Protocol A5481044

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

Statistical Analysis Plan
(SAP)

Version: **3**

Author: PPD

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

Version 2:
Per Protocol amendment 2, removing mITT population from the analysis set.
Specifying the secondary endpoints by using unstratified log-rank test.
Adding definition for BOR
Revising RDI (Relative Dose Intensity) definition
Specifying the 2 consecutive assessments for tumor assessment to 18 weeks.
Adding more timeline details for Palbociclib pharmacokinetic and biomarkers data.

Version 3:
Adding clinical benefit response (CBR) as second efficacy endpoint.
Adding clear definition on Study Day and Treatment Day

2. PER THE CHANGES IN PROTOCOL AMENDMENT 2 (31 MARCH 2016) AND ONCOLOGY STATISTICS RULEBOOK V3, THE REVISES ARE INCORPORATE IN THE AMENDED SAP. INTRODUCTION

This document describes the planned statistical analyses for Protocol A5481044 dated February 7, 2015. This analysis plan is meant to supplement the study protocol. Any deviations from this analysis plan will be described in the Clinical Study Report.

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.

2.1. 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/m^2 initial dose as a 120-minute intravenous (IV) infusion followed by 250 mg/m^2 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/m^2 initial dose as a 120-minute IV infusion followed by 250 mg/m^2 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 (e.g., 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 Section 10.1 Schedule Activities.

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.

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Examining and measuring the patient's subjective experience in this study will be accomplished using validated health-related quality of life questionnaires. Observations will be documented at specified time points throughout the study, plus 1 observation after treatment discontinuation (to measure the impact of progressive disease on the patient's quality of life).

2.2. Study 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 (e.g., 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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3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

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.

The study will use an External Data Monitoring Committee (E-DMC). The E-DMC membership and governance are outlined in a separate charter.

An independent third party External Data Monitoring Committee (E-DMC) will monitor 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.

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 in the data preparation. Clinical sites will be restricted from access to study results until the conclusion of the study.

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.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

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.

4.2. Sample Size Determination and Statistical Decision Rules

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.

This study will be considered a positive trial if the 1-sided, log-rank test for OS in all patients randomized to the study is significant at level of 0.1 at the final analysis.

5. ANALYSIS SETS

5.1. Intent-to-Treat Population (Full Analysis Set)

The intent-to-treat (ITT) population will include all patients who are randomized, with study drug assignment designated according to initial randomization, regardless of whether patients receive study drug or receive a different drug from that to which they were randomized. The ITT population will be the primary population for evaluating all efficacy endpoints and patient characteristics.

5.2. As-Treated (AT) Population (Safety Analysis Set)

The as-treated (AT) population or safety analysis set will include all patients who receive at least 1 dose of study medication, with treatment assignments designated according to actual study treatment received. The AT population will be the primary population for evaluating treatment administration/compliance and safety. Efficacy and clinical benefit endpoints may be assessed in this population as well.

5.3. Other Analysis Sets

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5.3.2. Biomarker Analysis Set

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

- [redacted]
- Archival Tumor Tissue Specimen - collected at screening only: AT population with screening assessment

[redacted]

5.3.3. Patient Reported Outcome (PRO) Analysis Set

A subset of ITT patients, who have both baseline and at least one follow-up PRO assessment before treatment discontinuation.

5.4. Treatment Misallocations

- If patients were *randomized but not treated*, then they will be reported under their randomized treatment group for efficacy analyses. However, they are by definition excluded from the safety analyses.
- If patients were *randomized but took incorrect treatment*, then they will be reported under their randomized treatment group for efficacy analyses, but will be reported under the treatment they actually received for all safety analyses.

5.5. Protocol Deviations

All deviations will be described when they appear and relate to the statistical analyses or populations.

5.5.1. Protocol Deviations Assessed Prior to Randomization

Deviations prior to randomization are typically not allowed. Major deviations that do occur will be tabulated.

5.5.2. Protocol Deviations Assessed Post Randomization

Major deviation is defined as having been treated according to the other treatment arm. Patients not treated with one of the protocol treatments are excluded from safety analyses. Otherwise patients are not excluded from analyses due to post-randomization deviations.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoints

6.1.1. Primary Endpoint

- **Overall Survival (OS)** is defined as the time from the date of randomization to the date of death due to any cause. OS (in months) is calculated as (date of death − randomization date +1)/30.4. For patients lacking survival data beyond the date of their last follow-up, the OS time will be censored on the last date they were known to be alive. Patients lacking survival data beyond randomization will have their OS times be censored at randomization.

  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.

6.1.2. Secondary Endpoints

- **Progression Free Survival (PFS)** is defined as the time from the date of randomization to the date of the first documentation of objective tumor progression as per RECIST v.1.1 or death due to any cause in the absence of documented PD, whichever occurs first. If tumor progression data include more than 1 date, the first date will be used. PFS (in months) will be calculated as (first event date − randomization date +1)/30.4.

  Tumor assessments will be performed every 8 weeks (± 7 days) from randomization until radiographically and/or clinically (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 (e.g., 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. Patients who discontinue study treatment for reasons other than radiographically and/or clinically (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 (e.g., 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.

  Patients last known to be 1) alive and 2) progression-free, are censored at the date of the last objective disease assessment that verified lack of disease progression (see Appendix 10.4 for determining the date in details). In addition,

- Patients with no baseline tumor assessment (including patients with an inadequate baseline assessment) or with no adequate post-baseline tumor assessments within 18 weeks after the randomization date will be censored on the randomization date, unless the patient dies within 18 weeks of the randomization date, in which case, death will be an event on date of death.

- If a new anti-cancer treatment is started prior to progression and death, then censorship is at the date of the last objective disease assessment that verified lack of disease progression prior to the new treatment.
- If patients are removed from the study (withdrew the consent, lost to follow up, etc.) prior to progression and death, then censorship is at the date of the last objective disease assessment that verified lack of disease progression.
- Patients with documentation of progression or death after an unacceptably long interval (≥2 consecutive assessments or > 18 weeks) since the last tumor assessment will be censored at the time of last objective assessment documenting no progression.

- **Objective Response (OR)** is defined as the overall complete response (CR) or partial response (PR) according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1; Appendix 10.3.). **Objective Response Rate (ORR)** is defined as the proportion of patients with best overall response (BOR) of CR or PR relative to all randomized. The BOR definition is described in Appendix 10.3. Patients who do not have on-study radiographic tumor re-evaluation, who receive anti-tumor treatment other than the study medication prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of ORR.

  Tumor response will be determined from tumor assessment data (where data meet the criteria for CR or PR as described in Appendix 10.3.).

  - **Clinical Benefit Response (CBR)** is defined as the overall complete response (CR), partial response (PR) , or stable disease (SD) ≥24 weeks according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1; Appendix 1). **Clinical Benefit Response Rate (CBRR)** is defined as the proportion of patients with CR, PR, or SD ≥24 weeks relative to (1) all randomized patients and randomized patients with measurable disease at baseline. Designation of best response of SD ≥24 weeks requires the criteria to be met at least 24 weeks after randomization. Patients who do not have on-study radiographic tumor re-evaluation, who receive anti-tumor treatment other than the study medication prior to reaching a CR or PR, a best response of SD ≥24 weeks, or who die, progress, or drop out for any reason prior to achieving reaching a CR or PR and a best response of SD ≥24 weeks will be counted as non-responders in the assessment of CBRR. Tumor response will be determined from tumor assessment data (where data meet the criteria for CR or PR and best response of SD as described in Appendix 10.3.).

