CLINICAL STUDY REPORT SYNOPSIS

Sponsor: Pfizer Inc

Investigational Product: Palbociclib (PD-0332991)

Clinical Study Report Synopsis: Protocol A5481044

Protocol Title: 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

Investigators: [redacted]

Study Centers: The study was conducted at 48 centers in Czech Republic, Hungary, Italy, Japan, Republic of Korea, Mexico, Poland, Romania, Russian Federation, Serbia, Slovakia, Spain, Taiwan, Ukraine, and United States. [redacted]

Publications Based on the Study: None

Study Initiation and Completion Dates: First Patient First Visit (FPFV): 10 September 2015; Primary Completion Date: 19 July 2018; Last Patient Last Visit (LPLV): Ongoing.

Report Date: 05 February 2019

Previous Report Date(s): Not applicable

Phase of Development: Phase 2

Study Objectives: The primary objective of the study was to demonstrate that the combination of palbociclib with cetuximab was superior to cetuximab in prolonging overall survival (OS) in human papillomavirus (HPV)-negative, cetuximab-naïve patients with recurrent/metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) in whom 1 prior platinum-containing chemotherapy had failed.

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

[redacted]

CLINICAL STUDY REPORT SYNOPSIS

[redacted]

METHODS

Study Design: This was 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 1 platinum-containing regimen. Approximately 120 patients were to be randomized 1:1 between the investigational arm (Arm A: palbociclib + cetuximab) and the comparator arm (Arm B: placebo + cetuximab). Crossover between treatment arms was prohibited. Patients randomized to Arm A (investigational arm) received oral palbociclib 125 mg 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) received oral placebo 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.

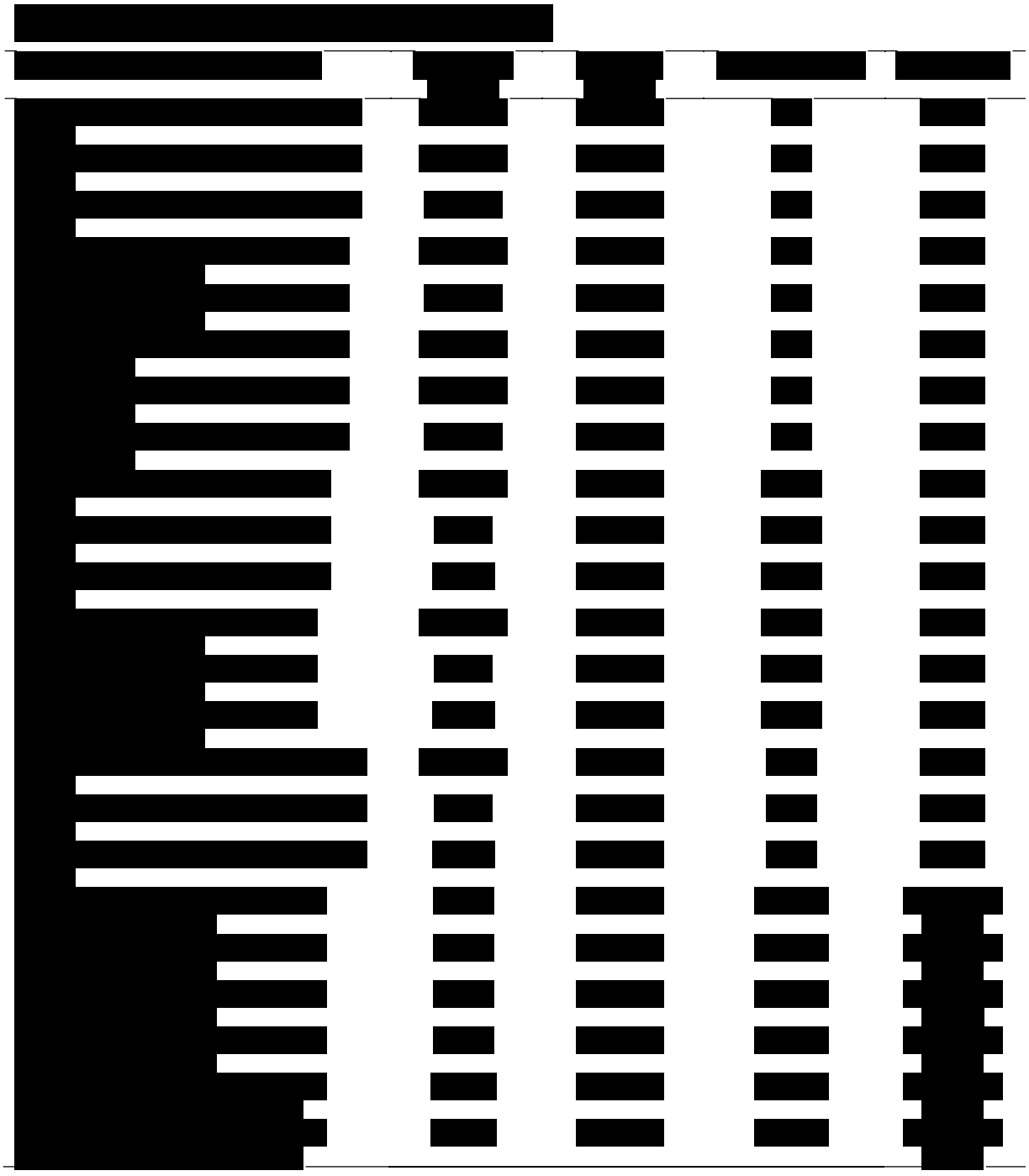
Diagnosis and Main Criteria for Inclusion: Confirmed HPV-negative SCCHN tumor of the oral cavity, oropharynx, hypopharynx or larynx, not amenable for salvage surgery or radiotherapy with measurable disease and documented progressive disease (PD) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 following receipt of at least 2 cycles of 1 platinum-containing chemotherapy regimen administered for R/M disease (minimum 50 mg/m^2 for cisplatin, minimum area under the curve [AUC] >4 for carboplatin). No prior nasopharyngeal cancer, salivary gland or sinus tumors. No prior use of cetuximab in the R/M disease treatment setting and any CDK4/6 or epidermal growth factor receptor (EGFR) inhibitor (except cetuximab during curative radiotherapy).

Study Treatment: [redacted] Palbociclib was supplied as capsules containing 75 mg, 100 mg, or 125 mg equivalents of palbociclib free base. The sponsor supplied the oral drug formulation to sites in high-density polyethylene (HDPE) bottles containing 75 mg, 100 mg, or 125 mg capsules. The capsules could be differentiated by their size and color.

Placebos for palbociclib were indistinguishable from the palbociclib capsules and were supplied as capsules matching in size and color the various palbociclib formulations. The sponsor supplied placebo to sites in HDPE bottles.

CLINICAL STUDY REPORT SYNOPSIS

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



CLINICAL STUDY REPORT SYNOPSIS

Efficacy Evaluations: The primary efficacy endpoint was OS. Following the End of Treatment visit, survival status was collected in all patients every 2 months (±7 days) from the last dose of study treatment. Secondary efficacy endpoints included progression-free survival (PFS), objective response (OR), clinical benefit response (CBR) and duration of response (DR), according to RECIST version 1.1, as assessed by investigator.

Pharmacokinetic, Biomarker, and Patient Reported Outcomes Evaluations:

Pharmacokinetics

Plasma PK samples (3 mL venous dipotassium ethylenediamine tetraacetic acid [K_2EDTA] blood) for palbociclib determination were to be collected prior to dosing (pre-dose) on Cycle 1 Day 15 (C1D15) and C2D15. Palbociclib samples were assayed using a validated, sensitive and specific high-performance liquid chromatography tandem mass spectrometric (LC-MS/MS) method.

Serum PK samples (3 mL venous blood samples were collected into appropriately labeled tubes containing no additives) for cetuximab determination were to be collected prior to IV infusion (pre-dose) and immediately prior to completion of the IV infusion (post-dose) on C1D15 and C2D15. Cetuximab samples were assayed using a validated, sensitive and specific enzyme-linked immunosorbent (ELISA) method.

Biomarkers

All patients had to provide a formalin-fixed paraffin embedded (FFPE) archival tumor specimen at Screening, specifically a FFPE tissue block that contained sufficient tissue to generate at least 15 unstained slides, each with tissue sections that were 5 microns thick, or at least 15 unbaked glass slides, each containing an unstained 5 micron FFPE tissue section if FFPE tissue block could not be submitted. Archival or de novo FFPE tumor tissue samples were used for biomarker analyses (Rb, p16 [redacted]) by immunohistochemistry (IHC).

[redacted] The detailed methods corresponding to biomarker analysis are going to be included in the supplemental clinical study report (CSR).

CLINICAL STUDY REPORT SYNOPSIS

Optional de novo tumor biopsy collected at Screening, C1D15 or C2D15 (pre-dose, 1 time point only) and at the time of progression/End of Treatment was strongly encouraged; no more than 3 time points were collected in total. In all cases, these specimens were provided in addition to the archival tumor tissue specimen that was required for enrollment.

