personnel will then be provided with a randomization number and dispensable unit (DU) or container number when drug is being supplied via the IRT. The IRT system will provide a confirmation report containing the patient number and DU or container number assigned. The confirmation report must be stored in the site's files.

There is a 24 hour a day, 365 days a year IRT helpdesk available for any questions or issues. The study specific IRT reference manual will provide the contact information and further details on the use of the IRT.

Note: The IRT is the source of the patient number. The IRT system will provide the patient number at the end of the first IRT patient transaction.

Eligible patients will be randomly assigned in a 1:1 ratio to either Arm A (investigational arm: palbociclib plus cetuximab) or Arm B (comparator arm: placebo plus cetuximab) stratified according to ECOG PS and prior use of immunotherapy (see [Section 4.3](#)).

Clinical sites must complete the screening CRFs for all registered and randomized patients, even if the patient is not subsequently treated in this study.

At the time of registration, the clinical site staff must provide site and patient identifiers and demographic information. The IRT will assign a unique patient identification number. The IRT system will also be used to assign study medication.

If a patient does not receive the correct study treatment for their allocated treatment arm, the reason must be clearly documented in CRF. The patient will remain on study, baseline data will be collected and follow up will continue as described in the [Schedule of Activities](#) table.

5.1.1. Screen Failure

Patients who completed the informed consent process but do **NOT** meet all eligibility criteria and therefore are **NOT** randomized to either treatment arm will be considered as screen failures. Please see [Section 4.1](#) and [Section 4.2](#) for detailed inclusion and exclusion criteria.

Clinical sites must provide for all screen failures the following information using the appropriate CRFs: screening number, demographic data as well as the final patient summary including the reason for screening failure.

5.2. Breaking the Blind

At the initiation of the trial, the trial site will be instructed on the method for breaking the blind. The method will be either a manual or electronic process. Blinding codes should only be broken in emergency situations for reason of patient safety. Blinding codes may also be broken after a patient discontinues treatment due to disease progression, as determined by the treating investigator using RECIST v.1.1, but only if deemed essential to allow the investigator to select the patient's next treatment regimen and after discussion and agreement with the sponsor. Code should not be broken in the absence of emergency situations or progressive disease as per RECIST v.1.1 (eg, in case of clinical deterioration, increase in tumor markers or any other evidence suggestive of disease progression but in the absence of RECIST-defined disease progression). When the blinding code is broken, the date and reason for unblinding must be fully documented in source documents and entered on the CRF. However, every effort should be made by the site staff to ensure that the treatment arm in which the unblinded patient is assigned is not communicated to any sponsor personnel or designee involved in the conduct of the trial.

5.3. Patient Compliance

Patients will be required to return all bottles of palbociclib/placebo as well as the completed patient diary at the beginning of each cycle for drug accountability. Drug accountability will be performed on Day 1 of every cycle prior to dispensing drug supply for the next cycle. The number of remaining capsules will be documented and recorded.

All doses of cetuximab will be administered by study staff, at the investigational site.

5.4. Drug Supplies

The investigational drugs used in the course of this trial are palbociclib/placebo.

5.4.1. Dosage Form(s) and Packaging

5.4.1.1. Palbociclib

Palbociclib will be supplied as capsules containing 75 mg, 100 mg, or 125 mg equivalents of palbociclib 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 Table 1. Labeling will occur according to local regulatory requirements.

Table 1. Palbociclib/Placebo Capsule Characteristics

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

5.4.1.2. Placebo for Palbociclib

Placebo for palbociclib will be indistinguishable from the palbociclib capsules and will be supplied as capsules matching in size and color the various palbociclib formulations (Table 1). The sponsor will supply placebo to sites in HDPE bottles. Labeling will occur according to local regulatory requirements.

5.4.1.3. Cetuximab

Cetuximab is commercially available in multiple presentations. Presentations containing 100 mg of cetuximab per vial will be used in this study. Commercial supplies of cetuximab will be centrally sourced and provided to sites. Detailed information about cetuximab formulation can be found in the locally approved package insert for Erbitux[®].

5.4.2. Preparation and Dispensing

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of palbociclib/placebo, and cetuximab.

See the locally approved package insert for instructions in how to prepare cetuximab for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

5.4.2.1. Palbociclib/Placebo

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.

Palbociclib/placebo 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.

5.4.2.2. Cetuximab

Cetuximab is commercially available in multiple presentations. Presentations containing 100 mg of cetuximab per vial will be used in this study. Commercial supplies of cetuximab will be centrally sourced and provided to sites.

Do not shake or dilute the medication, and discard unused portion after 8 hours at controlled room temperature (20° to 25°C; 68°F to 77°F) or after 12 hours at 2° to 8°C (36°F to 46°F). Detailed information about cetuximab preparation and dispensing can be found in the locally approved package insert for Erbitux[®].

5.5. Administration

5.5.1. Palbociclib/Placebo

Patients should be instructed to swallow one palbociclib/placebo capsule daily, whole, and not to chew them prior to swallowing. No capsule should be ingested if it is broken, cracked, or otherwise not intact. Patients should contact site personnel if capsules are not intact for replacement capsules. Patients should be encouraged to take their dose 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 palbociclib/placebo 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, palbociclib/placebo will be taken when instructed by the investigator.

Patients should take palbociclib/placebo with food.

One palbociclib/placebo capsule will be administered once a day, orally, for 21 days followed by 7 days off treatment in 28-day cycles.

Patients who miss a day's dose entirely 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. Also refer to [Section 8.4](#) for further details on medication errors and overdose.

Patients experiencing investigational product related toxicity may have their dose modified according to [Section 5.5.3](#).

Patients who become unable to swallow palbociclib/placebo capsules will discontinue study treatment.

5.5.2. Cetuximab

All patients will be premedicated with an H1 antagonist (eg, 50 mg of diphenhydramine) intravenously 30-60 minutes prior to the first dose. All patients will also be premedicated with a corticosteroid at least 1 hour prior to administration of the first dose of cetuximab. Premedication should be administered for subsequent cetuximab doses based upon clinical judgment and presence/severity of prior infusion reactions. *Note: Systemic dexamethasone use is not recommended due to possible drug-drug interactions.*

Administer 400 mg/m² (initial dose) as a 120-minute IV infusion with the maximum infusion rate of 10 mg/min. Subsequent weekly dose (all other infusions) is 250 mg/m² infused over 60 minutes with the maximum infusion rate of 10 mg/min. Detailed information can be found in the locally approved package insert for Erbitux[®]. Note: do not administer cetuximab as an IV push or bolus. Do not exceed an infusion rate of 10 mg/min. Body surface area will be calculated per institutional standard. Patients need to be closely monitored for all vital signs for the two hour duration of the initial cetuximab infusion, and for the one hour duration of subsequent infusions, plus an additional one hour after completion of all infusions.

5.5.3. Recommended Dose Modifications

Every effort should be made to administer study treatment on the planned dose and schedule. However, in the event of significant treatment-related toxicity, administration of study drugs (palbociclib/placebo or cetuximab) may need to be adjusted as described in the following sections. Depending on the nature of the toxicity observed, dosing adjustment may be required for just one or both study drugs in the combination.

In the event of significant treatment-related toxicity, palbociclib/placebo and/or cetuximab dosing may be interrupted or delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse sign or symptom.

Dose modifications may occur in three ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle;
- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start;
- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

Patients discontinuing palbociclib/placebo treatment due to treatment-related toxicity may continue on the active treatment phase of the study receiving cetuximab monotherapy as per the investigator's discretion. Patients discontinuing cetuximab treatment due to treatment-related toxicity must also discontinue palbociclib/placebo treatment.

5.5.3.1. Cetuximab Dose Modification Guidelines

Dose reduction of cetuximab by 1 and, if needed, 2 dose levels (Table 2) 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 and entered into the follow-up phase. All dose modifications/adjustments must be clearly documented in the patient's source notes and Investigational product administration CRF.

Table 2. Cetuximab Available Dose Levels

Dose Level	Cetuximab dose (after 400 mg/m ² loading dose)
Starting Dose	250 mg/m ²
-1	200 mg/m ²
-2	150 mg/m ²

*Cetuximab dose de-escalation below 150 mg/m² is not allowed.

5.5.3.1.1. Cetuximab 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), followed by famotidine 20 mg IV if symptoms remain after diphenhydramine. 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 famotidine 20 mg IV 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.

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, famotidine 20 mg IV, 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.

5.5.3.1.2. Cetuximab Infusion Reactions

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.

Cetuximab recommended dose modifications for infusion reactions:

- Reduce the infusion rate by 50% for National Cancer Institute Common Toxicity Criteria (NCI CTC v.4.03) Grade 1 or 2 and non-serious Grade 3 infusion reactions;
- Immediately and permanently discontinue cetuximab for serious infusion reactions, requiring medical intervention and/or hospitalization;
- Review the information found in the locally approved package insert for Erbitux®;
- If a patient experiences recurrent fever following premedication and post-dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be 50% of previous rate.

5.5.3.1.3. Cetuximab Dermatological Toxicities

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.

In patients with mild and moderate skin toxicity, treatment should continue without dose modification.

Cetuximab recommended dose modifications for severe (NCI CTC Grade 3 or 4) acneiform rash are described in Table 3.

Table 3. Cetuximab Dose Modifications in the Event of Acneiform Rash

	Toxicity (NCI CTC Grade 3 or 4, Version 4.03)		
Severe Rash	Cetuximab	Outcome	Dose Modification
1 st Occurrence	Delay Infusion 1 to 2 weeks	Improvement No Improvement	Continue at 250 mg/m ² Discontinue cetuximab
2 nd Occurrence	Delay Infusion 1 to 2 weeks	Improvement No Improvement	Reduce dose to 200 mg/m ² Discontinue cetuximab
3 rd Occurrence	Delay Infusion 1 to 2 weeks	Improvement No Improvement	Reduce dose to 150 mg/m ² Discontinue cetuximab
4 th Occurrence	Discontinue cetuximab		

5.5.3.1.4. Cetuximab Gastrointestinal Adverse Effects

Antiemetic agents may be administered prior to the administration of cetuximab. Diarrhea will be treated symptomatically with antidiarrheal agents. Should gastrointestinal toxicity become severe enough to require hospitalization or outpatient IV fluid replacement, all treatment should be discontinued temporarily until the patient's condition improves. Patients experiencing treatment-related Grade 4 vomiting or diarrhea should have their cetuximab and palbociclib/placebo treatments permanently discontinued.