- **Duration of Response (DR)** is defined as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of disease progression or to death due to any cause, whichever occurs first. If tumor progression data include more

than 1 date, the first date will be used. DR will be calculated as [the date response ended (i.e. date of PD or death) – first CR or PR date + 1)]/30. 4. DR will only be calculated for the subgroup of patients with an objective tumor response.

Patients last known to be 1) alive and 2) progression-free, are censored at the date of the last objective disease assessment that verified lack of disease progression. In addition,

- If a new anti-cancer treatment is started prior to progression and prior to 28 days after discontinuation of treatment, then censorship is at the date of the last objective disease assessment that verified lack of disease progression prior to the new treatment.
- If patients are removed from the study (withdrew the consent, lost to follow up, etc.) prior to progression and death, then censorship is at the date of the last objective disease assessment that verified lack of disease progression.
- Patients with documentation of progression or death after an unacceptably long interval (≥2 consecutive assessments or > 18 weeks) since the last tumor assessment will be censored at the time of last objective assessment documenting no progression.

6.2. Safety Data

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.

Overall safety profile as characterized by type, frequency, severity of adverse events as graded by NCI Common Toxicity Criteria for Adverse Events version 4 (NCI CTCAE v.4.03), timing and relationship to treatment on each arm, and laboratory abnormalities observed.

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.

Adverse events (AEs), hematology, blood chemistry will be assessed as described in the Schedule of Activities of the protocol.

Adverse events will be classified using the MedDRA classification system. The severity of the toxicities will be graded according to the NCI CTCAE version 4.03. For labs without CTCAE grade definitions, results are summarized as normal, abnormal (per Pfizer Data Standards (PDS)) or not done. For other AEs without specific CTCAE definitions, results are identified according to CTCAE “other” categories.

Adverse events leading to death or discontinuation of trial treatment, events classified as NCI CTCAE v.4.03 Grade 3 or higher, trial drug related events, and serious adverse events will be considered with special attention.

The hematologic and chemistry laboratory results will be graded according to the NCI CTCAE v.4.03 severity grade. For parameters for which an NCI CTCAE v.4.03 scale does not exist, the frequency of patients with values below, within, and above the normal range for the local lab will be summarized.

Patients who start treatment are assessed for toxicities up to 28 days after the final dose of treatment or start of new treatment (whichever comes first). Toxicities observed beyond 28 days and recorded in the database per Sponsor's agreement will be included in the summaries.

6.2.1. Treatment Emergent Adverse Event

An adverse event is considered treatment emergent if:

- The event occurs for the first time after the start of study treatment and before 28 days after final dose of study treatment and was not seen prior to the start of treatment or
- The event was seen prior to the start of treatment but increased in NCI CTCAE v.4.0 grade during study treatment.
- Disease progression is not considered a treatment emergent adverse event unless the patient dies of disease prior to 28 days after discontinuation of treatment.

6.2.2. Treatment Related Adverse Event

Adverse events defined as treatment emergent adverse events with cause possibly, probably or definitely related to treatment as judged by the investigator are defined as treatment related adverse events. Events that are continuation of baseline abnormalities are not considered treatment related unless there is an increase in grade, or if there is an increase following a decrease, and the increase is judged by the investigator to be caused by the treatment.

6.2.3. Laboratory Safety Assessments

Laboratory assessment will be assigned to cycles based on the collection date of the sample relative to the start dates of cycles from the study drug administration as described in the Schedule of Activities table in Appendix 10.1.

Baseline evaluations for laboratory are those collected

- Within 28 days prior to or on first day of study drug and
- If there is more than one baseline evaluation, closest to but any time prior to the 1st dosing on the first day of study treatment.

Blood tests will include the following:

Hematology	**Chemistry**
Hemoglobin	ALT
WBC	AST
Platelets	Alkaline Phosphatase
Absolute Neutrophils	Sodium

Absolute Lymphocytes	Potassium
	Magnesium
Coagulation	Chloride
PT or INR	Total Calcium
PTT	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 phosphastase.

For all patients, 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.

6.2.4. 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 Section 10.1. Schedule of Activities for details) to determine the mean QTc interval.

6.2.5. Other Safety Assessment

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: The Eastern Cooperative Oncology Group (ECOG) performance status scale will be used.

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6.3.3. Patient Reported Outcome Endpoints

Patient reported outcomes of functioning , symptoms and global QOL 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 (e.g., 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.

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

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 four point Likert scales with responses from "not at all" to "very much" and two 7 point Likert scales for global health and overall QOL. The scores are transformed to a 0 to 100 scale. For functional and global QOL scales, higher scores represent a better level of functioning/QOL while for symptom scales, a higher score represents more severe symptoms.

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

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.

6.4. Covariates and Stratification Factors

6.4.1. Covariates

The potential influences of baseline patient characteristics such as age, gender, ethnic origin, ECOG performance status, geographical region, selected biomarkers, and stratification factors on the primary endpoint OS, PFS, and OR endpoints may be evaluated.

6.4.2. Stratification Factors

- Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1)
- Prior use of immunotherapy (yes vs. no)

7. HANDLING OF MISSING VALUES

7.1. Missing Dates

In compliance with Pfizer standards, if the day of the month is missing for any date used in a calculation, the 1st of the month will be used to replace the missing date unless the calculation results in a negative time duration (e.g., date of onset cannot be prior to day one date). In this case, the date resulting in 1 day duration will be used. If the day of the month and the month is missing for any date used in a calculation, January 1 will be used to replace the missing date.

Missing dates for adverse events will be imputed based on the similar principle.

- For the start date, if the day of the month is missing, the 1st day of the month will be used to replace the missing date. If both day and month are missing, January 1 of the non-missing year will be used to replace the missing date. If the first dose date is later than this imputed date, then impute the start date again to the first dose date.
- For the stop date, if the day of the month is missing, the last day of the month will be used to replace the missing date. If both day and month are missing, December 31 of the non-missing year will be used to replace the missing date.

If the start date is missing for an AE, the AE is considered to be treatment emergent unless the collection date is prior to the treatment start date.

7.2. Missing Tumor Assessments

If baseline tumor assessment is inadequate the patient cannot be assessed for response.

Inadequate baseline assessment may include

- Not all required baseline assessments were done
- Assessments were done outside the required window
- Measurements were not provided for one or more target lesions
- One or more lesions designated as target were not measurable.

If measurements for one or more target lesions are missing for an evaluation and disease does not qualify as progression (or symptomatic deterioration if applicable), the objective status for that evaluation is Indeterminate.

If non-target disease was not assessed, then objective status cannot be a CR even if all target disease has disappeared. Otherwise, missing non-target disease assessments do not necessarily affect response determination. Such cases will be reviewed carefully.

If a lesion measurement is missing because it is documented as too small to measure, the value 5 mm will be assigned and objective status calculated accordingly.

In the assessment of OR, patients who do not have on study radiographic tumor re-evaluations will be counted as non-responders.

7.3. Missing Data in PFS Derivation

PFS cannot be assessed in patients with inadequate baseline tumor assessment. PFS cannot be assessed in patients who have no on-study assessments unless death occurs prior to the first planned assessment time.

If a substantial number of patients have questionable failure or censorship dates for either PFS definition (such as progression or death not documented until after multiple missing

assessments) scenarios such as best case (failure at time of documentation) and worst case (progression at earliest possible planned assessment date) will be investigated.

For PFS analysis, no values will be imputed for missing data. For time to event endpoints, non-event observations will be censored as defined in Section 6.