Patient Reported Outcomes

Patient reported global quality of life (QOL), functioning and disease/treatment related symptoms were assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30), and European Organization for Research and Treatment of Cancer Head and Neck Module 35 (EORTC QLQ-H&N35) instruments. Patients completed each instrument at pre-dose on Day 1 of Cycles 1-3, then on Day 1 of every other subsequent Cycle starting with Cycle 5 (eg, Cycles 5, 7, 9, etc), and then at the End of Treatment visit. Four (4) weeks after discontinuation of study treatment due to PD, patients, including patients starting post-study anti-cancer therapy, were completing the questionnaires at the Follow-up Visit.

Safety Evaluations: Safety evaluations included clinical monitoring, adverse events (AEs), safety laboratory tests, 12-lead electrocardiograms (ECGs), vital signs (heart rate, blood pressure [BP]), physical examination, and Eastern Cooperative Oncology Group (ECOG) performances.

Statistical Methods:

Efficacy Analysis

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

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

Primary Efficacy Analysis

OS was defined as the time from the date of randomization to the date of death due to any cause. OS (in months) was 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 was censored on the last date they were known to be alive. Patients lacking survival data beyond randomization had their OS times be censored at randomization. Following the End of

CLINICAL STUDY REPORT SYNOPSIS

Treatment visit, survival status was collected in all patients every 2 months (±7 days) from the last dose of study treatment. Information on subsequent anti-cancer therapy was also collected.

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

The log-rank (unstratified) test (1-sided, $\alpha = 0.1$) was used to evaluate the primary efficacy endpoint, OS, in the ITT population as well. The same analysis could be used in AT populations.

Secondary Efficacy Analyses

PFS was defined as the time from the date of randomization to the date of the first documentation of objective tumor progression as per RECIST version 1.1 or death due to any cause in the absence of documented PD, whichever occurred first. If tumor progression data included more than 1 date, the first date was used. PFS (in months) was calculated as (first event date − randomization date +1)/30.4.

PFS based on the assessment of investigators was summarized in the ITT population using the Kaplan-Meier method. The median event time and corresponding 2-sided 95% CI for the median were provided for PFS. The HR and its 80% and 95% CIs were estimated. A stratified (by ECOG) log-rank test and an unstratified log-rank test (1-sided, $\alpha = 0.1$) was used to compare PFS between the 2 treatment arms.

OR was defined as the overall complete response (CR) or partial response (PR) according to the RECIST version 1.1. Objective response rate (ORR) was defined as the proportion of patients with best overall response (BOR) of CR or PR relative to all randomized.

The number and proportion of patients achieving objective response (CR or PR) were summarized in the ITT population along with the corresponding exact 2-sided 95% CI calculated using a method based on Clopper-Pearson method. The Cochran-Mantel-Haenszel (CMH) test stratified by ECOG and exact test was used to compare OR between the 2 treatment arms.

CBR was defined as the overall CR, PR, or stable disease ≥24 weeks according to the RECIST version 1.1. Clinical benefit response rate (CBRR) was defined as the proportion of patients with CR, PR, or stable disease ≥24 weeks relative to all randomized patients and randomized patients with measurable disease at baseline.

The number and proportion of patients achieving disease control response (CR or PR or stable disease) were summarized in the ITT population along with the corresponding exact

CLINICAL STUDY REPORT SYNOPSIS

2-sided 95% CI calculated using a method based on Clopper-Pearson method. The CMH test stratified by ECOG and exact test were used to compare CBR between the 2 treatment arms.

The number and proportion of patients achieving CBR (CR or PR or stable disease≥24 weeks) were summarized in the ITT population along with the corresponding exact 2-sided 95% CI calculated using a method based on Clopper-Pearson method. The CMH test stratified by ECOG and exact test were used to compare CBR between the 2 treatment arms.

Unconfirmed BOR and CBR were in using. The unconfirmed CR/PR was presented as CR/PR.

DR was 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 occurred first. If tumor progression data included more than 1 date, the first date was used. DR was calculated as [the date response ended (ie, date of PD or death) – first CR or PR date + 1)]/30.4. DR was only calculated for the subgroup of patients with an objective tumor response.

DR was summarized using the Kaplan-Meier methods. DR was calculated for the subgroup of patients achieving objective disease response (CR or PR). The median event time and 2-sided 95% CI for the median were provided.

Pharmacokinetic Analysis

PK analysis set was defined as a subset of AT patients who were treated with the study treatments and had at least measured plasma concentration for at least 1 analyte (palbociclib and/or cetuximab).

Palbociclib PK concentrations were summarized descriptively by nominal time within the treatment arm. To be included within the descriptive summaries for PK parameters, each PK sample was required to fulfill the requirements of a palbociclib steady-state trough sample (steady-state pre-dose concentration [C_{trough}]). Palbociclib C_{trough} was defined as a pre-dose plasma concentration following at least 7 consecutive days of 125 mg daily dose without dosing interruption and the time window for the PK collection was to be between 24 hour ±2 hour and 24 minutes post-dose the day prior to PK collection and no more than 1 hour post-dose on the day of PK collection. Additionally, within-patient mean of the palbociclib C_{trough} (WPM-C_{trough}) was listed by patient and summarized descriptively within the treatment arm.

Cetuximab PK concentrations were summarized descriptively by nominal time within each treatment arm. To be included within the descriptive summaries for PK parameters, each PK sample had to meet the requirements of a cetuximab steady-state pre-dose or post-dose sample. A cetuximab C_{trough} was defined as serum sample collected prior to the start of a cetuximab IV infusion and after at least 2 consecutive weeks of cetuximab IV infusions

CLINICAL STUDY REPORT SYNOPSIS

without interruption or prior dose reduction for the Cycle 1 Day 15 collection or after at least 3 consecutive weeks of cetuximab IV infusions without interruption or prior dose reduction for other visits. A cetuximab steady-state end-of-infusion serum concentration (C_{endinf}) was defined as a as serum sample collected after at least 3 consecutive weeks of cetuximab IV infusions without interruption or prior dose reduction and was collected at the end of cetuximab infusion time ±10% of the actual duration of the cetuximab infusion (ie within ±6 minutes of the end of infusion time for a 60-minute infusion). Additionally, within-patient mean cetuximab C_{trough} (WPM-C_{trough}) and within-patient mean cetuximab C_{endinf} (WPM-C_{endinf}) were listed by patient and summarized descriptively by treatment arm.

Biomarker Analysis

The biomarker analysis set was defined as all patients treated with cetuximab in combination with placebo or palbociclib (AT population) who had at least 1 screening biomarker assessment. Analysis sets were defined separately for serum, plasma, archival tumor tissue, and de novo tumor biopsies. If a biomarker had both Screening and on treatment/End of Treatment assessments, the analysis set was defined as all patients treated with cetuximab in combination with placebo or palbociclib with paired biomarker assessments. [redacted]

Biomarkers were assessed separately from serum, plasma, archival tumor tissue and de novo tumor biopsies. In each case, summaries of baseline levels, ratio to baseline (where appropriate), expression and mutation were reported, by treatment group and combined. For continuous variables, summary statistics could include the mean, ratio to baseline, standard deviation, 25th median, and 75th quartile, percent coefficient of variation (%CV), and minimum/maximum levels of biomarker measures; for categorical variables, summary could include number and percentage, odds ratio as appropriate. Statistical analyses comparing treatment groups were 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 Kaplan-Meier analysis stratified by ≥ or < median biomarker value (for continuous biomarkers) or presence/absence (for discrete biomarkers) could be performed.

For p16 and Rb expression in the palbociclib and cetuximab treatment group, the relationship of the biomarkers (individually) with PFS and OS were explored at baseline. A sensitivity analysis of p16 (absent versus any staining intensity level) versus PFS was performed, such as p16 as a covariate in a Cox model. Receiver Operating Characteristic (ROC) curve analysis were performed using the baseline biomarkers as predictors of PFS and OS; the AUC was calculated. Curves were produced for median PFS and OS times, along with 4 months before median, 2 months before median, 2 months after median and 4 months after median. If increasing values of the biomarker led to better PFS/OS response, the actual value of the biomarker was used in the ROC analysis. If increasing values of the biomarker led to worse PFS/OS response, the ROC analysis was to be used the inverse of the biomarker value

CLINICAL STUDY REPORT SYNOPSIS

with 1/0 being set to 0. The biomarker value which produced the maximal sensitivity/1-specificity point was identified for each curve.

[redacted]

Patient Reported Outcome Analysis

PRO analysis set was defined as a subset of ITT patients, who had both baseline and at least 1 follow-up PRO assessment before treatment discontinuation. Change from baseline analyses were performed on the PRO evaluable population as appropriate. For each treatment group and at each time point, the number and percentage of patients who completed these instruments were summarized, as the reasons for non-completion of these measures. An instrument was considered completed if at least 1 item was answered by the patient. For each domain or scale a completion status table was 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 1, or all of the items for that domain or scale. Post treatment discontinuation observation was excluded from primary analyses set and only included in pre-specified sensitivities or post-hoc analyses.