5.5.3.1.5. Cetuximab 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.

5.5.3.1.6. Cetuximab 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.

5.5.3.2. Palbociclib/Placebo Dose Modification Guidelines

5.5.3.2.1. Palbociclib/Placebo Dosing Interruptions/Delays

Patients experiencing treatment-related Grade 4 vomiting, diarrhea, or hypertension should have their palbociclib/placebo and cetuximab treatments permanently discontinued.

Patients experiencing the following AEs should have their palbociclib/placebo treatment interrupted/delayed:

- Uncomplicated Grade 3 neutropenia ($ANC < 1000/mm^3$);
- Grade 3 neutropenia ($ANC < 1000/mm^3$) associated with a documented infection or fever $\geq 38.5^\circ C$;
- Grade 4 neutropenia ($ANC < 500/mm^3$);
- Grade 4 thrombocytopenia (Platelet count $< 25,000/mm^3$);
- Grade 3 non-hematologic toxicity (including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment);
- Grade 4 non-hematologic toxicities (see exceptions of vomiting, diarrhea, or hypertension above);
- Grade 3 QTc prolongation ($QTc \geq 501$ msec on at least two separate ECGs).

Appropriate follow up assessments should be done until adequate recovery occurs as assessed by the Investigator. Criteria required before treatment can resume are described in [Section 5.5.3.3](#).

Doses may be held as needed until toxicity resolution. Depending on when the AE resolved, a treatment interruption may lead to the patient missing all subsequent planned doses within that same cycle or even to delay the initiation of the subsequent cycle.

If the AE that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in [Section 5.5.3.4](#) unless expressly agreed otherwise following discussion between the investigator and the sponsor. If a dose reduction is applied in the same cycle, the patient will need to return to the clinic to receive new drug supply.

In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, non-cancer related surgery) lasting >2 weeks, treatment resumption will be decided in consultation with the sponsor.

5.5.3.3. Palbociclib/Placebo Retreatment

Retreatment following treatment interruption for treatment-related toxicity or at the start of any new cycle may not occur until all of the following parameters have been met:

- Platelet count $\geq 50,000/\text{mm}^3$;
- ANC $\geq 1000/\text{mm}^3$ and no fever;
- Grade 3 treatment-related non-hematologic AEs (including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment), with the exception of alopecia, have recovered to Grade ≤ 1 or baseline (or, at the investigator's discretion, Grade ≤ 2 if not considered a safety risk for the patient);
- Grade 4 treatment-related non-hematologic AEs with the exception of alopecia, have recovered to Grade ≤ 1 or baseline (or, at the investigator's discretion, Grade ≤ 2 if not considered a safety risk for the patient). Patients experiencing treatment-related Grade 4 vomiting, diarrhea, or hypertension should have their palbociclib/placebo and cetuximab treatments permanently discontinued. QTc <501 msec and potential reversible causes (eg, electrolyte imbalance, concomitant medications known to prolong QTc) corrected. If QTc remains above 480 msec, ECGs should be monitored more frequently as per the investigator's best medical judgment until QTc ≤ 480 msec.

If a treatment delay results from decline in hematologic parameters, the frequency of blood count assessments should be increased as clinically indicated.

If these parameters are met within 2 weeks of treatment interruption or cycle delay, palbociclib/placebo may be resumed. Refer to [Section 5.5.3.4](#) for AEs requiring dose reduction at the time of treatment resumption.

If these parameters have not been met after 2 weeks of dosing interruption (including the scheduled 1 week off treatment) or 2 weeks of cycle delay, permanent discontinuation of palbociclib/placebo treatment should be considered. Treatment resumption for patients recovering from treatment-related toxicity after >2 weeks of treatment interruption or cycle delay but deemed to be deriving obvious clinical benefit per the investigator's best medical judgment is left at the investigator's discretion.

If palbociclib/placebo treatment is delayed due to a palbociclib/placebo treatment-related toxicity within a cycle, the patient will continue cetuximab treatment and complete the 28-day cycle. A new cycle will begin after the end of the standard previous 28-day cycle. If the patient experiences prolonged palbociclib/placebo treatment-related toxicity beyond the standard one week break in the 28-day cycle (prior to Day 1 of the next cycle), Day 1 of the next cycle will begin when palbociclib/placebo treatment is resumed. The re-treatment of cetuximab will be handled independent of palbociclib/placebo treatment, based upon the dose modification guidelines for cetuximab, see [Section 5.5.3.1](#).

In the event that the start of a new cycle is delayed due to treatment related toxicity, procedures required on Day 1 of the given cycle will be performed when palbociclib/placebo is resumed. New cycle Day 1 procedures (ie, physical examination, ECOG performance status, ECG, Quality of Life questionnaires, blood chemistry, hematology, urinalysis, coagulation, and serum pregnancy test) that were performed prior to knowing the need to delay the start of the cycle do not need to be repeated (1) if not required to determine whether study drug may be resumed and (2) if performed within 7 days prior to study drug resumption. *All tumor assessments will occur as scheduled, independent of treatment delays, and of cycle start delays.*

5.5.3.4. Palbociclib/Placebo Dose Reductions

Following dosing interruption or cycle delay the palbociclib/placebo dose may need to be reduced when treatment is resumed.

No specific dose adjustments are recommended for Grade 1/2 treatment-related toxicity. However, investigators should always manage their patients according to their medical judgment based on the particular clinical circumstances.

Dose reduction of palbociclib/placebo by 1 and, if needed, 2 dose levels (Table 4) will be allowed depending on the type and severity of toxicity encountered. Patients requiring more than 2 dose reductions will be discontinued from palbociclib/placebo treatment and entered into the follow-up phase. All dose modifications/adjustments must be clearly documented in the patient's source notes and Investigational product administration CRF.

Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Dose re-escalation is not allowed.

Table 4. Palbociclib/Placebo Available Dose Levels

Dose Level	Palbociclib/Placebo for 3 out of 4 Weeks (3/1 Schedule)
Starting Dose	125 mg/day (d)
-1	100 mg/d
-2	75 mg/d*

* Palbociclib/placebo dose de-escalation below 75 mg/d is not allowed.

Palbociclib/placebo recommended dose modifications for treatment related toxicities requiring treatment interruption/delay or persisting despite optimal medical treatment are described in Table 5.

Table 5. Palbociclib/Placebo Dose Modifications for Treatment Related Toxicities Requiring Treatment Interruption/Delay or Persisting Despite Optimal Medical Treatment

Toxicity	Restart palbociclib/Placebo Treatment at:
Uncomplicated Grade 3 neutropenia (ANC<1000/mm ³)	Same dose level
Grade 3 neutropenia (ANC<1000/mm³) associated with a documented infection or fever ≥38.5°C	↓ 1 Dose Level
Grade 4 neutropenia (ANC<500/mm³)	↓ 1 Dose Level
Grade 4 thrombocytopenia (Platelet count <25,000/mm³)	↓ 1 Dose Level
Grade 3 non-hematologic toxicity (including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment)	↓ 1 Dose Level
Grade 4 non-hematologic toxicity	↓ 1 Dose Level (see exceptions of vomiting, diarrhea, or hypertension in which case patients should have their palbociclib/placebo <u>and</u> cetuximab treatments permanently discontinued)

5.5.3.5. QTc Prolongation Management

In the event of QTc prolongation, possible alternative reversible causes such as serum electrolytes abnormalities, or usage of concomitant medications with the potential to prolong the QTc interval should be evaluated.

If such reversible causes are identified, then they should be corrected accordingly (ie, correction of electrolyte abnormalities with supplements to within normal limits and/or discontinuation (if possible) of concomitant medications known to prolong the QT interval).

Recommended dose modifications in the event of QTc prolongation are provided in [Table 6](#).

Table 6. Palbociclib/Placebo Dose Modifications in the Event of QTc Prolongation

	Toxicity (NCI CTC Grade, Version 4.03)		
	Grade 2 QTc prolongation	Grade 3 QTc prolongation	Grade 4 QTc prolongation
Reversible cause identified	Treat reversible cause. Initiate more frequent ECG monitoring according to investigator's best medical judgment until QTc ≤480 msec. Continue at the <u>same dose level</u> . ⁽¹⁾	Treat reversible cause Withhold treatment until QTc <501 msec. Resume treatment at the <u>same dose level</u> . Monitor ECG more frequently as per investigator's best medical judgment until QTc ≤480 msec.	Permanently discontinue
No reversible cause identified	Initiate more frequent ECG monitoring according to investigator's best medical judgment until QTc ≤480 msec. Continue at the <u>same dose level</u> . ⁽¹⁾	Withhold treatment until QTc <501 msec. Resume treatment at the <u>next lower dose level</u> . ⁽²⁾ Monitor ECG more frequently as per investigator's best medical judgment until QTc ≤480 msec.	Permanently discontinue

1. If the QTc remains above 480 msec more than 2 cycles or if Grade 2 QTc prolongation recurs in the absence of other alternative causes or despite correction of alternative causes, dose adjustment and/or discontinuation should be considered in consultation with a cardiologist and the study medical monitor, taking into account the emerging safety data from palbociclib trials and the investigator's best medical judgment.
2. If the Grade 3 QTc prolongation occurs again after one dose reduction, further dose adjustment and/or discontinuation should be discussed with study medical monitor in consultation with a cardiologist, taking into consideration the emerging safety data from palbociclib trials and the investigator's best medical judgment.

5.6. Drug Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products, including any comparative agents and/or marketed products are stored in a secured area with controlled access under recommended storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the drug label.