7.4. Missing QTc Data

For QTc analysis, no values will be imputed for missing data except for averaging of triplicate measurements. If one or two of the triplicate measurements for an ECG parameter are missed, the average of the remaining two measurements or the single measurement can be used in the analyses. If all triplicate measurements are missing at a time point for an ECG parameter, no values will be imputed for this time point and no analyses related to this time point will be performed. If the triplicate is not good because of an artifact, then if the triplicate is repeated within about ± 15 minutes can be used at that nominal time. Patients who have data on other days or unscheduled ECGs but not at the times of the formal statistical analysis will be included in the categorical tables but not the statistical analyses.

7.5. Missing Patient Reported Outcome Data

For the EORTC-QLQ-C30 and EORTC-QLQ-H&N35, in cases where two answers are given to one item, the more severe answer will be counted. If at least half of the constituent items for the multi-item functional or symptom scale have been answered, then the score for that scale may be pro-rated based on the non-missing items. For subsequent analysis purposes, missing items will be considered missing; they will not be imputed.

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8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

8.1.1. Analyses for Time-to-Event Data

Time-to-event endpoints between the 2 treatment arms will be compared with a 1-sided log-rank test and/or a 1-sided stratified log-rank test at the α=0.1 overall significance level. Hazard ratios and 2-sided 80% and 95% confidence intervals will be estimated using Cox proportional hazards regression.

Cox proportional hazard models will also be used to explore the potential influences of the baseline stratification factors (as listed in Section 6.4.2) on time-to-event endpoints. In addition, potential influences of baseline patient characteristics such as age, gender, race, ethnic origin, geographical region, and selected biomarkers on the endpoints may be evaluated. A backward selection process (with treatment in the model) will be applied to these variables to identify the final set of relevant factors. Treatment-by-factor interactions will be explored only for the set of factors included in the final model. The estimated hazard ratio and 2-sided 80% and 95% confidence intervals will be provided. Additionally for each treatment arm, the median event time and a 2-sided 95% confidence intervals will be provided for each level of stratification factors or baseline characteristics.

Time-to-event endpoints will be summarized using the Kaplan-Meier method and displayed graphically when appropriate. Median event times and 2-sided 95% confidence intervals for each median will be provided.

The survival probability at 4, 6, and 12 months will be estimated using the Kaplan-Meier method and a 2-sided 95% confidence interval for the log [-log(X-year survival probability)] will be calculated using a normal approximation and then back transformed to give a confidence interval for the survival probability at 4, 6, and 12 month.

Since patients in both treatment arms may receive other available treatments after disease progression, the treatment effect on overall survival may not be able to estimate properly by above defined methods because of these confounding factors. Therefore, the proper testing statistics such as Wilcoxon test and methods like Rank-Preserving Structural Failure Time Model (RPSFTM) proposed by Robins and Tsiatis will be applied to the overall survival analysis.

8.1.2. Analyses of Binary Data

The rates of binary endpoints for the two treatments will be tested with a 1-sided significance level of 0.1 using an exact test. The odds ratio and its 80% and 95% confidence intervals will be calculated. In addition, point estimates of the rates for each treatment arm will be provided along with the corresponding exact 2-sided 95% confidence intervals using the exact method based on Clopper-Pearson method, while the point estimate of the difference of the rates between treatment arm will be provided along with corresponding approximate 2-sided 95% confidence intervals based on normal distribution.

8.1.3. Analyses of Continuous Data

Descriptive statistics, including the n, mean, standard deviation, median, minimum, and maximum values, will be provided for continuous endpoints. Descriptive statistics for biomarkers will include %CV.

8.1.4. Analyses for Categorical Data

The number and percentage of patients in each category will be provided for categorical variables.

8.1.5. Analyses for QTc Data

8.1.5.1. Derived Analysis Variables

All ECGs will be recorded in triplicate i.e. three ECGs taken 2 minutes apart. ECG assessments reported by the site will include the following parameters:

ECG Parameter	Units	Abbreviation
QTc, Fridericia's correction	msec	QTcF
QTc, Bazett's correction	msec	QTcB
QT Interval	msec	QT
Heart Rate	bpm	HR
PR Interval	msec	PR
RR Interval	msec	RR
QRS Complex	msec	QRS

The following variables will be derived as follows:

ECG Parameter	Units	Abbrev.	Derivation
QTc, study specific correction	msec	QTcS	$= QT/(RR)^S$ (derivation of S is given in section 8.1.5.2.)

Averaging of triplicate measurements:

After the above variables have been derived within each patient and scheduled time-point, each ECG parameter (including QTcF, QTcB, QTcS, QT, HR, PR, RR, QRS) should each be averaged as follows: (1^{st} measurement + 2^{nd} measurement + 3^{rd} measurement) / 3. All summary statistics, analyses and figures will be based on the triplicate averaged data.

8.1.5.2. Derivation of Study Specific QT Correction Factor

The study specific QT correction factor (ICH E14 Step 4, May 12, 2005) will be derived. The dataset will consist of Screening and baseline assessments of QT and RR.

Prior to estimating the regression, QT and RR will be transformed by the natural logarithm to Ln(QT) and Ln(RR), respectively. Ln (RR) will be treated in the regression as the

explanatory variable with Ln (QT) as the response variable. The regression equation will be as follows:

$$\text{Ln(QT)} = \text{Intercept} + S \times \text{Ln(RR)} + \text{Error}$$

Where S = slope of the regression line.

Once (S) is estimated, it will be used to derive the study specific QT correction, QTcS.

8.1.5.3. Assessment of QT Correction Methods

This assessment will utilize only Screening and baseline triplicate averaged data ("Study drug-free" ECG data).

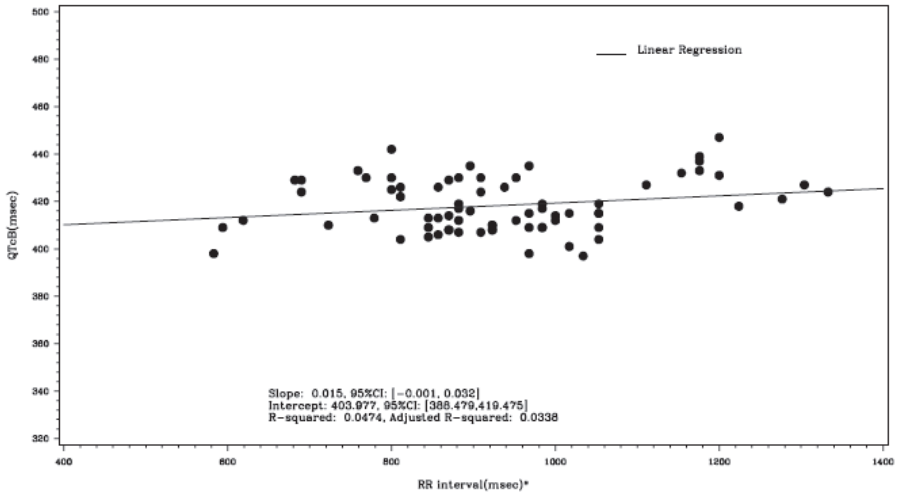
The relationship between QT/QTc and RR and the adequacy of each of the 3 QT correction methods will be assessed by the following scatterplots (see Figure 1):

- QT, QTcF, QTcB, and QTcS vs. RR

Interpretation of the scatterplots should give the following information:

- Variability of the QT/QTc relative to changing RR
- Slope or lack of slope and pattern to assess adequacy of QT correction method
- Apparent patterns in the data

Figure 1. A Sample scatterplot of relationship between QT/QTc and RR



8.1.5.4. Change from Baseline Definition

The change from baseline calculations for ECG measurements (abbreviated as "change") is derived from the triplicate averaged measurements. The baseline ECG assessment is defined as the triplicate ECG assessment taken pre-dose on Cycle 1 Day 1, or the most recent triplicate ECG assessment reported prior to the first administration of study drug. Change from baseline is defined as a patient's parameter value at a particular time-point minus the

appropriately matched baseline value (value - baseline value). Change from baseline calculations should only use post-dose ECG measurements.