Safety Analysis

All patients treated with at least 1 dose of study treatment (ie, palbociclib/placebo or cetuximab) were included in all the safety analyses. Listings of AE, serious AE (SAE), death, laboratory data, vital signs, and physical examinations were provided according to reporting standard.

CLINICAL STUDY REPORT SYNOPSIS

RESULTS

Patient Disposition and Demography:

Patient disposition is summarized in Table S2. By the time of data cutoff (19 July 2018), a total of 125 patients were randomized to palbociclib + cetuximab and placebo + cetuximab arms with 65 and 60 patients, respectively; among them, 124 patients received study treatments. One (1) patient in the palbociclib + cetuximab treatment arm was randomized but not treated. Twenty-six (26) patients were ongoing on the study as of data cutoff.

The demographic characteristics (ITT population) were well balanced in both treatment arms. The majority of patients were male (113 [90.4%]). The mean age for palbociclib + cetuximab arm was 58.3 years (range: 38 to 83 years) and mean body mass index (BMI) was 22.9 kg/m^2 (range: 14.35 to 34.52 kg/m^2). The mean age for placebo + cetuximab arm was 60.9 years (range: 32 to 80 years) and mean BMI was 21.9 kg/m^2 (range: 15.40 to 38.97 kg/m^2). The majority of patients (93 [74.4%]) were of White race.

The primary diagnosis for all patients (125) was SCCHN. The median (range) duration of the disease under study since histopathological diagnosis was 1.7 years (0.2 to 16.7 years) for patients in the palbociclib + cetuximab arm and 2.3 years (0.6 to 32.2 years) for patients in the placebo + cetuximab arm.

All patients (125) had a measurable disease presented at baseline and an adequate baseline assessment. Baseline characteristics were generally well balanced between both treatment arms, except some unbalance between treatment arms observed in primary diagnosis sites at hypopharynx and oropharynx, and in initial diagnosis at Stage II and III.

For the location of primary diagnosis (SCCHN), oral cavity was the most common site of disease (palbociclib + cetuximab arm: 25 [38.5%] vs placebo + cetuximab arm: 25 [41.7%]), followed by larynx (palbociclib + cetuximab arm: 18 [27.7%] vs placebo + cetuximab arm: 16 [26.7%]), oropharynx (palbociclib + cetuximab arm: 9 [13.8%] vs placebo + cetuximab arm: 14 [23.3%]), and hypopharynx (palbociclib + cetuximab arm: 13 [20.0%] vs placebo + cetuximab arm: 5 [8.3%]). About 31 (24.8%) patients had >4 disease sites involved (palbociclib + cetuximab arm: 16 [24.6%] vs placebo + cetuximab arm: 15 [25.0%]).

Most patients already had advanced SCCHN at the time of initial diagnosis with 23 (18.4%) patients in Stage III (palbociclib + cetuximab arm: 15 [23.1%] vs placebo + cetuximab arm: 8 [13.3%]), 45 (36.0%) patients in Stage IVA (25 [38.5%] vs 20 [33.3%]), 4 (3.2%) patients in Stage IVB (3 [4.6%] vs 1 [1.7%]) and 14 (11.2%) patients in Stage IVC (7 [10.8%] vs 7 [11.7%]). For the disease stage at baseline, majority of patients (92 [73.6%]) had SCCHN in Stage IVC (45 [69.2%] vs 47 [78.3%]). At the time of recurrence, most patients (58 [46.4%]) exhibited both distant and locoregional recurrence of disease (28 [43.1%] vs 30 [50.0%]).

CLINICAL STUDY REPORT SYNOPSIS

Table S2. Patient Disposition Summary

Number (%) of Patients	Palbociclib + Cetuximab	Placebo + Cetuximab	Total
	n (%)	n (%)	n (%)
Screened			226
Screen failed			101
Not met inclusion criteria only			84
Met exclusion criteria only			15
Not met inclusion and exclusion criteria			1
Died – inclusion/exclusion criteria not applicable			1
Randomized (ITT)	65 (100)	60 (100)	125 (100)
Treated	64 (98.5)	60 (100)	124 (99.2)
Randomized but not treated	1 (1.5)	0	1 (0.8)
Received at least 1 dose of both palbociclib/placebo and cetuximab	62 (95.4)	60 (100)	122 (97.6)
Received at least 1 dose of cetuximab but never received palbociclib/placebo	1 (1.5)	0	1 (0.8)
Received at least 1 dose of palbociclib/placebo but never received cetuximab	1 (1.5)	0	1 (0.8)
Ongoing on study	15 (23.1)	11 (18.3)	26 (20.8)
Discontinued from study	50 (76.9)	49 (81.7)	99 (79.2)
Patient died	45 (69.2)	42 (70.0)	87 (69.6)
Patient refused further follow-up	1 (1.5)	0	1 (0.8)
Lost to follow-up	1 (1.5)	2 (3.3)	3 (2.4)
Other	1 (1.5)	0	1 (0.8)
Withdrew consent	2 (3.1)	5 (8.3)	7 (5.6)
Ongoing on any study drug	4 (6.2)	7 (11.7)	11 (8.8)
Ongoing on study treatment palbociclib/placebo	4 (6.2)	7 (11.7)	11 (8.8)
Ongoing on study treatment cetuximab	4 (6.2)	7 (11.7)	11 (8.8)
Ongoing on both treatments	4 (6.2)	7 (11.7)	11 (8.8)
Discontinued from any study drug[a]	60 (92.3)	53 (88.3)	113 (90.4)
Discontinued from both study drugs	60 (92.3)	53 (88.3)	113 (90.4)
Discontinued from palbociclib/placebo only	0	0	0
Reason to discontinue from any study drug:			
Discontinued from palbociclib/placebo[b]	60 (92.3)	53 (88.3)	113 (90.4)
Objective progression or relapse	33 (50.8)	35 (58.3)	68 (54.4)
Global deterioration of health status	0	1 (1.7)	1 (0.8)
Adverse event	9 (13.8)	7 (11.7)	16 (12.8)
Patient died	10 (15.4)	5 (8.3)	15 (12.0)
Lost to follow-up	0	1 (1.7)	1 (0.8)
No longer willing to participate in study	2 (3.1)	3 (5.0)	5 (4.0)
Other	6 (9.2)	1 (1.7)	7 (5.6)
Discontinued from cetuximab[b]	60 (92.3)	53 (88.3)	113 (90.4)
Objective progression or relapse	33 (50.8)	36 (60.0)	69 (55.2)
Global deterioration of health status	0	1 (1.7)	1 (0.8)
Adverse event	9 (13.8)	5 (8.3)	14 (11.2)
Patient died	10 (15.4)	6 (10.0)	16 (12.8)
Lost to follow-up	0	1 (1.7)	1 (0.8)
No longer willing to participate in study	1 (1.5)	3 (5.0)	4 (3.2)
Other	7 (10.8)	1 (1.7)	8 (6.4)

ITT population included all patients who were randomized.
Abbreviations: ITT = intent-to-treat population; n = number of patients.
a. Palbociclib had to be discontinued if cetuximab was discontinued.
b. These categories were not mutually exclusive.

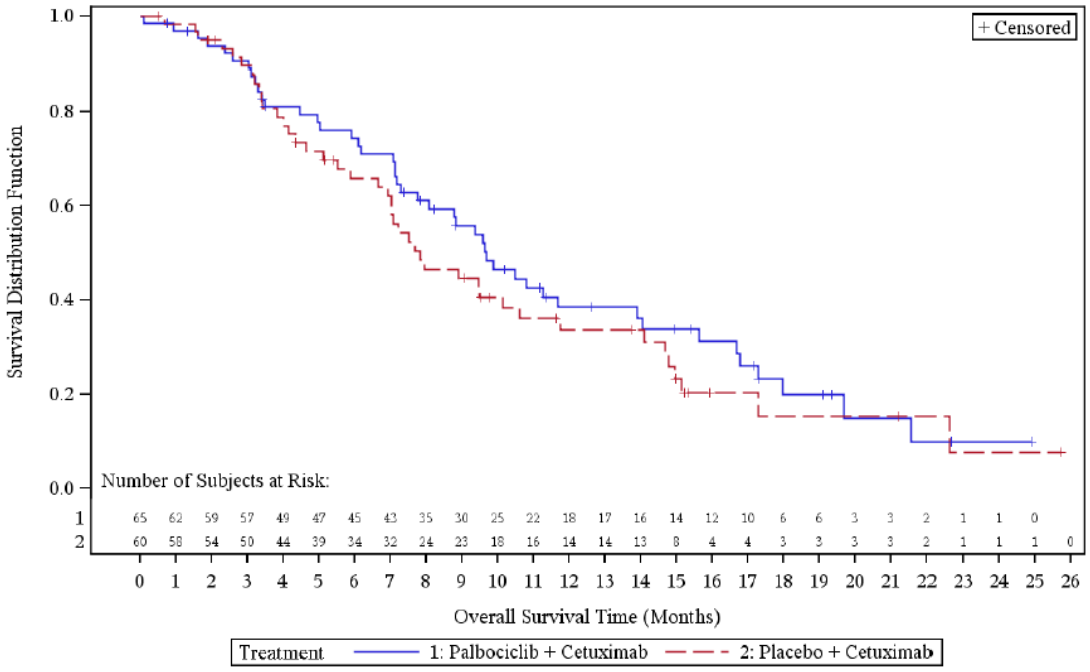
CLINICAL STUDY REPORT SYNOPSIS

Efficacy Results:

Overall Survival

The OS is summarized in Table S3 and plotted in Figure S1. At the data cutoff date (19 July 2018), there were 45 (69.2%) deaths in the palbociclib + cetuximab treatment arm and 42 (70.0%) deaths in the placebo + cetuximab treatment arm. The estimated median OS was 9.7 months (95% CI [7.3, 13.9]) in the palbociclib + cetuximab treatment arm and 7.8 months (95% CI [6.7, 10.6]) in the placebo + cetuximab treatment arm. The estimated HR using stratified (by ECOG per randomization) analysis was 0.820 (95% CI [0.536, 1.253]; p-value = 0.180), which showed a numerical trend in favor of palbociclib + cetuximab but was not statistically significant. The study did not meet its primary endpoint of OS with palbociclib + cetuximab treatment arm when compared with placebo + cetuximab treatment arm.

Figure S1. Kaplan-Meier Plot of Overall Survival - Intent-to-Treat Set



CLINICAL STUDY REPORT SYNOPSIS

Table S3. Summary of Overall Survival – Intent-to-Treat Set

	Palbociclib + Cetuximab (N = 65)	Placebo + Cetuximab (N = 60)
Number of deaths, n (%)	45 (69.2)	42 (70.0)
Cause of death, n (%)		
Disease under study	41 (63.1)	37 (61.7)
Study treatment toxicity	1 (1.5)	0
Unknown	3 (4.6)	2 (3.3)
Other	1 (1.5)	3 (5.0)
Number censored, n (%)	20 (30.8)	18 (30.0)
Reason for censorship, n (%)		
Patient remained in follow-up	18 (27.7)	16 (26.7)
Patient no longer being followed for survival	2 (3.1)	2 (3.3)
Survival probability at Month 6[a] (95% CI[b])	74.4 (61.6, 83.5)	65.9 (51.8, 76.7)
Survival probability at Month12[a] (95% CI[b])	38.4 (25.8, 50.9)	33.6 (21.0, 46.7)
Survival probability at Month 24[a] (95% CI[b])	9.9 (2.2, 24.7)	7.6 (0.8, 25.3)
Survival probability at Month 36[a] (95% CI[b])	NE	NE
Kaplan-Meier estimated of time to event (month) quartiles (95% CI)[c]		
25%	5.9 (3.2, 7.2)	4.3 (3.2, 6.9)
50%	9.7 (7.3, 13.9)	7.8 (6.7, 10.6)
75%	17.3 (13.9, 21.6)	14.9 (10.6, NE)
Stratified analysis[d]:		
Hazard ratio[e]	0.820	
80% CI of hazard ratio	0.621-1.082	
95% CI of hazard ratio	0.536-1.253	
p-value[f]	0.180040	
Unstratified analysis:		
Hazard ratio[e]	0.812	
80% CI of hazard ratio	0.616-1.070	
95% CI of hazard ratio	0.532-1.239	
p-value[f]	0.166827	

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; N/n = number of patients; NE = not estimable.

a. Estimated from the Kaplan-Meier curve.
b. Calculated from the product-limit method.
c. Based on the Brookmeyer and Crowley method.
d. Stratified by ECOG per randomization.
e. Assuming proportional hazards, hazard ratio less than 1 indicated reduction in hazard rate in favor of palbociclib + cetuximab.
f. One (1)-sided p-value from the log-rank test.

Progression Free Survival

Summary of PFS based on investigator assessment is presented in Table S4. At the data cutoff date (19 July 2018), 50 (76.9%) out of 65 patients in the palbociclib + cetuximab treatment arm and 47 (78.3%) out of 60 patients in the placebo + cetuximab treatment arm had experienced disease progression or death. The estimated HR using stratified (by ECOG per randomization) analysis was 1.000 (95% CI [0.669, 1.495]; p-value = 0.495), which showed no difference between the 2 treatment arms. The median PFS was 3.9 months

CLINICAL STUDY REPORT SYNOPSIS

(95% CI [3.6, 5.6]) in the palbociclib + cetuximab treatment arm and 4.6 months (95% CI [2.3, 5.5]) in the placebo + cetuximab treatment arm. The study did not meet its key secondary endpoint of PFS based on the investigator's assessment.

CLINICAL STUDY REPORT SYNOPSIS

Table S4. Summary of Progression Free Survival Based on Investigator Assessment - Intent-to-Treat Set

	Palbociclib + Cetuximab (N = 65)	Placebo + Cetuximab (N = 60)
Number with event, n (%)	50 (76.9)	47 (78.3)
Type of event, n (%)		
Objective progression	35 (53.8)	37 (61.7)
Death without objective progression	15 (23.1)	10 (16.7)
Number censored, n (%)	15 (23.1)	13 (21.7)
Reason for censorship, n (%)		
No on-study disease assessments	6 (9.2)	2 (3.3)
Given new anti-cancer treatment prior to tumor progression	1 (1.5)	0
Unacceptable gap (>18 weeks) between PD or death to the most recent prior adequate assessment	0	2 (3.3)
Discontinued treatment without disease progression or death	4 (6.2)	3 (5.0)
AE	1 (1.5)	0
Lost to follow-up / patient refused continued treatment for reason other than AE	1 (1.5)	3 (5.0)
Other	2 (3.1)	0
In follow-up for progression	4 (6.2)	6 (10.0)
Probability at Month 4[a] (95% CI[b])	46.8(33.4, 59.1)	50.2 (36.5, 62.4)
Probability at Month 6[a] (95% CI[b])	36.0 (23.7, 48.4)	32.8 (20.8, 45.3)
Probability at Month 12[a] (95% CI[b])	9.9 (3.3, 20.8)	16.6 (7.9, 28.0)
Kaplan-Meier estimated of time to event (month) quartiles(95% CI)[c]		
25%	2.9 (1.9, 3.6)	1.9 (1.7, 2.3)
50%	3.9 (3.6, 5.6)	4.6 (2.3, 5.5)
75%	9.4 (5.6, 11.3)	8.3 (5.5, 18.5)
Stratified analysis[d]:		
Hazard ratio[e]	1.000	
80% CI of hazard ratio	0.769-1.301	
95% CI of hazard ratio	0.669-1.495	
p-value[f]	0.495258	
Unstratified analysis:		
Hazard ratio[e]	0.994	
80% CI of hazard ratio	0.766-1.291	
95% CI of hazard ratio	0.667-1.483	
p-value[f]	0.488102	

Abbreviations: AE = adverse event; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; N/n = number of patients; PD = progressive disease.

a. Estimated from the Kaplan-Meier curve.
b. Calculated from the product-limit method.
c. Based on the Brookmeyer and Crowley method.
d. Stratified by ECOG per randomization.
e. Based on the Cox Proportional hazards model.
f. One (1)-sided p-value from the log-rank test reflected the sign of the test statistic (z-Score).

CLINICAL STUDY REPORT SYNOPSIS

Objective Response

Best Overall Response: Best overall response is summarized in Table S5. The odds ratio using stratified (by ECOG per randomization) analysis showed no difference between the 2 treatment arms.

Table S5. Summary of Best Overall Response – Intent-to-Treat Set

	Palbociclib + Cetuximab (N = 65)	Placebo + Cetuximab (N = 60)
Number of patients with measurable disease at baseline, n (%)	65 (100)	60 (100)
CR	2 (3.1)	0
PR	16 (24.6)	15 (25.0)
Stable/No response	11 (16.9)	14 (23.3)
Objective progression	9 (13.8)	20 (33.3)
Indeterminate	27 (41.5)	11 (18.3)
Objective response rate (CR+PR)	18 (27.7)	15 (25.0)
95% exact CI[a]	17.3, 40.2	14.7, 37.9
Stratified analysis[b]:		
Odds ratio[c] (95% exact CI)	1.137 (0.475, 2.734)	
p-value[d]	0.4570	
Unstratified analysis:		
Odds ratio[c] (95% exact CI)	1.149 (0.480, 2.772)	
p-value[d]	0.4457	

Unconfirmed best overall response was in using. The unconfirmed CR/PR was presented as CR/PR.
Abbreviations: CI = confidence interval; CR = complete response; ECOG = Eastern Cooperative Oncology Group; N/n = number of patients; PR = partial response.
a. CI was calculated using the exact (Clopper-Pearson) method based on binomial distribution.
b. Stratified by ECOG per randomization.
c. An odds ratio >1 means better response in favor of palbociclib + cetuximab.
d. One (1)-sided p-value was from exact test.