Storage conditions stated in the Study Reference Safety Document (ie, IB or SPC) will be superseded by the storage conditions stated in the labeling.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This must be captured from the time of investigational product receipt throughout study. Even for continuous monitoring systems, a log or site procedure which ensures active daily evaluation for excursions must be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, must be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions must be reported upon discovery. The site must actively pursue options for returning the product to labeled storage conditions, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the product(s) are briefly out of labeled temperature range are not considered excursions. More specific details will be provided to the sites separately.

Site staff will instruct patients on the storage requirements for take home medications.

5.7. Drug Accountability

The investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of the drug supplies.

Medication must be kept in a secured locked area at the study site in accordance with applicable regulatory requirements. Returned medication must be stored separately from medication that needs to be dispensed.

To ensure adequate records, palbociclib/placebo capsules will be accounted for as instructed by the sponsor. Patients are requested to return previously dispensed containers as well as their completed patient diary to the clinic at each visit for accountability purposes even if they will not be issued with new medication at that visit.

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer and all destruction must be adequately documented.

5.8. Concomitant Treatments

Patients must be instructed not to take any additional medications (over-the-counter or other products) during the study without prior consultation with the investigator. Any medications including herbal supplements, vitamins, or treatment taken by the patient from 28 days prior to the start of study treatment and up to 28 days following the last dose of investigational product and the reason for their administration must be recorded on the CRF, which includes H₁ antagonists pre-medication to alleviate cetuximab infusion reactions. If a patient begins new therapy before the 28-day time period is complete, concomitant medication information will not be recorded (from the start of the new therapy).

Routine postoperative care, such as dressing changes, suture removal, drain removal, or venous access (central or peripheral), does not need to be recorded. Anesthetics used for any surgical procedures performed during the patient's participation in the study can be recorded as "unspecified anesthesia" on the concomitant treatment records; it is not necessary to list the specific anesthetics. Palliative and supportive care for cancer-related symptoms will be offered to all patients in this study.

5.8.1. Prohibited Medications

The following treatments are prohibited throughout the duration of the active treatment phase:

- **Anticancer agents:** No additional investigational or commercial anticancer agents such as chemotherapy, targeted therapy, or biological response modifiers, will be permitted during the active treatment phase. In general, any drugs containing "for the treatment of SCCHN" on the product insert are not permitted on study.
- **Strong/Moderate CYP3A inhibitors/inducers:** Palbociclib is metabolized to multiple metabolites in a qualitatively similar manner in rat, dog and human liver microsomes. In vitro, palbociclib is primarily metabolized by CYP3A4 enzymes. Co-administration with drugs that are strong CYP3A inhibitors or inducers in vivo has been shown to change the plasma concentrations of palbociclib in humans. Data from a drug-drug interaction (DDI) study in healthy subjects indicate that coadministration of multiple 200-mg doses of the strong CYP3A inhibitor itraconazole with a single 125-mg palbociclib dose increased palbociclib total exposure (AUC_{inf}) and the peak exposure (C_{max}) by approximately 87% and 34%, respectively, relative to a single 125-mg palbociclib dose given alone. Data from a DDI study in healthy subjects indicate that coadministration of multiple 600-mg doses of the strong CYP3A inducer rifampin with a single 125-mg palbociclib dose decreased palbociclib AUC_{inf} and C_{max} by 85% and 70%, respectively, relative to a single 125-mg palbociclib dose given alone. The concurrent use of the compounds listed below is not allowed in the study:
 - Strong/Moderate CYP3A inhibitors, including but not limited to amprenavir, atazanavir, boceprevir, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, suboxone, telaprevir, telithromycin, verapamil, voriconazole, and grapefruit, grapefruit juice or any product containing grapefruit.
 - Strong/Moderate CYP3A inducers, including but not limited to carbamazepine, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifampin, rifabutin, rifapentin, and St. John's wort.
- **Drugs known to cause QT interval prolongation** are prohibited during the active treatment phase. Refer to [Appendix 6](#) for a list of drugs known to predispose to Torsade de Pointes.

5.8.2. Medications Not Recommended

The following treatments are not recommended throughout the duration of the active treatment phase. Alternative therapies should be considered whenever possible. If usage of the following treatments is deemed necessary, consultation and agreement with the sponsor is required prior to treatment initiation.

- The concurrent use of systemic dexamethasone is not recommended. Topical use of dexamethasone is permitted.
- **Chronic immunosuppressive therapies** should be avoided, including systemic corticosteroids. Steroids given as premedication for cetuximab infusion reactions, or short course of oral steroids, or inhaled/topical steroids are allowed.
- The use of **herbal medicine** is not recommended during the active treatment phase.

5.9. Concomitant Radiotherapy or Surgery

Any concurrent radiotherapy (except palliative radiotherapy as specified below) or cancer-related surgery are prohibited throughout the duration of the active treatment phase of the study. Patients requiring any of these procedures will be discontinued from the active treatment phase and will enter the follow-up phase.

Palliative radiotherapy is permitted for the treatment of painful bony lesions provided that the lesions were known to be present at the time of study entry and the investigator clearly documents that the need for palliative radiotherapy is not indicative of disease progression. In view of the current lack of data about the interaction of palbociclib with radiotherapy, palbociclib/placebo treatment should be interrupted during palliative radiotherapy, stopping 1 day before and resuming treatment 1 week after. For patients with bone involvement, it is suggested to institute palliative radiotherapy before study initiation if possible and clinically appropriate (eg, lesions at risk for spontaneous micro-fractures or painful lesions). Palliative radiotherapy during the active treatment phase will be considered alternative cancer therapy and will result in censoring of the PFS endpoint. The dates on which palliative radiotherapy is administered should be recorded on the appropriate CRFs.

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and palbociclib required to minimize the risk of impaired wound healing and bleeding has not been determined. Based on the available pharmacokinetic data, stopping palbociclib/placebo is recommended at least 7 days prior to elective surgery. Postoperatively, the decision to reinstate palbociclib/placebo treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

6. STUDY PROCEDURES

Prior to undergoing any study specific procedures (with the exception of certain imaging assessments if meeting the criteria defined in [Section 6.1](#)), patients must read and sign the consent form. All study procedures and the timing when they must be performed are detailed in the [Schedule of Activities](#). All data obtained for these assessments must be supported in the patients' source documentation.

For the purposes of this trial, 1 cycle is 28 days. A cycle could be longer than 28 days if persistent toxicity delays the initiation of the subsequent cycle.

When scheduled at the same nominal time, triplicate ECGs should be collected prior to any blood draws for PK, biomarkers, or safety labs and prior to placement of the IV line for cetuximab administration.

6.1. Screening

Voluntary, written, dated, and signed informed consent must be obtained before any study specific procedures are performed (with the exception of certain imaging assessments if meeting the criteria defined in this section); however, it may be obtained more than 28 days before randomization. See [Section 4.1](#) and [Section 4.2](#) for detailed inclusion and exclusion criteria.

Medical and oncological history must include information on prior anticancer treatments.

Baseline tumor related signs and symptoms will be recorded at the C1D1 visit prior to initiating treatment and then reported as AEs during the trial if they worsen in severity or increase in frequency.

Radiographic tumor assessments (as documented on the [Tumor Assessment Requirements Flowchart](#)) that were performed before the signing of the informed consent form as routine procedures (but within 28 days prior to randomization) do not need to be repeated and may be used as baseline assessments, as long as:

- The tests were performed per the method requirements outlined in the [Tumor Assessment Requirements Flowchart](#), and [Section 7.1](#), and
- Appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes.

Patients must be HPV-negative to participate in this study. Analytical method is per institutional standards.

For details on screening/baseline procedures, see the [Schedule of Activities](#).

6.2. Active Treatment Phase

For details on procedures during the active treatment phase, see the [Schedule of Activities](#).

Physical examination/vital signs, blood chemistry, hematology, urinalysis, coagulation, and 12-lead ECG are not required if acceptable screening assessment is performed within 7 days prior to randomization.

Patients must agree to use two methods of highly effective contraception throughout the study and continue for 6 months after the last dose of cetuximab. See [Section 4.4](#) for further information.

Hemoglobin A1c will be measured at C1D1, during the active treatment phase every 3 months from the date of randomization (ie, Cycle 4 Day 1, Cycle 7 Day 1, Cycle 10 Day 1, etc.), and at the End of Treatment visit. Fasting glucose will be acquired at baseline Cycle 1 Day 1, Cycle 1 Day 15, and Cycle 2 Day 1.

In the event that the start of a new cycle is delayed due to treatment-related toxicity, procedures required on Day 1 of the given cycle will be performed when palbociclib/placebo is resumed. New cycle Day 1 procedures (ie, physical examination, vital signs, ECOG performance status, ECG, Quality of Life questionnaires, blood chemistry, hematology, urinalysis, coagulation, and serum pregnancy test) that were performed prior to knowing the need to delay the start of the cycle do not need to be repeated (1) if not required to determine whether study drug may be resumed and (2) if performed within 7 days prior to study drug resumption.

6.3. End of Treatment Visit

The end of treatment visit will be performed as soon as possible but no later than 4 weeks (ie, 28 days) ± 7 days from last dose of investigational product and prior to the initiation of any new anticancer therapy.

For all patients, including patients starting post-study anticancer therapy, 8 weeks after the completion of therapy, blood chemistry panel consisting of magnesium, total calcium, and potassium must be checked.

Patients must continue to use two methods of highly effective contraception for 6 months after the last dose of cetuximab.

For details on procedures to be performed at the End of Treatment visit, see the [Schedule of Activities](#).

6.4. Follow-up Visit

After discontinuation of study treatment, post-study survival status (including post study anticancer therapies) will be collected approximately every 2 months (± 7 days) from the last dose of study treatment. Telephone contact is acceptable.

Patients who discontinue study treatment for reasons other than radiographically and/or clinically (ie, for photographed or palpable lesions) documented disease progression, as per RECIST v. 1.1 definitions, will continue to have tumor assessment performed during the follow-up visits every 8 weeks (± 7 days) from the date of randomization until disease progression, initiation of new anticancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first.

For details on follow-up visit procedures, see the [Schedule of Activities](#).