8.1.5.5. Outlier Analysis

QT/QTc outlier values will be summarized and tabulated by the following CTCAE grade v.4.03.

Grade	1	2	3	4	5
Prolonged QTc interval	QTc 450 – 480 msec	QTc 481 – 500 msec	QTc ≥501 msec on at least two separate ECGs	QTc ≥501 or >60 msec change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Death

The change from baseline will summarize occurrences of shift by ≥ 1 grade by CTC. Individual QT and QTc values ≥501 msec from each ECG within a triplicate will be flagged in data listings.

In addition, the maximum QTc value for each patient can be categorized and summarized in the following cut-offs. All post dose QTc interval data should be used in determining the maximum for a patient, including all scheduled and unscheduled ECG's.

Absolute QTc interval prolongation
QTc < 450 msec
450 msec ≤ QTc ≤ 480 msec
481 msec ≤ QTc ≤ 500 msec
QTc ≥501 msec

The maximum increase from baseline QTc value for each patient by treatment will be categorized and summarized as well. For reporting the maximum increase QTc value the following categories: <30 msec, 30-59 msec and ≥60 msec will be used.

8.2. Statistical Analyses

All efficacy analyses will be conducted on intent-to-treat (ITT) population. Some efficacy analyses will also be performed on the AT populations, if appropriate. All analyses will be performed by using SAS® Version 9.4 or higher.

The analyses of endpoints dependent on disease assessments (PFS, OR, and DR) will be based on investigator assessments of disease response and progression.

All primary and secondary analyses will be tested at a significance level of 0.1 (1-sided test). No adjustments are planned for multiple testing/comparisons in the secondary hypothesis tests.

8.2.1. Primary Efficacy Analysis

OS will be summarized in the ITT population using the Kaplan-Meier methods and displayed graphically where appropriate. The median event time and 2-sided 95% and 80% confidence intervals for the median will be provided. A stratified (by ECOG) log-rank test will be used to compare OS between two treatment arms and the hazard ratio and its 80% and 95% confidence intervals will be estimated.
The survival probabilities at 4, 6, and 12 months will be provided with their 95% confidence intervals.

The log-rank (unstratified) test (1-sided, α=0.1) will be used to evaluate the primary efficacy endpoint, OS, in the ITT population. The same analysis may be used in AT populations.

Since patients in both treatment arms may receive other available treatments after disease progression, the treatment effect on overall survival may not be able to estimate properly by above defined methods because of these confounding factors. Therefore, the proper testing statistics such as a Wilcoxon test and RPSFTM may be applied to the overall survival analysis if the OS data cannot be evaluated properly by the log-rank test because of subsequent treatments after disease progression.

8.2.2. Secondary Analyses

PFS based on the assessment of investigator will be summarized in the ITT population using the Kaplan-Meier method and displayed graphically where appropriate. The median event time and corresponding 2-sided 95% confidence interval for the median will be provided for PFS. The hazard ratio and its 80% and 95% confidence intervals will be estimated. A stratified (by ECOG) log-rank test and a unstratified log-rank test (1-sided, α=0.1) will be used to compare PFS between the two treatment arms.

The number and proportion of patients achieving objective response (CR or PR) will be summarized in the ITT population along with the corresponding exact 2-sided 95% confidence interval calculated using a method based on Clopper-Pearson method. The CMH test stratified by ECOG and exact test will be used to compare ORR between two treatment arms.

The number and proportion of patients achieving disease control response (CR or PR or SD) will be summarized in the ITT population along with the corresponding exact 2-sided 95% confidence interval calculated using a method based on Clopper-Pearson method. The CMH test stratified by ECOG and exact test will be used to compare CBR between two treatment arms.

The number and proportion of patients achieving clinical benefit response (CR or PR or SD≥24 weeks) will be summarized in the ITT population along with the corresponding exact

2-sided 95% confidence interval calculated using a method based on Clopper-Pearson method. The CMH test stratified by ECOG and exact test will be used to compare CBR between two treatment arms.

DR will be summarized using the Kaplan-Meier methods and displayed graphically where appropriate. DR will be calculated for the subgroup of patients achieving objective disease response (CR or PR). The median event time and 2-sided 95% confidence interval for the median will be provided.

8.2.3. Sensitivity Analyses for PFS

The efficacy analysis on PFS is based on well-documented and verifiable progression events and deaths due to any cause. Other data are censored on the day following the date of the last tumor assessment documenting absence of progressive disease and death. In addition, several sensitivity analyses on the PFS will be performed in determining whether the main PFS analysis is robust.

Influence of additional anti-cancer therapy prior to disease progression or death -A sensitivity analysis will be performed by following patients until PD after discontinuation of the study treatment regardless the initiation of additional anti-cancer therapies. PFS data will be censored on the day of the last tumor assessment documenting absence of progressive disease or death for patients who

- Are removed from the study prior to documentation of objective tumor progression; or
- Remaining on study without PD or death at the time of the analysis.

Influence of Disease Assessment Scheduling - A sensitivity analysis will be performed to investigate whether deviations in disease assessment scheduling influenced the outcome of the primary endpoint PFS. If disease progression is documented between 2 scheduled tumor assessments, then the date of progression will be assigned to the earlier scheduled tumor assessment. In the event of death, the date of the endpoint will not be adjusted. Handling of missed disease assessments will be similar to that in the primary analysis except that any missed assessment will result in censoring.

Influence of Censoring for Patients Who Discontinued from Study due to Adverse Event or Systemic Deterioration – A sensitivity analysis will be performed to investigate whether the censoring for patients discontinued without PD due to adverse event or systemic deterioration of health. In this analysis, the patients who are censored in primary analysis will be counted as events.

In addition, the potential influences of the stratification factors (as listed in Section 6.4.2) and baseline patient characteristics such as age, gender, ethnic origin, ECOG performance status, geographical region, and selected biomarkers on the primary PFS endpoint will be evaluated.

8.2.4. Standard Analyses

Descriptive statistics will be used to summarize study conduct and patient disposition, baseline characteristics, and treatment administration/compliance.

- **Study Conduct and Patient Disposition** - an accounting of the study patients will be tabulated including randomized (per stratification factors), treated, accrual by study center, assessed for AEs, laboratory data, biomarkers, PK, and QTc, etc. Patients not meeting the eligibility criteria will be identified. Patients not completing the study will be listed along with the reason for their premature discontinuation. Reasons for premature discontinuation will be summarized. Randomization errors and stratification errors will be described.