Clinical Benefit Response: CBR based on investigator assessment is summarized in Table S6, which showed no difference between the 2 treatment arms.

CLINICAL STUDY REPORT SYNOPSIS

Table S6. Summary of Clinical Benefit Response - Intent-to-Treat Set

	Palbociclib + Cetuximab (N = 65)	Placebo + Cetuximab (N = 60)
Number of patients with measureable disease at baseline, n (%)	65 (100)	60 (100)
CR	2 (3.1)	0
PR	16 (24.6)	15 (25.0)
SD ≥24 weeks	6 (9.2)	7 (11.7)
SD <24 weeks	5 (7.7)	7 (11.7)
Objective progression	9 (13.8)	20 (33.3)
Indeterminate	27 (41.5)	11 (18.3)
Benefit response (CR+PR+SD ≥24 weeks)	24 (36.9)	22 (36.7)
95% exact CI[a]	25.3, 49.8	24.6, 50.1
Stratified analysis[b]:		
Odds ratio[c] (95% exact CI)	1.013 (0.461, 2.230)	
p-value[d]	0.5605	
Unstratified analysis:		
Odds ratio[c] (95% exact CI)	1.011 (0.459,2.233)	
p-value[d]	0.5621	

Unconfirmed clinical benefit response was in using. The unconfirmed CR/PR was presented as CR/PR.
Abbreviations: CI = confidence interval; CR = complete response; ECOG = Eastern Cooperative Oncology Group; N/n = number of patients; PR = partial response; SD = stable disease.

a. CI was calculated using the exact (Clopper-Pearson) method based on binomial distribution.
b. Stratified by ECOG per randomization.
c. An odds ratio >1 means better response in favor of palbociclib + cetuximab.
d. One (1)-sided p-value was from exact test.

Duration of Objective Response

Duration of objective response is summarized only on the 18 patients in the palbociclib + cetuximab arm and 15 patients in the placebo + cetuximab arm who had objective tumor response (unconfirmed CR or PR), which showed in Table S7. The estimated median DR showed no differences between the 2 treatment arms.

CLINICAL STUDY REPORT SYNOPSIS

Table S7. Summary of Duration of Objective Response - Intent-to-Treat Set

	Palbociclib + Cetuximab (N = 65)	Placebo + Cetuximab (N = 60)
Patients with a response (CR/PR)	18	15
Number (%) of patients with objective progression or death	15 (83.3)	8 (53.3)
Number (%) of patients censored	3 (16.7)	7 (46.7)
Kaplan-Meier estimated of duration of response (CR/PR) in months quartiles(95% CI)[a]		
25%	3.7 (1.4, 7.5)	4.8 (1.4, 7.4)
50%	7.6 (3.7, 7.7)	7.4 (3.6, NE)
75%	7.7 (7.6, 15.8)	NE (7.4, NE)
Stratified analysis[b]:		
Hazard ratio[c]	1.451	
80% CI of hazard ratio	0.815-2.583	
95% CI of hazard ratio	0.601-3.504	
Unstratified analysis:		
Hazard ratio[c]	1.571	
80% CI of hazard ratio	0.889-2.776	
95% CI of hazard ratio	0.657-3.752	

Abbreviations: CI = confidence interval; CR = complete response; ECOG = Eastern Cooperative Oncology Group; N = number of patients; NE = not estimable; PR = partial response.

a. Based on the Brookmeyer and Crowley method.
b. Stratified by ECOG per randomization.
c. Assuming proportional hazards, hazard ratio <1 indicated reduction in hazard rate in favor of palbociclib + cetuximab.

Pharmacokinetic, Biomarker, and Patient Reported Outcomes Results:

Pharmacokinetic Results

Plasma Palbociclib PK: Following daily 125 mg oral doses of palbociclib with concomitant administration of cetuximab, palbociclib steady-state exposures were comparable on Day 15 of Cycles 1 and 2 (Table S8). A single palbociclib PK sample that was below the lower limit of quantitation (BLQ) reported supporting information within the case report form (CRF) that met the acceptance criteria for a C_{trough} parameter, and the reported geometric mean summary statistics for palbociclib Cycle 2 Day 15 C_{trough} and the WPM-C_{trough} were heavily influenced by this single sample. As a result, the interpretation of the palbociclib PK data from this study was focused on the arithmetic mean and %CV. The mean palbociclib WPM-C_{trough} was 71.64 ng/mL, which is consistent with data reported from prior studies dosing palbociclib at 125 mg QD in patients with advanced cancer.

CLINICAL STUDY REPORT SYNOPSIS

Table S8. Summary of Plasma Palbociclib Steady-State PK Parameters Following Daily 125 mg Oral Doses of Palbociclib with Concomitant Cetuximab Treatment

Parameter (Units)	PK Parameter Summary Statistics		
	N	Geometric Mean (Geometric Mean %CV)	Mean (%CV)
C_{trough} (ng/mL)			
Cycle 1 Day 15	27	64.11 (45)	69.75 (40)
Cycle 2 Day 15	28	40.96 (2622)	67.79 (43)
WPM-C_{trough} (ng/mL)[a]	37	47.66 (1231)	71.64 (42)

Abbreviations: %CV = percent coefficient of variation; C_{trough} = steady-state pre-dose concentration; N = number of patients contributing to the summary statistics; PK = pharmacokinetic(s); WPM-C_{trough} = within-patient mean steady-state pre-dose concentration.
a. Within-patient mean of steady-state C_{trough}.

Serum Cetuximab PK: Cetuximab PK parameters were comparable in the presence and absence of concomitant palbociclib treatment, based on similar median, geometric mean, and range of cetuximab C_{trough} and C_{endinf} across treatment arms (Table S9). From visual inspection of the data, it could be concluded that concomitant administration of palbociclib had no clinically significant effect on cetuximab PK.

Table S9. Summary of Serum Cetuximab Steady-State PK Parameters by Treatment

Parameter (Units)	Parameter Summary Statistics[a] by Treatment	
	Palbociclib + Cetuximab	Placebo + Cetuximab
C_{trough} (ng/mL)		
Cycle 1 Day 15	39706.407 (92)	42914.095 (62)
Cycle 2 Day 15	51005.307 (74)	52995.663 (71)
WPM-C_{trough} (ng/mL)[b]	45605.949 (83)	46796.538 (63)
C_{endinf} (ng/mL)		
Cycle 1 Day 15	145748.275 (43)	137185.479 (61)
Cycle 2 Day 15	149155.706 (38)	153310.061 (39)
WPM-C_{endinf} (ng/mL)[b]	149119.179 (36)	148063.341 (39)

Abbreviations: %CV = percent coefficient of variation; C_{endinf} = steady-state end-of-infusion concentration; C_{trough} = steady-state pre-dose concentration; PK = pharmacokinetic(s); WPM-C_{endinf} = within-patient mean steady-state end-of-infusion concentration; WPM-C_{trough} = within-patient mean steady-state pre dose concentration.
a. Geometric mean (%CV).
b. Within-patient mean of steady-state C_{trough} or C_{endinf} values, respectively.

Biomarker Results

In the following subgroup analysis, the 95% CIs and p-values were provided to help gauge the precision of the estimates but they were not adjusted for multiplicity.

CLINICAL STUDY REPORT SYNOPSIS

IHC Biomarker Assessment (p16, Rb, [redacted])

In general, the analyses showed that staining for these cell cycle related markers was broadly distributed for all parameters considered. All samples submitted for analysis were successfully stained and analyzed. In general, there was not significant difference between the 2 treatment arms for Rb [redacted] staining parameter. For p16, however, there was a trend toward greater positive tumor cells in the placebo + cetuximab arm versus the palbociclib + cetuximab arm (p-value = 0.0926), and this was further illustrated by a significant difference in the percent positive cell at the cytoplasmic staining level (p-value = 0.0463), and a trend for the H-score for the cytoplasmic staining (p-value = 0.0502).

p16 Analysis

A total of 113 patients were included in the IHC analyses: 58 in palbociclib + cetuximab arm and 55 in placebo + cetuximab arm. Two (2) analysis methods based on the p16 IHC analysis were utilized, one based on a conventional cutoff to consider a sample HPV-negative (<70% p16-positive tumor cells) and the other based on an optimized cutoff for the activity of the test arm (palbociclib + cetuximab) derived from an ROC curve analysis.

Conventional 70% p16-Positive Tumor Cell Cutoff: Initial analysis of the p16 status was based on the conventional cutoff of 70% p16-positive tumor cells to call out cases that might be considered HPV-positive. Specifically, p16 expression was scored as positive if strong and diffuse nuclear and cytoplasmic staining was present in at least 70% of the tumor cells. Testing and interpretation were centralized. Based on this cutoff, 54 of the 58 samples tested in the palbociclib + cetuximab arm and 48 of 55 samples tested in the placebo + cetuximab arm were considered qualified as HPV-negative and included in the PFS and OS analyses.