6.5. Post-Study Patient Interview

Four weeks after discontinuation of study treatment due to progressive disease, patients will be asked to complete the EORTC-QLQ-C30 ([Appendix 3](#)) and EORTC-QLQ-H&N35 ([Appendix 4](#)) assessments. For details, see the [Schedule of Activities](#).

6.6. Patient Withdrawal

6.6.1. Active Treatment Phase Discontinuation

The term "interruption" refers to a patient stopping the investigational product during the course of the study, but then re-starting it at a later time in the study. The reason for dosing interruption will be collected on the appropriate CRF.

The term "discontinuation" refers to a patient's withdrawal from the active treatment phase. The reason for discontinuation from treatment will be collected on the appropriate CRF.

Patients may be withdrawn from the active treatment phase in case of:

- Disease progression as per RECIST v.1.1;
- Symptomatic deterioration (ie, development of inability to swallow or global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression as per RECIST v.1.1);
- Need for additional anticancer therapy not specified in the protocol;
- Unacceptable toxicities;
- Investigator conclusion that it is in the patient's best interest to discontinue therapy (eg, poor compliance with either protocol monitoring or with taking the study medications, etc.);
- Lost to follow-up;*
- Patient choice to withdraw from treatment (follow-up permitted by patient);
- Withdrawal of patient consent (cessation of follow-up);
- Death.

*If a patient does not return for a scheduled visit, every effort should be made to contact the patient. Lost to follow-up is defined by the inability to reach the patient after a minimum of three documented phone calls, faxes, or emails as well as lack of response by the patient to one registered mail letter. All attempts should be documented in the patient's medical records. If it is determined that the patient has died, the site will use permissible local methods to obtain the date and cause of death. If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the patient's

informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining patient's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the patient remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the patient's medical records.

Patient who discontinue from the active treatment phase must have End of Treatment/Withdrawal evaluations performed as soon as possible but no later than 4 weeks from the last dose of investigational product and prior to initiation of any new anticancer therapy. Data to be collected for the end of study treatment/withdrawal are described in the [Schedule of Activities](#).

Patients who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a patient specifically withdraws consent for any further contact with him/her or persons previously authorized by patient to provide this information. Patients should notify the investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the patient is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

If a patient opts to discontinue from the active treatment phase as a result of an unacceptable adverse drug reaction, "withdrawal of consent" should not be the reason for discontinuation. Instead, the reason for discontinuation of active treatment phase must be recorded as "Unacceptable toxicity" and an appropriate action taken must be assigned on the AE CRF to the AE leading to the patient's withdrawal of consent.

6.6.2. Study Discontinuation

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site.

Patients will be withdrawn from study in the case of:

- Withdrawal of consent (ie, refuses tumor assessments or survival status after end of treatment);
- Lost to follow-up;*
- Administrative study closure by sponsor;
- Death.

*If a patient does not return for a scheduled visit, every effort should be made to contact the patient. If after three unsuccessful attempts to contact the patient, one of which is by registered letter, the patient should be considered “lost to follow-up”. Steps taken to contact the patient (eg, dates of telephone calls, registered letters, etc.) must be clearly documented in the source documents. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, requests the patient to return all unused investigational product(s), request the patient to return for a final visit, if applicable, and follow-up with the patient regarding any unresolved AEs.

Data to be collected for the end of study treatment/withdrawal are described in the [Schedule of Activities](#).

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

All study procedures are described in the [Schedule of Activities](#) table and footnotes.

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions which he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Efficacy Assessments

7.1.1. Tumor Assessments

The importance of timely and complete disease assessments in this study cannot be understated. Disease assessments must be performed as scheduled according to the calendar, regardless of treatment delays resulting from toxicity, to prevent the introduction of bias into the assessment of efficacy. Failure to perform any of the required disease assessments will result in the inability to determine disease status for that time point. A series of incomplete disease assessments will result in censoring of the secondary endpoint of PFS back to the time of the last full assessment that did not show progression. Frequent off schedule or incomplete disease assessments have the potential to weaken the conclusion of this clinical trial.

Objective tumor response will be measured using RECIST v. 1.1. All measurements should be recorded in metric notation using a ruler or calipers.

MRI of the abdomen can be substituted for CT if MRI adequately depicts the disease. However, MRI of the chest should not be substituted for CT of chest even if IV contrast is contraindicated. In such case CT will be performed without contrast. If MRI is used to follow-up bone lesion(s) it must be performed a few days before any treatment that may affect bone-marrow cellularity (eg, G-CSF).

7.1.1.1. Screening/Baseline Tumor Assessment

Screening/baseline tumor assessment will be carried out within 28 days before randomization (unless otherwise specified below).

Disease assessment for all patients at baseline will include:

- Computed tomography (CT) or magnetic resonance imaging (MRI) scan of the head and neck (oral cavity, oropharynx, hypopharynx, larynx);
- CT or MRI scan of the chest and abdomen (including the liver);
- CT or MRI scan of any other sites of disease as clinically indicated.

Baseline brain scans are required in patients with a history of metastatic brain disease. Brain scans performed before the signing of informed consent as routine procedures (but within 6 weeks before randomization) do not need to be repeated and may be used as baseline assessments as long as (1) tests were performed using the method requirements outlined in RECIST v.1.1 (2) the same technique/modality can be used to follow identified lesions throughout the trial for a given patient (3) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes. Post-baseline brain scans will be required only if new metastases are suspected.

Clinical assessment of superficial disease which will include photographs of all superficial metastatic lesions. All lesion measurements must be recorded in the CRF.

7.1.1.2. Post-Baseline Tumor Assessments

Post-baseline tumor assessments will be performed every 8 weeks (± 7 days) from randomization until radiographically and/or clinically (ie, for photographed or palpable lesions) documented PD as per RECIST v.1.1, initiation of new anticancer therapy, or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up). Imaging assessments are to be scheduled using the randomization date as the reference date for all time-points and are NOT to be scheduled based on the date of the previous imaging time-point. Imaging assessment delay to conform to treatment delay is not permitted.

Patients who discontinue study treatment for reasons other than radiographically and/or clinically (ie, for photographed or palpable lesions) documented disease progression as per RECIST definitions will continue to have tumor assessment performed during the follow-up visits every 8 weeks (± 7 days) until documented disease progression, initiation of new

anticancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first. Every effort should be made to perform a last tumor assessment before starting a new anticancer therapy. Additional unscheduled tumor assessments may be performed as clinically indicated at any time.

Post-baseline tumor assessments will include:

- Clinical assessment of sites of superficial disease identified at baseline. Clinical assessment of superficial disease must coincide with the imaging studies and will include photographs of all superficial metastatic lesions. All lesion measurements must be recorded in the CRF.
- The CT scans, including brain CT scan if applicable, should be performed with contrast agents unless contraindicated for medical reasons. If IV contrast is medically contraindicated, the imaging modality to be used to follow the disease (either CT without contrast or MRI) should be the modality which best evaluates the disease, and the choice should be determined by the investigator in conjunction with the local radiologist.
- CT or MRI scan of the head and neck (oral cavity, oropharynx, hypopharynx, larynx).
- CT or MRI scan of the chest and abdomen (including the liver).
- CT or MRI scan of any other sites of disease identified at baseline.

The same method and technique should be used to characterize each lesion identified and reported at baseline, during the study treatment period and during follow-up. The use of plain-film X-rays is discouraged. The use of positron emission tomography (PET) imaging as the only imaging modality is not permitted.

7.1.2. Overall Survival

Following the End of Treatment visit, survival status will be collected in all patients every 2 months (± 7 days) from the last dose of study treatment. Information on subsequent anticancer therapy will also be collected.

7.2. Pregnancy Testing

For female patients of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory, will be performed on 2 occasions prior to starting study therapy—once at the start of screening and once at the baseline visit, immediately before investigational product administration. A negative pregnancy result is required before the patient may receive the investigational product. Pregnancy tests will also be routinely repeated at Day 1 of each cycle during the active treatment period, at the End of Treatment Visit, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be undertaken if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the patient will be withdrawn from study medication and will be

withdrawn from the study. Two methods of highly effective contraception must be used throughout the study and continue for 6 months after the last dose of cetuximab. See [Section 4.4](#) for further information.

7.3. Safety Assessments

Safety assessment will consist of monitoring of all AEs, including SAEs, regular monitoring of hematology, serum chemistry, and routine monitoring of ECGs, physical examinations, vital signs, and ECOG performance status.

AE assessment will include type, incidence, severity (graded by the NCI CTCAE, Version 4.03, [Section 8.8](#)), timing, seriousness, and relatedness.

Baseline tumor-related signs and symptoms will be recorded at the Cycle 1 Day 1 visit and then reported as AEs during the trial if they worsen in severity or increase in frequency.

7.3.1. Laboratory Safety Assessments

Blood tests will include the following:

Hemoglobin	Chemistry
Hemoglobin	ALT
WBC	AST
Platelets	Alkaline Phosphatase
Absolute Neutrophils	Sodium
Absolute Lymphocytes	Potassium
	Magnesium
Coagulation	Chloride
PT or INR	Total Calcium
PTT/aPTT	Total Bilirubin *
	BUN or Urea
	Creatinine
	Uric Acid
	Glucose (fasted)
	HbA1c
	Albumin
	Phosphorus or Phosphate

*For potential Hy's law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, and alkaline phosphatase.

Blood tests will be drawn at the time points described in the [Schedule of Activities](#), and analyzed at local laboratories. Additional blood tests may be performed at the investigator's discretion as clinically indicated for the purpose of planning treatment administration, dose modification, or following AEs.

For all patients, including patients starting post-study anticancer therapy, 8 weeks after the completion of therapy, blood chemistry panel consisting of magnesium, total calcium, and potassium must be checked. If abnormalities are observed, an ECG can be performed at the discretion of the investigator to check QTc.

Urinalysis will be conducted via urine dipstick for urine protein: if the result is positive, further diagnostic testing will be performed as clinically indicated.

Patients must be HPV-negative to participate in this study. Analytical method is per institutional standards.

Refer to the [Schedule of Activities](#) for laboratory assessment details.