- **Baseline Characteristics** - patient characteristics such as patient age, height, weight, gender, race, ethnicity, ECOG performance status, primary diagnosis, ER and HER2 status, prior therapy (radiotherapy, surgery, systemic therapy), baseline disease site, prior medication, medical history, and signs and symptoms at study entry will be summarized in frequency tables, and descriptive statistics will be provided for quantitative variables.
- **Treatment Administration and Compliance**

  - **Extent of Treatment**

    The extent of treatment will be summarized as follows:
    - The number and % of patients on treatment and off for each reason
    - Treatment assigned vs. actual received
    - The number and percent of patients beginning 1, 2, 3, 4, 5+ cycles of either study drug
    - The number of cycles started (median, minimum, maximum) will be reported (overall and by study treatment).
    - Duration of treatment (overall and by study treatment)
    - Cumulative dose and relative dose intensity (see Appendix 10.6 for details) (overall and by cycle; by study treatment)

  - **Treatment Delays and Dose Modifications**

    Treatment delays and dose modifications of study treatments will be summarized as follows including number and percent (see Appendix 10.6 for details):

    - The number of patients with at least one palbociclib or cetuximab dose reduction and the number of patients with at least one palbociclib or cetuximab dose omission at any time during drug administration will be reported.
    - The number of patients with at least one palbociclib or cetuximab dose reduction due to an adverse event will be reported.
    - The number of patients with at least one palbociclib dose (i.e. start of following cycle is delayed) or cetuximab dose delay (i.e. start of following dose is delayed) and percentage due to each reason for the delay will be reported

- **Concomitant medications and Non-drug treatments**

  Concomitant and non-drug treatments refer to all drug and non-drug treatments taken while on active treatment (during the effective duration of study treatment), whether or not they are recorded at baseline (i.e. have stop day greater than or equal to day 1 relative to first dose of study drug). Concomitant medication will be summarized in frequency tables by treatment.

- **Follow-Up Therapy**

  Follow-up cancer therapy will be summarized by treatment as patients with number of regimens (0, 1, 2, ≥3), and patients with particular agents.

8.2.5. Safety Analyses

Listings of AE, SAE, death, lab data, vital signs, and physical examinations will be provided according to reporting standard.

8.2.5.1. Adverse Events

All patients treated with at least one dose of study treatment (i.e. palbociclib/Placebo or cetuximab) will be included in all the safety analyses.

Adverse events will be classified using the medical dictionary for regulatory activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE v.4.03 whenever possible (http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an adverse event or a group of adverse events. Except for selected events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation. The 3-tier approach facilitates this exploratory analysis.

Adverse events will be summarized by treatment and by the frequency of patients experiencing treatment emergent adverse events corresponding to body systems and MedDRA preferred term. Adverse events will be graded by worst NCI CTCAE v.4.03 grade. Adverse events will be summarized by cycle and by relatedness to trial treatment. Detailed information collected for each AE will include a description of the event, duration, whether the AE was serious, intensity, relationship to study drug, action taken, and clinical outcome. Emphasis in the analysis will be placed on AEs classified as treatment emergent.

Adverse events leading to death or discontinuation of trial treatment, events classified as NCI CTCAE v.4.03s Grade 3 or higher, trial drug related events, and serious adverse events will be considered with special attention.

The percentage of patients with an event will be calculated using the number of patients in the as-treated population as the denominator. The denominator for summary tables for each laboratory parameter will be all patients in the as-treated population with at least one evaluable cycle for that parameter.

- For Tier-1 events, the MedDRA preferred term, treatment arm, n (%) for each MedDRA preferred term per arm, risk difference, 95% confidence interval and P-values for the risk difference will be provided. Graphical format may be presented as well. Presented in descending p-value order.

- For Tier-2 events, the MedDRA preferred term, treatment arm, n (%) for each MedDRA preferred term per treatment arm, risk difference and 95% confidence intervals for the risk difference will be provided in tabular format. Table by AE for All Grade and for Grade 3/4/5 will be provided. Graphical format may be presented as well. Presented in descending risk difference order.

- Tier-3 events will be presented by observed event proportions. The following will be provided:

    - Incidence and grades of treatment emergent (all causality, preferred term, and by System Organ Class) AEs for all cycles combined.

    - Incidence and grades of treatment emergent (all causality, preferred term) AEs for all cycles combined in descending frequency order.

    - Incidence and grades of treatment emergent (treatment related, preferred term and by System Organ Class) AEs for all cycles combined.

    - Incidence and grades of treatment emergent (treatment related, preferred term) AEs for all cycles combined in descending frequency order.

- Disease progression will not be included

- There will be no adjustment for multiplicity

The following summaries of treatment emergent adverse events will also be provided by arm:

- Discontinuations Due to Adverse Events including causality: all cause, treatment related, including relationship to specific study treatment of cetuximab, palbociclib, and placebo

- Temporary Discontinuations or Dose Reductions Due to Adverse Events including causality and relationship to specific study treatment of cetuximab, palbociclib, and placebo

- Treatment-Emergent Adverse Events (All Causality, and Treatment Related) including the number of patients evaluable for adverse events, total number of

adverse events (counting each unique preferred term across all patients), number of patients with serious adverse events, number of patients with Grades 3 and 4 adverse events, number of patients with Grade 5 adverse events, and number with dose reductions or temporary discontinuations due to adverse events

- Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term and Maximum NCI CTCAE v.4.03 Grade (All Causality, and Treatment related)

- Treatment-Emergent Adverse Events by MedDRA Preferred Term sorted by Descending Order of AE Frequency (All Causality, and Treatment related)

- Treatment-Emergent Adverse Events by Preferred Term – Grade 3/4/5 events with number of patients experienced Grade 3-5 AEs and total number of Grade 3-5 AEs, sorted by Descending Order of AE Frequency (All Causality, and Treatment Related)

A summary of Serious Adverse Events and listing of deaths reported as serious adverse events will be provided.

8.2.5.2. Laboratory abnormalities

Hematologic, chemistry and urinalysis laboratory data will be summarized by cycle. The hematologic and chemistry laboratory results will be graded according to the NCI CTCAE v.4.03 severity grade. For parameters for which an NCI CTCAE v.4.03 scale does not exist, the frequency of patients with values below, within, and above the normal range for the local lab will be summarized. Each patient will be summarized by the worst severity grade observed for a particular laboratory parameter. This will be provided for all cycles as well as by cycles.

8.2.6. QTc Analyses

All ECGs obtained during the study will be evaluated for safety. 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 population, individual change in QTc (QTcF, QTcB, QTc S) will be calculated for each nominal post-baseline time point. These individual changes will be summarized using descriptive statistics.

For all patients in the safety analysis population, categorical analysis of the QTcF/QTcB/QTcS data will be conducted and summarized as follows:

1. QT/QTc outlier values will be summarized and tabulated by the following CTCAE grade v.4.03 according to 8.1.6.7.

2. The change from baseline will summarize occurrences of shift by ≥ 1 grade by CTC.

3. Individual QT and QTc values ≥501 msec from each ECG within a triplicate will be flagged in data listings.

4. The number of and percentage patients with maximum post-dose QTcF/QTcB/QTcS (<450, 450-480, 481-500, and ≥501 ms), including all scheduled and unscheduled ECG's.

5. The number and percentage of patients with maximum increase from baseline in QTcF/QTcB/QTcS (<30, 30- 60, and > 60 ms), including all scheduled and unscheduled ECG's.

6. PR changes from baseline ≥ 50% if absolute baseline value was < 200 ms, and ≥ 25% if absolute baseline value was > 200 ms.

7. QRS changes from baseline ≥ 50% if absolute baseline value was < 100 ms, and ≥ 25% if absolute baseline value was > 100 ms.