The median PFS were similar between the palbociclib + cetuximab and the placebo + cetuximab treatments, 3.7 months (95% CI: 3.2, 5.6) and 5.0 months (95% CI: 3.3, 7.2), respectively (HR = 1.228; 95% CI: 0.789, 1.911; p-value = 0.364). The PFS analyses for p16-negative groups derived from the specified cutoff point are summarized in Table S10.

The median OS were similar between the palbociclib + cetuximab and the placebo + cetuximab treatments, 9.9 months (95% CI: 7.1, 13.9) and 8.0 months (95% CI: 7.0, 14.7), respectively (HR = 0.947; 95% CI: 0.589, 1.521; p-value = 0.824). The OS analyses for p16-negative groups derived from the specified cutoff point are summarized in Table S11.

CLINICAL STUDY REPORT SYNOPSIS

Table S10. Summary of Progression Free Survival Based on Investigator Assessment for p16 Negative – Biomarker Analysis Set

	Palbociclib + Cetuximab	Placebo + Cetuximab
p16 Status: Negative[a]		
Number of patients	45	39
Number with event	34 (75.6)	30 (76.9)
Type of event		
Objective progression	25 (55.6)	21 (53.8)
Death without objective progression	9 (20.0)	9 (23.1)
Number censored	11 (24.4)	9 (23.1)
Reason for censorship		
No adequate baseline assessments	0	0
No on-study disease assessments	4 (8.9)	2 (5.1)
Given new anti-cancer treatment prior to tumor progression	1 (2.2)	0
Unacceptable gap (>18 weeks) between progressive disease or death to the most recent prior adequate assessment	0	2 (5.1)
Discontinued treatment without disease progression or death	3 (6.7)	1 (2.6)
AE	0	0
Global deterioration of health status	0	0
Lost to follow-up/patient refused continued treatment for reason other than AE	1 (2.2)	1 (2.6)
Other	2 (4.4)	0
In follow-up for progression	3 (6.7)	4 (10.3)
Probability of being event free at Month 4[b] (95% CI[c])	34.7 (20.2, 49.6)	55.4 (37.8, 69.9)
Probability of being event free at Month 6[b] (95% CI[c])	29.4 (16.0, 44.1)	40.8 (24.7, 56.3)
Probability of being event free at Month 12[b] (95% CI[c])	11.4 (3.2, 25.5)	20.0 (8.6, 34.7)
Kaplan-Meier estimated of time to event (month) quartiles(95% CI)[d]		
25%	1.9 (1.8, 3.2)	2.6 (1.6, 3.7)
50%	3.7 (3.0, 4.0)	4.7 (3.3, 7.3)
75%	7.2 (3.8, 14.1)	9.3 (5.6, NE)
Versus placebo + cetuximab		
Hazard ratio[e]	1.331	
80% CI of hazard ratio	0.963-1.840	
95% CI of hazard ratio	0.811-2.184	
p-value[f]	0.258	
p16 Status: Negative (with Specified Cutoff Point)[g]		
Number of patients	54	48
Number with event	43 (79.6)	37 (77.1)
Type of event		
Objective progression	29 (53.7)	28 (58.3)
Death without objective progression	14 (25.9)	9 (18.8)
Number censored	11 (20.4)	11 (22.9)
Reason for censorship		
No adequate baseline assessments	0	0
No on-study disease assessments	4 (7.4)	2 (4.2)
Given new anti-cancer treatment prior to tumor progression	1 (1.9)	0
Unacceptable gap (>18 weeks) between progressive disease or death to the most recent prior adequate assessment	0	2 (4.2)
Discontinued treatment without disease progression or death	3 (5.6)	1 (2.1)
AE	0	0

CLINICAL STUDY REPORT SYNOPSIS

Table S10. Summary of Progression Free Survival Based on Investigator Assessment for p16 Negative – Biomarker Analysis Set

	Palbociclib + Cetuximab	Placebo + Cetuximab
Global deterioration of health status	0	0
Lost to follow-up/patient refused continued treatment for reason other than AE	1 (1.9)	1 (2.1)
Other	2 (3.7)	0
In follow-up for progression	3 (5.6)	6 (12.5)
Probability of being event free at Month 4[b] (95% CI[c])	40.9 (26.9, 54.4)	55.5 (39.9, 68.6)
Probability of being event free at Month 6[b] (95% CI[c])	34.4 (21.3, 47.9)	39.3 (25.1, 53.3)
Probability of being event free at Month 12[b] (95% CI[c])	8.1 (2.2, 19.3)	19.9 (9.4, 33.1)
Kaplan-Meier estimated of time to event (month) quartiles(95% CI)[d]		
25%	2.0 (1.8, 3.5)	1.9 (1.6, 3.4)
50%	3.7 (3.2, 5.6)	5.0 (3.3, 7.2)
75%	9.4 (5.5, 11.3)	9.3 (7.1, NE)
Versus placebo + cetuximab		
Hazard ratio[e]	1.228	
80% CI of hazard ratio	0.919-1.639	
95% CI of hazard ratio	0.789-1.911	
p-value[f]	0.364	

If event count ≤8 in either of the comparison group, the hazard ratio and p-value were not provided.
Abbreviations: AE = adverse event; CI = confidence interval; IHC = immunohistochemistry; NE = not estimable; PFS = progression-free survival; ROC = Receiver Operating Characteristic.

a. p16 status was utilizing the cutoff points identified by the ROC analysis for the PFS and the p16-positive tumor cells. For the palbociclib + cetuximab treatment arm, p16 IHC negative was defined as % positive tumor cells ≤1. For the placebo + cetuximab treatment arm, p16 IHC negative was defined as %positive tumor cells ≤4.
b. Estimated from the Kaplan-Meier curve.
c. Calculated from the product-limit method.
d. Based on the Brookmeyer and Crowley Method.
e. Based on the Cox Proportional hazards model.
f. Two (2)-sided p-value from the log-rank test.
g. p16 status was utilizing the specified cutoff points, p16 IHC negative was defined as %positive tumor cells <70%.

CLINICAL STUDY REPORT SYNOPSIS

Table S11. Summary of Overall Survival for p16 Negative – Biomarker Analysis Set

	Palbociclib + Cetuximab	Placebo + Cetuximab
p16 Status: Negative[a]		
Number of patients	45	31
Number of deaths	29 (64.4)	22 (71.0)
Cause of death		
Disease under study	26 (57.8)	18 (58.1)
Study treatment toxicity	1 (2.2)	0
Unknown	3 (6.7)	1 (3.2)
Other	0	3 (9.7)
Number censored	16 (35.6)	9 (29.0)
Reason for censorship		
Patient remained in follow-up	14 (31.1)	9 (29.0)
Patient no longer being followed for survival	2 (4.4)	0
Survival probability at Month 6[b] (95% CI[c])	72.3 (56.3, 83.2)	69.6 (49.6, 82.9)
Survival probability at Month12[b] (95% CI[c])	44.0 (28.3, 58.6)	33.5 (17.0, 50.9)
Survival probability at Month 24[b] (95% CI[c])	15.2 (3.6, 34.4)	12.0 (1.2, 36.0)
Survival probability at Month 36[b] (95% CI[c])	NE	NE
Kaplan-Meier estimated of time to event (month) quartiles(95% CI)[d]		
25%	5.0 (3.0, 7.2)	5.1 (2.6, 7.0)
50%	9.7 (7.1, 15.6)	7.5 (5.9, 14.1)
75%	18.0 (13.9, NE)	14.8 (10.2, NE)
Versus placebo + cetuximab		
Hazard ratio[e]	0.870	
80% CI of hazard ratio	0.605-1.251	
95% CI of hazard ratio	0.499-1.517	
p-value[f]	0.627	
p16 Status: Negative (with Specified Cutoff Point)[g]		
Number of patients	54	48
Number of deaths	37 (68.5)	32 (66.7)
Cause of death		
Disease under study	33 (61.1)	27 (56.3)
Study treatment toxicity	1 (1.9)	0
Unknown	3 (5.6)	2 (4.2)
Other	1 (1.9)	3 (6.3)
Number censored	17 (31.5)	16 (33.3)
Reason for censorship		
Patient remained in follow-up	15 (27.8)	15 (31.3)
Patient no longer being followed for survival	2 (3.7)	1 (2.1)
Survival probability at Month 6[b] (95% CI[c])	73.2 (59.0, 83.2)	73.3 (57.7, 83.9)
Survival probability at Month12[b] (95% CI[c])	38.8 (25.0, 52.4)	38.6 (23.9, 53.2)
Survival probability at Month 24[b] (95% CI[c])	12.2 (2.9, 28.6)	9.7 (1.0, 30.7)
Survival probability at Month 36[b] (95% CI[c])	NE	NE
Kaplan-Meier estimated of time to event (month) quartiles(95% CI)[d]		
25%	5.9 (3.1, 7.1)	5.9 (3.3, 7.1)
50%	9.9 (7.1, 13.9)	8.0 (7.0, 14.7)
75%	17.3 (11.7, NE)	17.3 (11.8, NE)
Versus placebo + cetuximab		
Hazard ratio[e]	0.947	
80% CI of hazard ratio	0.694-1.291	
95% CI of hazard ratio	0.589-1.521	
p-value[f]	0.824	