- Electrocardiogram (ECG);
- All ECGs will be performed using a 12-lead (with a 10-second rhythm strip) tracing. ECG measurements will include PR interval, QT interval, RR interval, and QRS complex. It is preferable that the machine used has a capacity to calculate the standard intervals automatically.

ECG interval readings by the ECG recorder's algorithm will be read and interpreted at the investigational site for eligibility determination and patient safety monitoring and documentation stored in the source documents.

Triplicate ECGs will be performed for all patients.

- **All ECGs should be obtained after a fast of at least 1 hour.** When scheduled at the same nominal time/visit, triplicate ECGs should be collected prior to any blood draws for PK, biomarkers, or safety labs and prior to placement of the IV line for cetuximab administration.
- Triplicate ECGs will be obtained for safety monitoring at Screening, and 0 hour (palbociclib pre-dose) on C1D1, C1D15 and C2D15, then on Day 1 of Cycles 4, 7, and 10. ECGs will be obtained at the time of End of Treatment or Withdrawal. ECGs beyond Cycle 10 will be performed as clinically indicated.

Additional ECGs may be performed as clinically indicated at any time.

For the purpose of the study, triplicate ECGs are defined as three consecutive ECGs performed approximately 2 minutes apart but within 10 minutes for all 3 ECGs at the protocol specified timepoints (see the [Schedule of Activities](#) for details) to determine the mean QTc interval.

If at any time during the course of treatment, the mean QTc is prolonged (≥ 501 msec on at least two separate ECGs, ie, CTCAE Grade ≥ 3), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading confirms a QTc of

≥501 msec, immediate search for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTc interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTc interval falls below 501 msec.

- If QTc interval reverts to less than 501 msec, and in the judgment of investigator(s) in consultation with the sponsor the cause is determined to be other than study drug, treatment may be continued with regular ECG monitoring under hospital supervision.
- If in that timeframe the QTc intervals remain above 501 msec the study drug will be held until the QTc interval decreases to <501 msec.

Prior to concluding that an episode of prolongation of the QTc interval is due to study drug, thorough consideration should be given to potential precipitating factors (eg, change in patient clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist.

If investigational product causality cannot be ruled out, Investigational product dose adjustment and/or discontinuation should be performed according to instructions provided in [Section 5.5.3](#). Additional triplicate ECGs may be performed as clinically indicated.

When matched with PK sampling, ECG must be carried out before PK sample drawing such that the PK samples are collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections).

7.3.2. Other Safety Assessments

A full physical examination including an examination of all major body systems (including head, ears, eyes, nose, mouth, throat, neck, thyroid, lungs, heart, breasts, abdomen, and musculoskeletal), height (at screening only), weight, blood pressure and pulse rate which may be performed by a physician, registered nurse or other qualified health care provider, will be required at screening, and Day 1 of Cycles 1 and 2.

Symptom directed physical examinations, blood pressure and pulse rate will be performed at subsequent visits.

Performance Status: ECOG performance status scale will be used (see [Appendix 5](#)).

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The actual times may change but the number of samples will remain the same. All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. However, pre-infusion samples drawn within 30 minutes of the start of infusion and post-infusion samples collected within 10% of the planned nominal time (eg, within 6 minutes of the end of a 60 minute infusion) from dosing will not be captured as protocol deviations, as long as the exact time of the sample collection and the exact infusion start/stop times are noted on the source document and data collection tool (eg, CRF).

One 3 mL sample of venous blood, to provide a minimum of 1 mL serum for PK analysis, will be collected into appropriately labeled collection tubes containing no additives at the protocol-specified times. Samples will be kept in an ice bath prior to processing.

Samples will be analyzed for cetuximab using a validated analytical method in compliance with Pfizer standard operating procedures.

As part of understanding the pharmacokinetics of the study drug, samples may be used for metabolite identification and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the Clinical Study Report.

Samples collected for this purpose will be retained in accordance to local regulations and if not used within this timeframe, will be destroyed.

Additional blood samples may be requested from patients experiencing unexpected or serious AEs, or AEs that lead to discontinuation.

Blood samples for PK assessments of cetuximab will be collected from all participating patients prior to IV infusion (pre-dose) and immediately prior to completion of the IV infusion (post-dose) on Day 15 of Cycles 1 and 2. In the event a pre-dose or post-dose sample cannot be/is not collected on Day 15 of Cycle 1 or Cycle 2 as scheduled, every effort should be made to collect a makeup sample on Day 22 of the same cycle or on Day 15 or Day 22 of any subsequent cycles beyond Cycle 2 following the same rules described above. Blood samples for post-dose PK assessments of cetuximab should not be collected from the same arm that the cetuximab IV infusion was administered.

When assessments are scheduled on the same visit, whenever possible, efforts should be made to coordinate collection of pre-infusion PK and biomarker blood draws within a 30-minute window.

Refer to the Study Manual for detailed collection, processing and shipping procedures.

7.5. Biomarker Assessments

Archival tumor tissues are required from all patients for study participation.

Submission of formalin-fixed paraffin embedded (FFPE) tumor samples (blocks preferred) of adequate size (to generate at least 15 sections of 5-micron each) are needed. If FFPE tissue block cannot be provided, a minimum of 15 glass slides each containing an unstained

5-micron FFPE tissue section, will be required for patient participation. If an archival tumor tissue sample is not available, a de novo tumor specimen must be obtained. Specimens will be sent to the Sponsor-designated central laboratory. Details for the handling of these specimens, including processing, storage, and shipment will be provided in the Study Manual. Table 7 summarizes the biomarker assessments currently planned for the study.

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7.7. Patient Reported Outcomes

Patient reported outcomes of health-related quality of life and health status will be assessed using the EORTC-QLQ-C30, and EORTC-QLQ-H&N 35 instruments.

Patients will complete each instrument at pre-dose on Day 1 of Cycles 1-3, then on Day 1 of every other subsequent Cycle starting with Cycle 5 (eg, Cycles 5, 7, 9, etc.), and then at the End of Treatment visit. This schedule is based on the schedule for the assessment of clinical activity. Four weeks after discontinuation of study treatment due to progressive disease, patients, including patients starting post-study anticancer therapy, will be completing the questionnaires at the Follow-up Visit.

Patients must complete these instruments in clinic (cannot be taken home) and prior to having any tests and to any discussion of their progress with healthcare personnel at the site. Interviewer administration in clinic may be used under special circumstances (eg, patient forgot their glasses or feels too ill), but family members are not permitted to assist with questionnaire administration. The instruments will be given to the patient in the appropriate language for the site.

7.7.1. European Organisation for Research and Treatment of Cancer Quality of Life Instrument (EORTC QLQ-C30) (Appendix 3)

The EORTC QLQ C30 is a 30 item questionnaire composed of five multi item functional subscales (physical, role, cognitive emotional, and social functioning), three multi item symptom scales (fatigue, nausea/vomiting, and pain), a global health/quality of life (QOL) subscale, and six single items assessing other cancer related symptoms (dyspnea, sleep disturbance, appetite, diarrhea, constipation, and the financial impact of cancer). The questionnaire employs 28 4 point Likert scales with responses from “not at all” to “very much” and two 7 point Likert scales for global health and overall QOL. For functional and global QOL scales, higher scores represent a better level of functioning and are converted to a 0 to 100 scale. For symptom oriented scales, a higher score represents more severe symptoms.

7.7.2. European Organisation for Research and Treatment of Cancer Head and Neck Module 35 (EORTC QLQ-H&N35) (Appendix 4)

The EORTC QLQ-H&N35 is designed to be used together with the core QLQ-C30. The time frame of the module is “during the past week,” and the format is similar to that of the core questionnaire. Items hn 1 to hn30 are scored on four-point Likert-type categorical scales (“not at all,” “a little,” “quite a bit,” “very much”). Items hn31 to hn35 have a “no/yes” response format. The scores are transformed into 0-to-100 scales, with a high score implying a high level of symptoms or problems, in the same way as scoring for symptom scales and single items of the QLQ-C30.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a patient after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

AEs (serious and nonserious) should be recorded on the CRF from the time the patient has taken at least 1 dose of investigational product through the patient's last visit.

If a patient begins a new anticancer therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;

- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.
- Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong patient, at the wrong time, at the wrong dosage strength, or inadvertent exposure. Such medication errors occurring to a study participant are to be captured on the medication error CRF which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AE(s) are captured on an AE CRF page.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of protocol-stipulated dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 (see the section on [Severity Assessment](#)).

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see the section on [Serious Adverse Event Reporting Requirements](#)).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥ 3 times the upper limit of normal (X ULN) concurrent with a total bilirubin value ≥ 2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤ 2 X ULN or not available;
- For patients with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:
 - For patients with preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥ 2 times the baseline values and ≥ 3 X ULN, or ≥ 8 X ULN (whichever is smaller).

Concurrent with

- For patients with preexisting values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 X ULN **or** if the value reaches ≥ 3 X ULN (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, physical assessment, and primary or secondary hepatic neoplasia should be considered.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/ international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pre-treatment laboratory abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

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

Investigators report AEs using concise medical terminology (verbatim) as well as collect on the CRF the appropriate Common Terminology Criteria (CTC) term for AEs (Version 4.03, Publish Date: June 14, 2010, <http://ctep.cancer.gov/reporting/ctc.html>) listed in the Cancer Therapy Evaluation Program.

The investigator will use the following definitions of Severity in accordance with the current CTC Version to describe the maximum intensity of the AE.

GRADE	Clinical Description of Severity
0	No change from normal or reference range (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.)
1	MILD AE
2	MODERATE AE
3	SEVERE AE
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO AE

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and nonserious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see the section on [Reporting Requirements](#)). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study patient or study patient's partner becomes or is found to be pregnant during the study patient's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on a SAE Report Form and EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

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

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study patient with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the Investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a patient enrolled in the study, the information is not reported on a CRF, however a copy of the completed SAE Report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events (See Also Section on [Patient Withdrawal](#))

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a patient withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient/legally acceptable representative. In addition, each study patient/legally acceptable representative will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant

medications, vaccines, and/or illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.14.2. Nonserious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determination

The primary objective of this study is to demonstrate that the combination of palbociclib with cetuximab is superior to cetuximab in prolonging OS in the target population. This study is designed to test the null hypothesis of equal survival between the treatment arms versus the alternative hypothesis of improved survival in the palbociclib + cetuximab arm compared with the placebo + cetuximab arm.