8. The number and percentage of individuals with abnormal ECG findings.

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[redacted]

8.2.8. Biomarkers Analyses

Biomarkers will be assessed separately from [redacted] archival tumor tissue [redacted] In each case, summaries of baseline levels, ratio to baseline (where appropriate), expression and mutation will be reported, by treatment group and combined. 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. Statistical analyses comparing treatment groups will be performed using the appropriate method (exact Wilcoxon Rank Sum test for continuous variables, Fisher's exact test or Wilcoxon signed rank for discrete variables.) Cox proportional hazard methods for biomarkers included as covariates to predict PFS/OS, or K-M analysis split ≥ or < median biomarker value (for continuous biomarkers) or presence/absence (for discrete biomarkers) may be performed, following the methods described in Section 8.2.1.

For p16 and Rb expression in the palbociclib and cetuximab treatment group, the relationship of the biomarkers (individually) with PFS and OS will be explored using graphical methods such as box plots, at baseline. [redacted]

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[redacted]

8.2.9. Patient Reported Outcomes Analyses

The primary analysis set for the PRO endpoints will be the ITT population. Change from baseline analyses will be performed on the PRO evaluable population as appropriate.

The PRO analysis endpoints will be based on the instruments QLQ-C30 and QLQ-H&N35. For each treatment group and at each time point, the number and percentage of patients who completed these instruments will be summarized, as will the reasons for non-completion of these measures. An instrument is considered completed if at least one item was answered by the patient.

For each endpoint a completion status table will be provided showing the numbers and percentages of patients at each visit and the numbers and percentages of patients at that visit who completed none, at least one, or all of the items for that endpoint. Post treatment discontinuation observation will be excluded from primary analyses set and only included in pre-specified sensitivities or post hoc analyses.

8.2.9.1. EORTC QLQ-C30

This questionnaire contains 30 questions organized into 5 multi-item functional scales, 3 multi-item symptom scales, a global quality of life scale, and 6 single item symptom scales. For each of the 15 scales, the results will be summarized using means (and standard deviation), 95% confidence interval, and medians (and range) for each treatment group at each time point. This will be done based on the observed values as well as changes from baseline where both within group and between group differences will be displayed.

For each of the 15 scales, statistical comparison between the two treatment groups will be based on a longitudinal repeated measures analysis using a mixed effects model for observed scores and change from baseline scores controlling for baseline. The variables in the model will be treatment, time, treatment-by-time, with baseline used as a covariate. Parameter estimates will be based on a restricted maximum likelihood method and an unstructured covariance matrix will be used. Should convergence not be obtained with the unstructured covariance matrix, other structures can be considered. No adjustments for multiple comparisons will be made.

For each of the 15 scales, a graphical display of means over time as well as mean changes from baseline over time will also be provided.

8.2.9.2. EORTC QLQ-H&N35

This questionnaire contains 35 questions organized into 7 multi-item scales and 11 single-item scales. As with C30, the analysis of the H&N35 scales will consist of descriptive statistics on observed and changes from baseline scores, and a between treatment comparison using a longitudinal mixed effects model. Also, as with C30, graphical displays of means and changes from baseline over time will also be provided for each H&N35 scale.

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8.3. Summary of Key Clinical Efficacy Analyses

Type of Analysis	Endpoint	Analysis Set	Statistical Method
Primary	OS	ITT (See 8.2.1)	Stratified log-rank test (stratified by ECOG) (1-sided, α=0.1), K-M method (median and 95% CI) HR, 80% and 95% CI from the Cox model
Secondary	OS	ITT (See 8.2.1)	Unstratified Log-rank test (1-sided, α=0.1), K-M method (median and 95% CI) HR, 80% and 95% CI from the Cox model Wilcoxon test RPSFT method Survival probability at 4, 6, and 12 months
Secondary	OS	AT (See 8.2.1)	Unstratified Log-rank test (1-sided, α=0.1), K-M method (median and 95% CI) HR, 80% and 95% CI from the Cox model
Secondary	PFS	ITT Investigator assessment (See 8.2.2)	Stratified log-rank test (stratified by ECOG) and Unstratified Log-rank test (1-sided, α=0.1), K-M method (median and 95% CI) HR, 80% and 95% CI from the Cox model
Secondary *Sensitivity analysis 1- 3*	PFS	ITT Investigator assessment (See 8.2.3)	Unstratified Log-rank test K-M method (median and 95% CI) HR, 80% and 95% CI from the Cox model
Secondary	OR	ITT Investigator assessment (See 8.2.2)	CMH Stratified by ECOG and Exact test Exact CI based on Clopper-Pearson method (95% CI)
Secondary	CBR	ITT Investigator assessment (See 8.2.2)	CMH Stratified by ECOG and Exact test Exact CI based on Clopper-Pearson method (95% CI)
Secondary	DR	ITT patients with a CR or PR Investigator assessments (See 8.2.2)	K-M method (median and 95% CI)

Abbreviations:
ITT: intent-to-treat; At: as-treated
DR: duration of response; OR: objective response; OS: overall survival; PFS: progression-free survival.

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10. APPENDICES

10.1. Schedule of Activities

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

Visit Identifier	**Screening**	**Active Treatment Phase**[Error! Reference source not found.] **(One Cycle = 28 days)**			**End of Treatment / Withdrawal**[Error! Reference source not found.]	**4 weeks Post-Treatment**	**8 weeks Post-Treatment**	**Post-Treatment Follow-Up**[Error! Reference source not found.]
		Cycles 1 and 2[Error! Reference source not found.]		**Cycles ≥3**				
Study Day	**Within 28 days prior to randomization unless specified otherwise**	**Day 1**[Error! Reference source not found.]	**Day 15**	**Day 1**[Error! Reference source not found.]				
Time Window		**±3d**	**±3d**	**±3d**		**±7d**	**±7d**	**±7d**
Baseline Documentation								
Informed Consent Process[Error! Reference source not found.]	X							
Medical / Oncological History[Error! Reference source not found.]	X							
Baseline Signs / Symptoms[Error! Reference source not found.]		X						
Human Papillomavirus (HPV)-status analysis[Error! Reference source not found.]	X							
Physical Examination/Vital signs[Error! Reference source not found.]	X	X[Error! Reference source not found.]		X	X			
Serum Pregnancy Test[Error! Reference source not found.]	X	X		X	X			
ECOG Performance Status	X	X		X	X			
Laboratory Studies								
Hematology[Error! Reference source not found.]	X	X[Error! Reference source not found.]	X	X	X			
Blood Chemistry[Error! Reference source not found., Error! Reference source not found.]	X	X[Error! Reference source not found., Error! Reference source not found.]	X	X	X		X	

Visit Identifier	**Screening**	**Active Treatment Phase** Error! Reference source not found. **(One Cycle = 28 days)**			**End of Treatment / Withdrawal** Error! Reference source not found.	**4 weeks Post-Treatment**	**8 weeks Post-Treatment**	**Post-Treatment Follow-Up** Error! Reference source not found.
		Cycles 1 and 2 Error! Reference source not found.		**Cycles ≥3**				
Study Day	**Within 28 days prior to randomization unless specified otherwise**	**Day 1** Error! Reference source not found.	**Day 15**	**Day 1** Error! Reference source not found.				
Time Window		**±3d**	**±3d**	**±3d**		**±7d**	**±7d**	**±7d**
Coagulation **Error! Reference source not found.**	X	X Error! Reference source not found.	X	X	X			
Urinalysis Error! Reference source not found.	X	X Error! Reference source not found.	X	X	X			
12-Lead ECG (in triplicate) **Error! Reference source not found.**	X	X Error! Reference source not found. (C1 only)	X	X (C4, C7, C10)	X			