CLINICAL STUDY REPORT SYNOPSIS

Table S11. Summary of Overall Survival for p16 Negative – Biomarker Analysis Set

	Palbociclib + Cetuximab	Placebo + Cetuximab

If event count ≤8 in either of the comparison group, the hazard ratio and p-value were not provided.
Abbreviations: CI = confidence interval; IHC = immunohistochemistry; NE = not estimable; OS = overall survival; ROC = Receiver Operating Characteristic.

a. p16 status was utilizing the cutoff points identified by the ROC analysis for the OS and the p16-positive tumor cells. For the palbociclib + cetuximab treatment arm, p16 IHC negative was defined as % positive tumor cells ≤1. For the placebo + cetuximab treatment arm, p16 IHC negative was defined as %positive tumor cells ≤0.
b. Estimated from the Kaplan-Meier curve.
c. Calculated from the product-limit method.
d. Based on the Brookmeyer and Crowley Method.
e. Assuming proportional hazards, hazard ratio less than 1 indicated reduction in hazard rate in favor of palbociclib + cetuximab.
f. Two (2)-sided p-value from the log-rank test.
g. p16 status was utilizing the specified cutoff points, p16 IHC negative was defined as %positive tumor cells <70%.

ROC Curve Analysis for the Determination of Cutpoint: To further ascertain the sensitivity and specificity of the p16 IHC staining assay beyond the conventional cutoff and to optimize the cutoff for the activity of each test arm, ROC curve analyses were performed for correlation with PFS and with OS.

Disease-Free Survival Association Analysis: p16 status was established utilizing the cutoff points identified by the ROC analysis for the PFS and the p16-positive tumor cells. For the palbociclib + cetuximab treatment arm, p16-negative was defined as ≤1% positive tumor cells. For the placebo + cetuximab treatment arm, p16-negative was defined as ≤4% positive tumor cells. Based on these cutpoints, 45 of the 58 samples tested in the palbociclib + cetuximab arm and 39 of 55 samples tested in the placebo + cetuximab arm were considered qualified as p16-negative and included in the PFS analysis. The median PFS were similar between the palbociclib + cetuximab and the placebo + cetuximab treatments, 3.7 months (95% CI: 3.0, 4.0) and 4.7 months (95% CI: 3.3, 7.3), respectively (HR = 1.331; 95% CI: 0.811, 2.184; p-value = 0.258).

Overall Survival Association Analysis: p16 status was established utilizing the cutoff points identified by the ROC analysis for the OS and the p16-positive tumor cells. For the palbociclib + cetuximab treatment arm, p16-negative was defined as ≤1% positive tumor cells. For the placebo + cetuximab treatment arm, p16-negative was defined as ≤0% positive tumor cells. Based on these cutpoints, 45 of the 58 samples tested in the palbociclib + cetuximab arm and 31 of 55 samples tested in the placebo + cetuximab arm were considered qualified as p16-negative and included in the OS analysis.

The median OS were similar between the palbociclib + cetuximab and the placebo + cetuximab treatments, 9.7 months (95% CI: 7.1, 15.6) and 7.5 months (95% CI: 5.9, 14.1), respectively (HR = 0.870; 95% CI: 0.499, 1.517; p-value = 0.627).

CLINICAL STUDY REPORT SYNOPSIS

Rb Analysis

Rb protein-loss was rare, with a total of 3 (2.7%) cases detected in the 113 tumors tested, 1 in the palbociclib + cetuximab arm and 2 in the placebo + cetuximab arm, respectively.

Disease-Free Survival Association Analysis: In the group of patients whose tumors were Rb-positive (as defined by Rb IHC with ≥1% positive tumor cells), the median PFS were similar between the palbociclib + cetuximab and the placebo + cetuximab arms, 3.9 months (95% CI: 3.5, 6.2) and 4.6 months (95% CI: 2.6, 5.6), respectively (HR = 1.038; 95% CI: 0.679, 1.588; p-value = 0.860). Since there were so few Rb-negative tumor cases no analysis could be conclusive.

Overall Survival Association Analysis: In the group of patients whose tumors were Rb-positive, the median OS for the palbociclib + cetuximab arm was numerically superior when compared to the placebo + cetuximab arm, 10.5 months (95% CI: 7.1, 15.6) versus 7.8 months (95% CI: 6.9, 11.8), HR = 0.815 (95% CI: 0.519, 1.281; p-value = 0.376). Since there were so few Rb-negative tumor cases no analysis could be conclusive.

[redacted]

CLINICAL STUDY REPORT SYNOPSIS

CLINICAL STUDY REPORT SYNOPSIS

[redacted]

CLINICAL STUDY REPORT SYNOPSIS

CLINICAL STUDY REPORT SYNOPSIS

CLINICAL STUDY REPORT SYNOPSIS

CLINICAL STUDY REPORT SYNOPSIS

Patient Reported Outcomes Results

EORTC QLQ-C30

Completion Rate: The percentage of patients completing at least 1 question at baseline on EORTC QLQ-C30 are 96.9% (n = 63 patients) in the palbociclib + cetuximab treatment arm

CLINICAL STUDY REPORT SYNOPSIS

and 96.7% (n = 58 patients) in the placebo + cetuximab treatment arm. The percentage of patients completing at least 1 question on EORTC QLQ-C30 dropped to less than 10% after Cycle 11 in the palbociclib + cetuximab treatment arm and after Cycle 15 in the placebo + cetuximab treatment arm.

Global Quality of Life: Baseline mean scores for global QOL were similar between palbociclib + cetuximab and placebo + cetuximab treatment arms (50.9 [95% CI: 45.4, 56.5] vs 50.4 [95% CI: 44.6, 56.3]). The between-treatment comparison in mean change from baseline scores showed no statistically significant difference (0.132 [95% CI: -6.02, 6.28], p-value = 0.9662).

EORTC QLQ-C30 Functional Scales: The EORTC QLQ-C30 functional scales consist of the 5 scales: physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning. Baseline scores for all 5 functional scales were similar between the 2 treatment arms. Baseline scores for the functional scales depicted high functional levels in both treatment arms.

The overall change from baseline scores for all 5 functional scales was not found to be statistically significantly different between the 2 treatment arms.

Symptom Scales: The EORTC QLQ-C30 symptom scales consist of the 9 symptoms: fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. Mean baseline scores for the symptoms of the EORTC QLQ-C30 were similar in both treatment arms for all symptoms. Baseline scores for the symptoms indicate low symptom severity in both treatment arms.

The overall change from baseline scores for all 9 symptom scales was not found to be statistically significantly different between the 2 treatment arms. The overall change from baseline within each treatment arm indicated numerical improvement in fatigue (palbociclib + cetuximab arm: -2.788 [95% CI: -7.04, 1.46] vs placebo + cetuximab arm: -5.124 [95% CI: -9.50, -0.75]), nausea and vomiting (-0.869 [95% CI: -2.63, 0.90] vs -1.040 [95% CI: -2.82, 0.74]), pain (-5.977 [95% CI: -11.06, -0.90] vs -6.096 [95% CI: -11.32, -0.87]), insomnia (-4.623 [95% CI: -10.33, 1.08] vs -5.018 [95% CI: -10.88, 0.84]), constipation (-4.120 [95% CI: -10.30, 2.06] vs -1.326 [95% CI: -7.72, 5.07]), and financial difficulties (-5.258 [95% CI: -11.61, 1.10] vs -0.273 [95% CI: -6.83, 6.29]) while worsening in dyspnoea (3.074 [95% CI: -2.15, 8.30] vs 5.086 [95% CI: -0.27, 10.45]) and diarrhoea (4.255 [95% CI: 1.34, 7.17] vs 1.744 [95% CI: -1.24, 4.73]) for both treatment arms. Appetite loss score showed improvement in placebo + cetuximab arm (-0.687 [95% CI: -7.04, 5.67]) while worsening in palbociclib + cetuximab arm (2.247 [95% CI: -3.89, 8.38]). The within treatment arm change from baseline scores were not statistically significant (based on 95% CI) for either treatment arm for most symptoms except pain (both treatment arms), fatigue (placebo + cetuximab arm) and diarrhea (palbcociclib + cetuximab arm).

CLINICAL STUDY REPORT SYNOPSIS

EORTC QLQ-H&N35

Mean baseline scores for the symptoms of the EORTC QLQ-H&N35 were similar in both treatment arms for all symptoms except nutritional supplements (palbociclib + cetuximab: 20.6 vs placebo + cetuximab: 34.5), opening mouth (23.8 vs 32.8), weight gain (19.0 vs 10.3) and feeding tube (8.1 vs 13.8). Baseline scores for the symptoms indicate low symptom severity in both treatment arms except pain killers (63.5 vs 63.8).