Assuming a median OS of 6 months in the comparator arm, approximately 79 total events (deaths) are required for 1:1 randomization to have at least 80% power to detect a true hazard ratio of 0.6 (corresponding to a median OS of 10 month in the palbociclib arm) using a one-sided, log-rank test at a significance level of 0.1. The formal futility boundary will be constructed using the Gamma family of spending function with parameter = 0.05. With 40 observed events at the interim analysis, the futility boundary is p-value = 0.36 (corresponding to HR = 0.9). The boundary at final analysis is p-value = 0.1.

Approximately 120 patients will be enrolled in about 16 months and followed for additional 6 months to observe the required number of events. This estimation is based on the following assumptions on the enrollment rates: 1) 5 patients per month (on average) during the first 6 months; 2) 10 patients per month (on average) thereafter.

9.2. Efficacy Analysis

9.2.1. Analysis of Primary Endpoint

All randomized patients will be included in this analysis. Survival time is defined as the time from the date of randomization to the date of death. Since the date of randomization and the date of death should be counted as a full day, 1 day will be added to each calculation. Patients alive will have their survival times censored on the last date of known contact that the patient was documented to be alive. Patients lacking data beyond the day of randomization will have their survival times censored at Day 1.

For each arm, estimates of the survival curves from the Kaplan-Meier method will be presented. Median survival times and 2-sided 95% and 80% confidence intervals (CIs) for the medians will be provided using the Brookmeyer-Crowley method. The survival probabilities at 4, 6 and 12 months will be estimated.

Differences in survival between treatment arms will be tested using the stratified log-rank test where the stratification factors are ECOG performance status (0 vs. 1) and prior use of immunotherapy (yes vs. no). The stratified analysis will be the primary analysis. As a sensitivity analysis, the unstratified log-rank analysis will also be performed. The hazard ratio estimates and their 95% and 80% CIs will be generated using stratified and unstratified Cox proportional hazards models. Rank-preserving structural failure time (RPSFT) method, as supportive/exploratory analysis for OS, will also be conducted.

9.2.2. Analysis of Secondary Endpoints

9.2.2.1. Progression-Free Survival

PFS which is defined as the time from the date of randomization to the date of the first documentation of objective progression of disease (PD) or death due to any cause, whichever is earlier. For patients who do not have objective tumor progression and who do not die while on study, PFS data will be censored on the date of the last adequate tumor assessment on study. Patients lacking an evaluation of tumor response after randomization will have their PFS time censored on the date of randomization with duration of 1 day.

For each arm, estimates of the PFS curves from the Kaplan-Meier method will be presented. Median PFS and 2-sided 95% and 80% CIs for the medians will be provided using the Brookmeyer-Crowley method. The PFS probabilities at 4, 6 and 12 months will be estimated.

Differences in PFS between treatment arms will be tested using the unstratified log-rank test. The hazard ratio estimates and their 95% and 80% CIs will be generated using unstratified Cox proportional hazards models.

9.3.2. Biomarkers

9.3.2.1. Biomarker Analysis Set

The biomarker analysis set is defined as all patients treated with cetuximab in combination with placebo or palbociclib who have at least one baseline biomarker assessment. Analysis sets will be defined separately for CCI [REDACTED], archival tumor tissue CCI [REDACTED]
[REDACTED]

9.3.2.2. Statistical Analysis of Biomarker Endpoints

Biomarkers will be assessed separately CCI [REDACTED], archival tumor tissue CCI [REDACTED]
[REDACTED] In each case, summaries of baseline levels, changes from baseline (where appropriate), expression and mutation will be reported. For continuous variables, summary statistics may include the mean, ratio to baseline, standard deviation, 25th median, and 75th quartile, % CV, and minimum/maximum levels of biomarker measures; for categorical variables, summary may include number and percentage, odds ratio as appropriate.

CCI [REDACTED]

[REDACTED]

[REDACTED]

9.3.3. Patient-Reported Outcomes (PROs)

Health-Related Quality of life and Head and Neck scores and change from baseline scores will be compared between the treatment arms using a mixed model repeated measures approach adjusting for specified covariates. In addition, analyses will be performed to determine if the change from baseline scores achieve the appropriate minimally important difference (MID) cut-off for the scale being examined.

In addition to the above analyses, an examination of the time to deterioration (TTD) composite endpoint will be carried out using survival analysis methods. A composite definition for deterioration based on death, tumor progression, and/or SCCHN cancer-specific quality of life subscale MIDs may be used.

9.4. Safety Analysis

All patients who receive any study treatment will be included in the final summaries and listings of safety data. In addition, the relationship between exposure and efficacy and safety endpoints will be explored, as necessary, based on emerging efficacy and safety data. Refer to SAP for details of the analyses. The results of these modeling analyses may be reported separately from the clinical study report.

9.4.1. Adverse Events

Frequencies of patients experiencing at least 1 AE will be summarized by system organ class (SOC) and preferred term according to MedDRA terminology. The number and percent of patients with AE will be tabulated by treatment and by cycle.

Detailed information collected for each AE will include: a description of the event; duration; whether the AE was serious; intensity (severity) of event; relationship to study drug; action taken; and clinical outcome. Intensity (severity) of the AEs will be graded according to NCI CTCAE version 4.03.

AEs leading to death or discontinuation of treatment, classified as Grade ≥ 3 , or drug related, and SAEs will be considered with special attention.

9.4.2. Laboratory Abnormalities

Hematology and chemistry laboratory data will be summarized by treatment and by cycle. The laboratory results will be graded according to the NCI CTCAE v4.03 severity grade. The frequencies of the worst severity grade observed will be displayed by study treatment. Shift tables will be provided to examine the distribution of laboratory toxicities. For parameters for which an NCI CTCAE v4.03 scale does not exist, the frequency of patients with values below, within, and above the normal ranges will be summarized by treatment.

9.4.3. Electrocardiogram (ECG)

For the analysis of ECG data, the triplicate data will be averaged and all summary statistics and data presentations will use the triplicate averaged data. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates.

For all patients in the safety analysis set, individual changes in QTc (QTcF, QTcB and QTcS) will be calculated for each nominal post-baseline time point and summarized using descriptive statistics. Categorical analysis of the QTc data will be performed as follows:

- The number and percentage of patients with maximum increase from baseline in QTc (<30, 30-60, and ≥ 60 msec).
- The number of and percentage patients with maximum post-dose QTc (<450, 450-<480, 480-<500, and >500 msec).

- The number of and percentage patients with PR changes from baseline $\geq 50\%$ if absolute baseline value was < 200 msec, and $\geq 25\%$ if absolute baseline value was > 200 msec.
- The number of and percentage patients with QRS changes from baseline $\geq 50\%$ if absolute baseline value was < 100 msec, and $\geq 25\%$ if absolute baseline value was > 100 msec.
- The number and percentage of individuals with abnormal ECG findings.

9.5. Interim Analysis

An interim analysis will be performed when at least 50% of the required number of events (40 deaths) is observed. The purpose of this interim analysis is to stop the study early for futility. The formal futility boundary will be constructed using the Gamma family of spending function with parameter = 0.05. With 40 observed events at the interim analysis, the futility boundary is p-value = 0.36 (corresponding to HR = 0.9). The boundary at final analysis is p-value = 0.1.

9.6. Data Monitoring Committee

This study will use an E-DMC.

The E-DMC will be responsible for ongoing monitoring of the efficacy and safety of patients in the study according to the Charter. The E-DMC will make recommendation as to whether or not the trial should continue based on ongoing reviews of safety data. In addition, the E-DMC will also evaluate interim efficacy data and make a recommendation regarding study continuation based on observed results of the study. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate. The sponsor will designate a biostatistician not affiliated with the project to prepare data for E-DMC review. Only if action or consultation with Health Authorities is required will other sponsor staff be involved. Clinical sites will be restricted from access to study results until the conclusion of the study.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be patient to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Ethics Committee (EC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data is compiled for transfer to Pfizer and other authorized parties, patient names, addresses, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify study patients. The study site will maintain a confidential list of patients who participated in the study linking their numerical code to the patient's actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study patient, or his or her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a patient's legally acceptable representative, the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a patient's decisional capacity is so limited he/she cannot reasonably be consulted, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, then the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his/her own consent, the source documents must record why the patient did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (eg, parent, spouse) and that the patient's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each patient's signed consent document.

12.4. Patient Recruitment

Advertisements approved by ECs and investigator databases may be used as recruitment procedures.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of patients have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application

in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as last patient last visit (LPLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of palbociclib at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within one week of notification. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to on www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer has no objection to publication by an investigator of any information collected or generated by the investigator, whether or not the results are favorable to the investigational drug. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

The investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information (other than the study results themselves) before disclosure.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, patient to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, <http://www.icmje.org/index.html#authorship>, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

16. REFERENCES

1. Pignon JP, le Maître A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol.* 2009;92:4-14.
2. Siegel R, Ma J, Zou Z, Jemal A. Cancer Statistics, 2014. *CA Cancer J Clin* 2014; 64(1): 9-29.
3. Bosetti C, Bertuccio P, Malvezzi M, Levi F, Chatenoud L, Negri E, La Vecchia C. Cancer mortality in Europe, 2005-2009, and an overview of trends since 1980. *Ann Oncol.* 2013;24(10):2657-71.
4. Hashibe M, Brennan P, Benhamou S, Castellsague X, Chen C, Curado MP, Dal Maso L, Daudt AW, Fabianova E, Wunsch-Filho V, Franceschi S, Hayes RB, Herrero R, Koifman S, La Vecchia C, Lazarus P, Levi F, Mates D, Matos E, Menezes A, Muscat J, Eluf-Neto J, Olshan AF, Rudnai P, Schwartz SM, Smith E, Sturgis EM, Szeszenia-Dabrowska N, Talamini R, Wei Q, Winn DM, Zaridze D, Zatonski W, Zhang Z-F, Berthiller J, Boffetta P. Alcohol drinking in never users of tobacco, cigarette smoking in neverdrinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *J Natl Cancer Inst* 2007; 99(10):777-89.
5. D'Souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM, Westra WH, Gillison ML. Case-control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med* 2007;356(19):1944-56.
6. Ortholan C, Lusinchi A, Italiano A. Oral cavity squamous cell carcinoma in 260 patients aged 80 years or more. *Radiother Oncol.* 2009;93:516-23.
7. Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottery S, Erfan J, Zabolotnyy D, Kienzer HR, Cupissol D, Peyrade F, Benasso M, Vynnychenko I, DeRaucourt D, Bokemeyer C, Schueler A, Amellal N, Hitt R. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med* 2008;359(11):1116-27.
8. Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, Jacobsen A, Byrne CJ, Heuer ML, Larsson E, Antipin Y, Reva B, Goldberg AP, Sander C, Schultz N. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov* 2012;2(5):401-4.
9. Ang KK, Berkey BA, Tu X, Zhang H-Z, Katz R, Hammond EH, Fu KK, Milas L. Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma. *Cancer Res* 2002;62(24):7350-6.