Visit Identifier	**Screening**	**Active Treatment Phase**[Error! Reference source not found.] **(One Cycle = 28 days)**			**End of Treatment / Withdrawal**[Error! Reference source not found.]	**4 weeks Post-Treatment**	**8 weeks Post-Treatment**	**Post-Treatment Follow-Up**[Error! Reference source not found.]
		Cycles 1 and 2[Error! Reference source not found.]		**Cycles ≥3**				
Study Day	**Within 28 days prior to randomization unless specified otherwise**	**Day 1**[Error! Reference source not found.]	**Day 15**	**Day 1**[Error! Reference source not found.]				
Time Window		**±3d**	**±3d**	**±3d**		**±7d**	**±7d**	**±7d**
Special Laboratory Studies								
CCI [redacted]			[redacted]					
[redacted]	[redacted]				[redacted]			
Archival Tumor Tissue Specimen[Error! Reference source not found.]	X							
De Novo Tumor Specimens[Error! Reference source not found.]	X		X		X			
Blood Sample for Thymidine Kinase Assessments[Error! Reference source not found.]		$X_{(C1\ only)}$	$X_{(C1\ only)}$	$X_{(C3\ only)}$	X			
CCI [redacted]		[redacted]		[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[Error! Reference source not found.]	X	◄--► Performed every 8 weeks (±7 days) from the date of randomization			X			X

Visit Identifier	**Screening**	**Active Treatment Phase**[Error! Reference source not found.] **(One Cycle = 28 days)**			**End of Treatment / Withdrawal**[Error! Reference source not found.]	**4 weeks Post-Treatment**	**8 weeks Post-Treatment**	**Post-Treatment Follow-Up**[Error! Reference source not found.]
		Cycles 1 and 2[Error! Reference source not found.]		**Cycles ≥3**				
Study Day	**Within 28 days prior to randomization unless specified otherwise**	**Day 1**[Error! Reference source not found.]	**Day 15**	**Day 1**[Error! Reference source not found.]				
Time Window		**±3d**	**±3d**	**±3d**		**±7d**	**±7d**	**±7d**
	Other Clinical Assessments							
Drug Compliance[Error! Reference source not found.]		◄--►						
Adverse Event (AE) Reporting[Error! Reference source not found.]	X	X	X	X	X	X	X	X
Review Concomitant Medications/Treatments[Error! Reference source not found.]	X	X	X	X	X			
Quality of Life Questionnaire (EORTC-QLQ-C30 and EORTC-QLQ-H&N35) [Error! Reference source not found.]		X		X	X	X		
Survival Follow-up								X

Visit Identifier	Screening	Active Treatment Phase[Error! Reference source not found.] (One Cycle = 28 days)			End of Treatment / Withdrawal[Error! Reference source not found.]	4 weeks Post-Treatment	8 weeks Post-Treatment	Post-Treatment Follow-Up[Error! Reference source not found.]
		Cycles 1 and 2[Error! Reference source not found.]		Cycles ≥3				
Study Day	**Within 28 days prior to randomization unless specified otherwise**	**Day 1**[Error! Reference source not found.]	**Day 15**	**Day 1**[Error! Reference source not found.]				
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 ; 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

a. **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.
b. **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.
c. **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, 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.
d. **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.
e. **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.
f. **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.
g. **Medical/Oncological History:** To include information on prior anticancer treatments.
h. **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 occassions 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 **Error! Reference source not found.** 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, 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.
o. **12-Lead ECG**: All ECGs should be obtained after a fast of at lease 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 timpoints to determine the mean QTc interval.

[redacted]

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.

t. **Blood Sample for Thymidine Kinase Assessments**: 6 ml blood specimen optimized for serum preparation for TK activity assessment will be collected at C1D1 (pre dose), C1D15 (pre-dose), C3D1 (pre-dose) and at End of Treatment. Details for handling of these specimens including processing, storage, and shipment will be provided in the Study Manual.

u. **Blood Sample for CNA Profiling**: 10 ml blood specimen optimized for plasma preparation for nucleic acid analysis will be collected at C1D1 (pre dose), C3D1 (pre-dose) and at End of Treatment. Details for handling of these specimens including processing, storage, and shipment will be provided in the Study Manual.

v. **Disease Assessments:** Please refer to the

w. Tumor Assessment Requirements for details and timing of procedures.
x. **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.
y. **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.
z. **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.
aa. **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 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.

10.2. 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, f]	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.

10.3. 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 (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

OBJECTIVE 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 (e.g., 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 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	SD
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 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

* New lesions must be unequivocal

BOR Based on Unconfirmed Objective Status

Unconfirmed CR (uCR): One objective status of CR documented before progression or start of new anti-cancer therapy.

Unconfirmed PR (uPR): One objective status of PR documented before progression and start of new anti-cancer therapy, but not qualifying as uCR.

SD: At least one objective status of SD or better documented at least X (>=12) weeks after start date and before progression and the start of new anti-cancer therapy but not qualifying as uCR or uPR.

PD: Progression documented within Z (<=12) weeks after start date and not qualifying as uCR, uPR or SD.

NE: All other cases. Note that reasons for NE should be summarized and the following reasons could be used:

- Early death (*Note: death prior to X (<12) weeks after start date)*
- No post-baseline assessments
- All post-baseline assessments have overall response NE
- New anti-cancer therapy started before first post-baseline assessment
- SD too early (<X (12)) weeks after start date)
- PD too late (>Z (12) weeks after start date)

  Special and rare cases where BOR is NE due to both early SD and late PD will be classified as 'SD too early'.

An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases by less than 20% from the nadir, but enough that a previously documented 30% decrease from baseline no longer holds.

10.4. Rules for Determining PFS Status and Date

Situation	Date of Progression/Censoring[1]	Outcome
Inadequate baseline assessment	Randomization date (Day 1)	Censored
No on-study assessments	Randomization date (Day 1)	Censored
Alive and no Progression	Date of last objective tumor assessment documenting no progression	Censored
Progression Documented on or between scheduled tumor assessments	Date of first objective tumor assessment documenting objective progression	Progressed (Event)
Patients are removed from the study (withdrew the consent, lost to follow up, etc.) prior to progression or death	Date of last objective tumor assessment documenting no progression	Censored
New anticancer treatment prior to progression or death	Date of last objective tumor assessment documenting no progression prior to new anticancer treatment	Censored
Death prior to first planned tumor assessment	Date of death	Death (Event)
Death without objective progression prior to treatment discontinuation[2]	Date of death	Death (Event)
Death or progression after 2 or more missed tumor assessments	Date of last objective tumor assessment documenting no progression prior to the event	Censored

[1] For date of censorship, if a tumor assessment takes place over a number of days (e.g., superficial lesions one day, scans another), the last date is used as the assessment date.