10. Hirama T, Koeffler HP. Role of the Cyclin-Dependent Kinase Inhibitors in the Development of Cancer. *Blood* 1995;86:841-54.
11. Musgrove E, Caldon E, Barraclough J, Stone A, Sutherland R. Cyclin D as a therapeutic target in cancer. *Nature Reviews Cancer* 2011;11:558-72.
12. Smeets S, Braakhuis BJM, Abbas S, Snijders PJF, Ylstra B, van de Wiel MA, Meijer GA, Leemans CR, Brakenhoff RH. Genome-wide DNA copy number alterations in head and neck squamous cell carcinomas with or without oncogene-expressing human papillomavirus. *Oncogene* 2006;25:2558–64.
13. Bova R, Quinn DI, Nankervis JS, Cole IE, Sheridan BF, Jensen MJ, Morgan, GJ, Hughes CJ, Sutherland RL. Cyclin D1 and p16INK4A expression predict reduced survival in carcinoma of the anterior tongue. *Clin Cancer Res* 1999;5:2810-19.
14. Akervall J, Michalides RJAM, Mineta H, Balm A, Borg A, Dictor MR, Jin Y, Loftus B, Mertens F, Wennerberg JP. Amplification of cyclin D1 in squamous cell carcinoma of the head and neck and the prognostic value of chromosomal abnormalities and cyclin D1 overexpression. *Cancer* 1997;79:380-9.
15. Liu S-C, Zhang SY, Babb JS, Ridge JA, Klein-Szanto AJP. Image cytometry of cyclin D1: a prognostic marker for head and neck squamous cell carcinomas. *Cancer Epidemiol Biomark Prev* 2001;10:455-9.
16. Kyomoto R, Kumazawa H, Toda Y, Sakaida N, Okamura A, Iwanaga M, Shintaku M, Yamashita T, Hiai H, Fukumoto M. Cyclin-D1-gene amplification is a more potent prognostic factor than its protein over-expression in human head-and-neck squamous-cell carcinoma. *Int J Cancer* 1997;74:576-81.
17. Mineta H, Miura K, Takebayashi S, Ueda Y, Misawa K, Harada H, Wennerberg J, Dictor M. Cyclin D1 overexpression correlates with poor prognosis in patients with tongue squamous cell carcinoma. *Oral Oncol* 2000;36:194-8.
18. Michalides R. Overexpression of cyclin D1 indicates a poor prognosis in squamous cell carcinoma of the head and neck. *Arch Otolaryngol Head Neck Surg* 1997;123:497-502.
19. Zhang P, Zhang Z, Zhou X, Qiu W, Chen F, Chen W. Identification of genes associated with cisplatin resistance in human oral squamous cell carcinoma cell line. *BMC Cancer* 2006;6:224.
20. Zhou X, Zhang Z, Yang X, Chen W, Zhang P. Inhibition of cyclin D1 expression by cyclin D1 shRNAs in human oral squamous cell carcinoma cells is associated with increased cisplatin chemosensitivity. *Int J Cancer* 2009;124:483-9.

21. Feng Z, Guo W, Zhang C, Xu Q, Zhang P, Sun J, Zhu H, Wang Z, Li J, Wang L, Wang B, Ren G, Ji T, Tu W, Yang X, Qiu W, Mao L, Zhang Z, Chen W. CCND1 as a Predictive Biomarker of Neoadjuvant Chemotherapy in Patients with Locally Advanced Head and Neck Squamous Cell Carcinoma. *PLoS ONE* 2011;6:e26399.
22. Fry D, Harvey PJ, Keller PR, Elliott WL, Meade MA, Trachet E, Albassam M, Zheng XX, Leopold WR, Pryer NK, Toogood PL. Specific Inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. *Mol Cancer Ther* 2004;3:1427-37.
23. Finn RS, Dering J, Conklin D, Kalous O, Cohen DJ, Desai AJ, Ginther C, Atefi M, Chen I, Fowst C, Los G, Slamon DJ. PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. *Breast Cancer Res* 2009;11:1-13.
24. Reed AL, Califano J, Cairns P, Westra WH, Jones RM, Koch W, Ahrendt S, Eby Y, Sewell D, Nawroz H, Bartek J, Sidransky D. High frequency of p16 (CDKN2/MTS-1/INK4A) inactivation in head and neck squamous cell carcinoma. *Cancer Res* 1996;56:3630-3.
25. Smeets SJ, van der Plas M, Schaaïj-Visser TBM, van Veen EAM, van Meerloo J, Braakhuis BJM, Steenbergen RDM, Brakenhoff RH. Immortalization of oral keratinocytes by functional inactivation of the p53 and pRb pathways. *Int J Cancer* 2011;128:1596-1605.
26. Lin S-Y, Makino K, Xia W, Matin A, Wen Y, Kwong KY, Bourguignon L, Hung M-C. Nuclear localization of EGF receptor and its potential new role as a transcription factor. *Nature Cell Biol* 2001;3:802-8.
27. Kalish LH, Kwong RA, Cole IE, Gallagher RM, Sutherland RL, Musgrove EA. Deregulated Cyclin D1 Expression Is Associated with Decreased Efficacy of the Selective Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Gefitinib in Head and Neck Squamous Cell Carcinoma Cell Lines. *Clin Cancer Res* 2004;10:7764-74.
28. Bonner JA, Harai PM, Giralt J, Azarnia N, Shin DM, Cohen RB, Jones CU, Sur R, Raben D, Jassem J, Ove R, Kies MS, Baselga J, Yossoufian H, Amellal N, Rowinsky EK, Ang KK. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006;354(6):567-78.
29. Bonner JA, Harai PM, Giralt J, Azarnia N, Cohen RB, Jones CU, Sur R, Raben D, Baselga J, Spencer SA, Zhu J, Yossoufian H, Rowinsky EK, Ang KK. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncology* 2010;11:21-28.

30. Baselga J, Trigo JM, Bourhis J, Tortochaux J, Cortes-Funes H, Hitt R, Gascon P, Amellal N, Harstrick A, Eckardt A. Phase II multicenter study of the antiepidermal growth factor receptor monoclonal antibody cetuximab in combination with platinum-based chemotherapy in patients with platinum-refractory metastatic and/or recurrent squamous cell carcinoma of the head and neck. *J Clin Oncol* 2005;23:5568–77.
31. Herbst RS, Arquette M, Shin DM, Dicke K, Vokes EE, Azarnia N, Hong WK, Kies MS. Epidermal growth factor receptor antibody cetuximab and cisplatin for recurrent and refractory squamous cell carcinoma of the head and neck: a phase II, multicenter study. *J Clin Oncol* 2005;23:5578–87.
32. Vermorken JB, Trigo J, Hitt R, Koralewski P, Diaz-Rubio E, Rolland F, Knecht R, Amellal N, Schueler A, Baselga J. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. *J Clin Oncol* 2007;25:2152–55.
33. Vermorken JB, Herbst R, Leon X, Amellal N, Baselga J. Overview of the efficacy of cetuximab in recurrent and/or metastatic squamous cell carcinoma of the head and neck in patients who previously failed platinum-based therapies. *Cancer* 2008;112:2710–19.
34. Schwartz GK, LoRusso PM, Dickson MA, Randolph SS, Shiak MN, Wilner KD, Courtney R, O'Dwyer PJ. Phase I study of PD 0332991, a cyclin-dependent kinase inhibitor, administered in 3-week cycles (Schedule 2/1). *Brit J Cancer* 2011;104:1862-68.
35. Flaherty KT, LoRusso PM, DeMichele A, Abramson VG, Courtney R, Randolph SS, Shaik MN, Wilner KD, O'Dwyer PJ, Schwartz GK. Phase I, Dose-Escalation Trial of the Oral Cyclin-Dependent Kinase 4/6 Inhibitor PD 0332991, Administered Using a 21-Day Schedule in Patients with Advanced Cancer. *Clin Cancer Res* 2012;18:568-76.
36. Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, Ettl J, Patel R, Pinter T, Schmidt M, Shparyk Y, Thummala AR, Voytko NL, Breazna A, Kim ST, Randolph S, Slamon DJ. Results of a randomized phase 2 study of PD 0332991, a cyclin-dependent kinase (CDK) 4/6 inhibitor, in combination with letrozole vs letrozole alone for first-line treatment of ER+/HER2- advanced breast cancer (BC). *Cancer Res* 2012;72:S1-6.
37. Leonard JP, LaCasce AS, Smith MR, Noy A, Chirieac LR, Rodig SJ, Yu JQ, Vallabhajosula S, Schoder H, English P, Neuberg DS, Martin P, Millenson MM, Ely SA, Courtney R, Shaik N, Wilner KD, Randolph S, Van den Abbeele AD, Chen-Kiang SY, Yap JT, Shapiro GI. Selective CDK4/6 inhibition with tumor responses by PD0332991 in patients with mantle cell lymphoma. *Blood* 2012;119:4597-607.

38. Dickson MA, Tap WD, Keohan ML, D'Angelo SP, Gounder MM, Antonescu CR, Landa J, Qin LX, Rathbone DD, Condy MM, Ustoyev Y, Crago AM, Singer S, Schwartz GK. Phase II trial of the CDK4 inhibitor PD0332991 in patients with advanced CDK4-amplified well-differentiated or dedifferentiated liposarcoma. *J Clin Oncol* 2013;31(16):2024-8.
39. Summary of Product Characteristics for Erbitux[®]
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000558/human_med_000769.jsp&mid=WC0b01ac058001d124.

Appendix 1. Adkins, D. Protocol # 201404139

Adkins D, Lewis J, Michel L, Trinkaus K, Wildes T. Phase I/II Trial of the Addition of PD 0332991 to Cetuximab in Patients with Incurable SCCHN. Washington Univeristy School of Medicine, Division of Oncology Protocol # 201404139, Version Date 05/06/2014.

Appendix 2. RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 Guidelines

Adapted from *E.A. Eisenhauer, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247*

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

- Lesions that can be accurately measured in at least one dimension.
- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical examination that are not measurable by reproducible imaging techniques.

- Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.

- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

Recording Tumor Assessments

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Target lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.
- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-target disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

Target disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis < 10 mm). All target lesions must be assessed.
- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.
- Stable: Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.
- Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.
- Indeterminate. Progression has not been documented, and
 - one or more target measurable lesions have not been assessed,
 - or assessment methods used were inconsistent with those used at baseline,
 - or one or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure),
 - or one or more target lesions were excised or irradiated and have not reappeared or increased.

Non-target disease

- CR: Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be 'normal' in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.
- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

- Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.
- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective progression

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

Table 1. Objective Response Status at each Evaluation			
Target Lesions	Non-target Disease	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate, or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate, or Missing	No	Stable
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

If the protocol allows enrollment of patients with only non-target disease, the following table will be used:

Table 2. Objective Response Status at each Evaluation for Patients with Non-Target Disease Only		
Non-target Disease	New Lesions	Objective status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Indeterminate	No	Indeterminate
Unequivocal progression	Yes or No	PD
Any	Yes	PD

Appendix 3. European Organisation for Research and Treatment of Cancer Quality of Life Instrument (EORTC-QLQ-C30)

Protocol ID: _____

CENTER SUBJECT ID

DATE OF VISIT
 - -
dd MMM yyyy

Visit: _____

EORTC QLQ-C30 - Page 1 of 2

(1) NOT DONE Language Administered: (999) English Standard

We are interested in some things about you and your health. Please answer all of the questions yourself by marking the box 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?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
2. Do you have any trouble taking a <u>long</u> walk?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
3. Do you have any trouble taking a <u>short</u> walk outside of the house?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
4. Do you need to stay in bed or a chair during the day?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
During the past week:				
6. Were you limited in doing either your work or other daily activities?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
7. Were you limited in pursuing your hobbies or other leisure time activities?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
8. Were you short of breath?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
9. Have you had pain?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
10. Did you need to rest?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
11. Have you had trouble sleeping?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
12. Have you felt weak?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
13. Have you lacked appetite?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
14. Have you felt nauseated?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
15. Have you vomited?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4

Please go on to the next page.

Appendix 4. European Organisation for Research and Treatment of Cancer Head and Neck Module 35 (EORTC-QLQ-H&N35)



EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Have you had pain in your mouth?	1	2	3	4
32. Have you had pain in your jaw?	1	2	3	4
33. Have you had soreness in your mouth?	1	2	3	4
34. Have you had a painful throat?	1	2	3	4
35. Have you had problems swallowing liquids?	1	2	3	4
36. Have you had problems swallowing pureed food?	1	2	3	4
37. Have you had problems swallowing solid food?	1	2	3	4
38. Have you choked when swallowing?	1	2	3	4
39. Have you had problems with your teeth?	1	2	3	4
40. Have you had problems opening your mouth wide?	1	2	3	4
41. Have you had a dry mouth?	1	2	3	4
42. Have you had sticky saliva?	1	2	3	4
43. Have you had problems with your sense of smell?	1	2	3	4
44. Have you had problems with your sense of taste?	1	2	3	4
45. Have you coughed?	1	2	3	4
46. Have you been hoarse?	1	2	3	4
47. Have you felt ill?	1	2	3	4
48. Has your appearance bothered you?	1	2	3	4

Please go on to the next page

During the past week:		Not at all	A little	Quite a bit	Very much
49.	Have you had trouble eating?	1	2	3	4
50.	Have you had trouble eating in front of your family?	1	2	3	4
51.	Have you had trouble eating in front of other people?	1	2	3	4
52.	Have you had trouble enjoying your meals?	1	2	3	4
53.	Have you had trouble talking to other people?	1	2	3	4
54.	Have you had trouble talking on the telephone?	1	2	3	4
55.	Have you had trouble having social contact with your family?	1	2	3	4
56.	Have you had trouble having social contact with friends?	1	2	3	4
57.	Have you had trouble going out in public?	1	2	3	4
58.	Have you had trouble having physical contact with family or friends?	1	2	3	4
59.	Have you felt less interest in sex?	1	2	3	4
60.	Have you felt less sexual enjoyment?	1	2	3	4

During the past week:		No	Yes
61.	Have you used pain-killers?	1	2
62.	Have you taken any nutritional supplements (excluding vitamins)?	1	2
63.	Have you used a feeding tube?	1	2
64.	Have you lost weight?	1	2
65.	Have you gained weight?	1	2

Appendix 5. Eastern Cooperative Oncology Group (ECOG) Performance Status

Description	Grade
Fully active, able to carry on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, ie, light house work, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4

Appendix 6. List of Drugs Known to Predispose to Torsade de Pointes

Generic Name	Brand Name(s)
Amiodarone	Cordarone [®] , Pacerone [®]
Arsenic trioxide	Trisenox [®]
Astemizole	Hismanal [®]
Azithromycin	Zithromax [®]
Bepidil	Vasor [®]
Chloroquine	Aralen [®]
Chlorpromazine	Thorazine [®]
Cisapride	Propulsid [®]
Citalopram	Celexa [®]
Clarithromycin	Biaxin [®]
Disopyramide	Norpace [®]
Dofetilide	Tikosyn [®]
Domperidone	Motilium [®]
Droperidol	Inapsine [®]
Erythromycin	Erythrocin [®] , E.E.S. [®]
Flecainide	Tambocor [®]
Halofantrine	Halfan [®]
Haloperidol	Haldol [®]
Ibutilide	Corvert [®]
Levomethadyl	Orlaam [®]
Mesoridazine	Serentil [®]
Methadone	Dolophine [®] , Methadose [®]
Moxifloxacin	Avelox [®]
Ondansetron*	Zofran [®]
Pentamidine	Pentam [®] , NebuPent [®]
Pimozide	Orap [®]
Probucol	Lorelco [®]
Procainamide	Pronestyl [®] , Procan [®]
Quinidine	Cardioquin [®] , Quinaglute [®]
Sotalol	Betapace [®]
Sparfloxacin	Zagam [®]
Terfenadine	Seldane [®]
Thioridazine	Mellaril [®]
Vandetanib	Caprelsa [®]

*when administered intravenously at high dose (32 mg).

Adapted from the University of Arizona Cancer Center for Education and Research on Therapeutics: "Torsades List: Drugs with a Risk of Torsades de Pointes," drugs that are generally accepted by the QTdrugs.org Advisory Board to carry a risk of Torsades de Pointes on the University of Arizona CERT website: <http://www.crediblemeds.org/>. This list is not meant to be considered all inclusive. See website for current list.

Appendix 7. Bone Marrow Reserve in Adult

Adapted from R.E. ELLIS: The Distribution of Active Bone Marrow in the Adult, Phy. Med. Biol. 5, 255-258, 1961

Marrow Distribution of the Adult

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
CRANIUM AND MANDIBLE	Head:			136.6		
	Cranium	165.8	0.75	124.3	13.1	13.1
	Mandible	16.4	0.75	12.3		
HUMERI, SCAPULAE, CLAVICLES	Upper Limb Girdle :			86.7		
	2 Humerus, head & neck	26.5	0.75	20.0	8.3	8.3
	2 Scapulae	67.4	0.75	50.5		
	2 Clavicles	21.6	0.75	16.2		
STERNUM AND RIBS	Sternum	39.0	0.6	23.4	2.3	
	Ribs:			82.6		
	1 pair	10.2	All 0.4	4.1		10.2
	2	12.6		5.0		
	3	16.0		6.4		
	4	18.6		7.4		
	5	23.8		9.5	7.9	
	6	23.6		9.4		
	7	25.0		10.0		
	8	24.0		9.6		
	9	21.2		8.5		
	10	16.0		6.4		
	11	11.2		4.5		
12	4.6		1.8			
PELVIC BONES	Sacrum	194.0	0.75	145.6	13.9	
	2 os coxae	310.6	0.75	233.0	22.3	36.2
FEMUR	2 Femoral head and neck	53.0	0.75	40.0		3.8

MARROW DISTRIBUTION OF THE ADULT (CONT'D)

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
VERTEBRAE	Vertebrae (Cervical):			35.8	3.4	28.4
	1	6.6	All 0.75	5.0		
	2	8.4		6.3		
	3	5.4		4.1		
	4	5.7		4.3		
	5	5.8		4.4		
	6	7.0		5.3		
	7	8.5		6.4		
	Vertebrae (Thoracic):			147.9	14.1	
	1 pair	10.8	All 0.75	8.1		
	2	11.7		8.8		
	3	11.4		8.5		
	4	12.2		9.1		
	5	13.4		10.1		
	6	15.3		11.5		
	7	16.1		12.1		
	8	18.5		13.9		
	9	19.7		14.8		
	10	21.2		15.9		
	11	21.7		16.3		
	12	25.0		18.8		
Vertebrae (Lumbar):			114.1	10.9		
1 pair	27.8	All 0.75	20.8			
2	29.1		21.8			
3	31.8		23.8			
4	32.1		24.1			
5	31.4		23.6			
TOTAL		1497.7		1045.7	100.0	100.0