10.5. Data Derivation Details

Enrollment/Randomization	Date of assignment of the randomization number
Study Day 1	Randomization day
Study Day (At/Post randomization date)	Assessment Date – randomization Date +1
Study Day (Prior randomization date)	Assessment Date – randomization date
Treatment Day 1	1st Dose date
Treatment Day (At/Post 1st dose date)	Assessment Date – 1st Dose Date +1
Treatment Day (Prior 1st dose date)	Assessment Date – 1st dose date
Treatment start	Day 1 of Cycle 1
Day 1 (cycle start date) of Cycle x	Day 1 of a cycle is every 28 days unless there is a dosing delay.
Cycle length (all but final cycle)	Cycle length is 28 days (previous cycle length may exceed planned length if there is a delay in study treatment administration).
Final cycle	For patients off treatment, from Day 1 of final cycle to 28 days after final dose or until start of new anticancer treatment (whichever comes first). For patients on treatment, from Day 1 of most recent cycle start to protocol specified cycle length.
Follow-up Period for AEs	From 28 days after final dose until start of new anticancer treatment (whichever comes first).
Baseline lab values	From date closest to, but prior to, start of study treatment.
Baseline triplicate ECGs	Cycle 1 Day 1 dose or from date closest to, but prior to, start of study treatment if C1D1 is not available.
Tumor assessment baseline values	From date closest but prior to first dose.
Adequate baseline tumor assessment	Within 35 (28 + 7) days prior to first dose. Maximum diameter reported for each target lesion listed. All required pre-treatment scans done.
Cycle k treatment delayed.	If study treatment administration is delayed for cycle k then cycle k-1 is extended.

10.6. Study Treatment Modification and Compliance

10.6.1. Dose Modification

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.

10.6.2. Summarizing Relative Dose Intensity (RDI)

The following types of summaries are proposed for administration of palbociclib and cetuximab.

When palbociclib is administered orally once a day for 21 days of every 28-day cycle followed by 7 days off treatment (cyclical dosing) in combination with cetuximab (IV), the following summaries can be presented:

- RDI for palbociclib: by Cycle and Overall
- RDI for cetuximab: by Cycle and Overall

Note: the denominator for tables summarizing "cetuximab" will be all patients who received at least one dose of cetuximab and for tables summarizing "palbociclib" will be all patients who took at least one dose of palbociclib.

Examples for the summaries described in above are included in the tables below.

Conventions:

- The Intended Dose Intensity is the same for all cycles: the daily dose is fixed at the start of treatment rather than start of a cycle and the intended treatment duration is the same for the entire dosing period, including last cycle (e.g. for a 3/1 dosing schedule, all cycles have an intended duration of 4 weeks);
- Actual Dose Intensity is calculated based on actual cycle length in all but last cycle where it is fixed at the intended length (e.g. 4 weeks for a 3/1 dosing schedule)

Table 1

Treatment/ Summary Type	Calculation of Relative Dose Intensity (RDI)
Palbociclib or Placebo / By Cycle	$RDI = \frac{ActualDailyDoseIntensity}{IntendedDailyDose} * 100$ %Where: ***Intended Daily Dose*** (mg/day in 21/7 schedule) = 125 ***Actual Daily Dose Intensity*** (mg/day in 21/7 schedule) = Actual Average Daily Dose (mg/day in x/y schedule) * (Actual Dose Days / Intended Dose Days) * (Intended Cycle Duration / Actual Cycle Duration) • Actual Average Daily Dose (mg/day in x/y schedule) = Actual Total Dose / Actual Dose Days • Intended Dose Days = For non-last cycle: 21 For last cycle: minimum (21, Actual Cycle Duration) • Intended Cycle Duration = For non-last cycle: 28 For last cycle: minimum (28, Actual Cycle Duration)
Palbociclib or Placebo / Overall	$RDI = \frac{ActualDailyDoseIntensity}{IntendedDailyDose} * 100$ % Where: ***Intended Daily Dose*** (mg/day in 21/7 schedule) = 125 ***Actual Daily Dose Intensity*** (mg/day in 21/7 schedule) = Actual Average Daily Dose (mg/day in x/y schedule) * (Actual Dose Days / Intended Dose Days) * (Intended Cycle Duration / Actual Cycle Duration) • Actual Average Daily Dose (mg/day in x/y schedule) = Sum over all cycles of "Actual Total Dose" / Sum over all cycles of "Actual Dose Days" • Intended Dose Days = Sum over all cycles of "Intended Dose Days" • Intended Cycle Duration = Sum over all cycles of "Intended Cycle Duration"

Treatment/ Summary Type	Calculation of Relative Dose Intensity (RDI)
Cetuximab / By Cycle *Possible dose reductions or potential overdose, and dose interruptions*	$RDI = \frac{ActualAverageDoseIntensity}{IntendedAverageDose} * 100\ \%$ Where: ***Intended Average Dose*** ((mg/sqm)/Q7d) = $\begin{cases} 400 & \text{for Cycle 1 Week 1} \\ 250 & \text{All cycles, exc C1W1} \end{cases}$ ActualAverageDoseIntensity = Actual Average Dose ((mg/sqm)/Qxd) in the Cycle **Factor in dose interruptions:* • *Factor in dose reductions or potential overdose:* Actual Average Dose ((mg/sqm)/Qxd) in the Cycle = Actual Total Dose in the Cycle / Actual Freq of Qxd in the Cycle • *Factor in dose interruptions:* *For Last Cycle:* Actual Freq of Qxd in the Cycle / CEIL (Actual Cycle Duration in the Cycle/ 7) *ForC1W1:* 1 / (Actual Cycle Duration of C1W1 in the Cycle/ 7) *For Cycle 1 (exclude C1W1):* 'Actual Freq of Qxd in the Cycle 1 – 1 (exclude C1W1) / (Actual Cycle Duration - actual duration of C1W1) in the Cycle/ 7) *For other Cycles:* Actual Freq of Qxd in the Cycle / (Actual Cycle Duration in the Cycle/ 7)

Cetuximab / Overall *Possible dose reductions or potential overdose, and dose interruptions* ***Footnote: Overall column for 'Overall Actual Average Dose, Overall Intended Average Dose, Overall Actual Dose Intensity, and RDI are excluding C1W1***	$RDI = \frac{ActualAverageDoseIntensity}{IntendedAverageDose} * 100\ \%$ ***Overall Intended Average Dose*** ((mg/sqm)/Q7d) = 400 – for C1W1 250 – for all other cycle's overall ***Overall Actual Dose Intensity*** ((mg/sqm)/Q7d) = Overall Actual Average Dose (mg/Qxd) * [Overall Actual Freq of Qxd -1] / [CEIL(Overall Actual Cycle Duration / 7) - 1] } • *Factor in dose reductions or potential overdose:* Overall Actual Average Dose ((mg/sqm)/Qxd) (exclude C1W1) = [Overall Actual Total Dose - Actual dose of C1W1 *(Note: Exclude C1W1)*] / [Overall Actual Freq of Qxd - 1*(Note: Exclude C1W1)*] • *Factor in dose interruptions:* [Overall Actual Freq of Qxd - 1 *(Note: Exclude C1W1)*] / [CEIL(Overall Actual Cycle Duration) / 7) – 1] • O. Actual Freq of Qxd = Sum over all cycles of "Actual Freq of Qxd" • O. Actual Cycle Duration = Sum over all cycles of "Actual Cycle Duration"
Cetuximab (Q7d) / Overall – RDI (Include C1W1)	$RDI = \frac{OverallActualTotalDose}{400 + [CEIL(OverallActualCycleTotalDuration / 7) - 1] * 250} * 100$ %

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

EORTC QLQ-C30 (version 3)

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

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

10.8. 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

10.9. List of Abbreviation

Abbreviation	Term
AE	Adverse Event
ALT	Alanine Aminotransfersae
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransfersae
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	[redacted]
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 Section 10.1. 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
$t_{½}$	Terminal Elimination Half-life
TdP	Torsade de Pointes
CC	[redacted]
T_{max}	Time for C_{max}
CCI	[redacted]
ULN	Upper Limit of Normal
US	United States
v	version
WBC	White Blood Cells