The overall change from baseline in dry mouth was found to be statistically significant favoring palbociclib + cetuximab arm compared with placebo + cetuximab arm (-6.300 [95% CI: -10.50, -2.10]) vs 3.444 [95% CI: -0.82, 7.71]; p-value = 0.0016). The overall change from baseline in sticky saliva was found to be statistically significant favoring palbociclib + cetuximab arm compared with placebo + cetuximab arm (-3.912 [95% CI: -9.70, 1.88]) vs 4.680 [95% CI: -1.22, 10.58]; p-value = 0.0423). The overall change from baseline in feeding tube was found to be statistically significant favoring palbociclib + cetuximab arm compared with placebo + cetuximab arm (-6.364 [95% CI: -9.58, -3.15]) vs -0.107 [95% CI: -3.30, 3.08]; p-value = 0.0070). The estimated difference in overall change from baseline score for dry mouth, sticky saliva, and feeding tube were -9.744 (95% CI: -15.75, -3.74), -8.592 (95% CI: -16.88, -0.30), and -6.258 (95% CI: -10.79, -1.73), respectively.

Time to Deterioration of Patient Reported Pain Symptom as Assessed by EORTC QLQ-H&N35: Time to deterioration in patient reported pain symptom as an increase of ≥10 points from baseline as assessed by the EORTC QLQ H&N35 is provided in Table S13. Patients who had an event of pain deterioration of ≥10 points while on study were 25 (38.5%) in the palbociclib + cetuximab arm and 19 (31.7%) in the placebo + cetuximab arm. The median time to deterioration for pain was 8.6 months (95% CI: 1.9, not estimable [NE]) in the palbociclib + cetuximab arm and 16.7 months (95% CI: 3.7, NE) in the placebo + cetuximab arm. The HR for time to deterioration of pain was 1.304 (95% CI: 0.717-2.368; p-value = 0.382) with no statistically significant differences between treatment arms observed.

CLINICAL STUDY REPORT SYNOPSIS

Table S13. Time to Deterioration in Patient Reported Pain Symptom – Increase of ≥10 Points from Baseline as Assessed by the EORTC QLQ-H&N35 - Intent-to-Treat Set

	Palbociclib + Cetuximab (N = 65)	Placebo + Cetuximab (N = 60)
Patient had symptom of pain deterioration of ≥10 points while on study (n [%])	25 (38.5)	19 (31.7)
Patient did not have symptom of pain deterioration of ≥10 points while on study (n [%])	40 (61.5)	41 (68.3)
Reason for censorship		
No symptom of pain assessment or no baseline	2 (3.1)	2 (3.3)
Off treatment prior to symptom of pain deterioration	27 (41.5)	32 (53.3)
Patient died in study prior to symptom of pain deterioration	9 (13.8)	3 (5.0)
Patient alive and in study without symptom of pain deterioration at time of analysis	2 (3.1)	4 (6.7)
Kaplan-Meier estimates of time to event (month)		
Quartiles (95% CI)[a]		
25%	1.2 (1.0, 1.9)	1.9 (1.0, 6.0)
50%	8.6 (1.9, NE)	16.7 (3.7, NE)
75%	NE (13.0, NE)	NE (16.7, NE)
Unstratified analysis:		
Hazard ratio[b] (95% exact CI)	1.304 (0.717-2.368)	
p-value[c]	0.382	

Abbreviations: CI = confidence interval, EORTC QLQ-H&N35 = European Organization for Research and Treatment of Cancer Head and Neck Module 35; N/n = number of patients; NE = not estimable.

a. Based on the Brookmeyer and Crowley method.
b. Assuming proportional hazards, a hazard ratio <1 indicated a reduction in hazard rate in favor of palbociclib + cetuximab.
c. Used a 2-sided unstratified log-rank test and an unstratified Cox proportional hazards model.

Time to Deterioration in Swallowing from Baseline as Assessed by the EORTC QLQ-H&N35: EORTC QLQ-H&N35 symptom of swallowing time to deterioration as an increase of ≥10 points is provided in Table S14. Patients who had event of swallowing deterioration of ≥10 points while on study were 14 (21.5%) in the palbociclib + cetuximab arm and 19 (31.7%) in the placebo + cetuximab arm. The median time to deterioration for swallowing was 13.0 months (95% CI: 8.6, NE) in the palbociclib + cetuximab arm and 9.3 months (95% CI: 9.3, NE) in the placebo + cetuximab arm. The HR for time to deterioration of swallowing was 0.655 (95% CI: 0.327-1.312; p-value = 0.241), which indicated a trend in favor of the palbociclib + cetuximab arm compared with the placebo + cetuximab arm, though not statistically significant.

CLINICAL STUDY REPORT SYNOPSIS

Table S14. Time to Deterioration in Swallowing as Assessed with EORTC QLQ-H&N35 – Increase of ≥10 Points from Baseline- Intent-to-Treat Set

	Palbociclib + Cetuximab (N = 65)	Placebo + Cetuximab (N = 60)
Patient had symptom of swallowing deterioration of ≥10 points while on study (n [%])	14 (21.5)	19 (31.7)
Patient did not have symptom of swallowing deterioration of ≥10 points while on study (n [%])	51 (78.5)	41 (68.3)
Reason for censorship		
No symptom of swallowing assessment or no baseline	2 (3.1)	2 (3.3)
Off treatment prior to symptom of swallowing deterioration	35 (53.8)	32 (53.3)
Patient died in study prior to symptom of swallowing deterioration	10 (15.4)	3 (5.0)
Patient alive and in study without symptom of swallowing deterioration at time of analysis	4 (6.2)	4 (6.7)
Kaplan-Meier estimates of time to event (month)		
Quartiles (95% CI)[a]		
25%	7.4 (1.9, 13.0)	3.5 (1.4, 9.3)
50%	13.0 (8.6, NE)	9.3 (9.3, NE)
75%	NE (11.4, NE)	NE (10.1, NE)
Unstratified analysis:		
Hazard ratio[b] (95% exact CI)	0.655 (0.327-1.312)	
p-value[c]	0.241	

Abbreviations: CI = confidence interval; EORTC QLQ-H&N35 = European Organization for Research and Treatment of Cancer Head and Neck Module 35; N/n = number of patients, NE = not estimable.

a. Based on the Brookmeyer and Crowley method.
b. Assuming proportional hazards, a hazard ratio <1 indicated a reduction in hazard rate in favor of palbociclib + cetuximab.
c. Used a 2-sided unstratified log-rank test and an unstratified Cox proportional hazards model.

Safety Results:

Overall, 116 (93.5%) of all patients (as-treated population) experienced a total of 884 treatment-emergent AEs (TEAEs): 60 (93.8%) patients in the palbociclib + cetuximab arm experienced 512 TEAEs and 56 (93.3%) patients in the placebo + cetuximab arm experienced 372 TEAEs. A higher percentage of patients reported Grade 3 or 4 TEAEs in the palbociclib + cetuximab arm than in the placebo + cetuximab arm (palbociclib + cetuximab arm: 33 [51.6%] vs placebo + cetuximab arm: 18 [30.0%]). The proportion of patients with Grade 5 TEAEs (palbociclib + cetuximab arm: 15 [23.4%] vs placebo + cetuximab arm: 11 [18.3%]) and SAEs (palbociclib + cetuximab arm: 25 [39.1%] vs placebo + cetuximab arm: 19 [31.7%]) were slightly higher in the palbociclib + cetuximab arm.

Similar percentages of patients in each treatment arm had TEAEs that were associated with permanent discontinuation of study (palbociclib + cetuximab arm: 14 [21.9%] vs placebo + cetuximab arm: 10 [16.7%]) and permanent discontinuation of treatment

CLINICAL STUDY REPORT SYNOPSIS

(palbociclib + cetuximab arm: 17 [26.6%] vs placebo + cetuximab arm: 12 [20.0%]); 15 (23.4%) of the patients discontinued palbociclib in the palbociclib + cetuximab arm, and 12 (20.0%) of patients discontinued placebo in the placebo + cetuximab arm. A comparable percentage of patients permanently discontinued the treatment with cetuximab due to TEAEs in both treatment arms (palbociclib + cetuximab arm: 16 [25.0%] vs placebo + cetuximab arm: 11 [18.3%]).

A larger proportion of patients in the palbociclib + cetuximab arm (57 [89.1%]) had treatment-related TEAEs when compared with the patients in the placebo + cetuximab arm (47 [78.3%]). The percentages of patients with treatment-related Grade 3 or Grade 4 TEAEs and SAEs were higher in the palbociclib + cetuximab arm (34 [53.1%] and 7 [10.9%]) than in the placebo + cetuximab arm (9 [15.0%] and 2 [3.3%]). There was 1 (1.6%) Grade 5 treatment-related TEAE was reported in palbociclib + cetuximab arm and no patient in the placebo + cetuximab arm reported Grade 5 treatment-related TEAEs. The patient with Grade 5 treatment-related TEAE died due to cardio-respiratory arrest, which was considered to be related to cetuximab as well as disease under study.

In the palbociclib + cetuximab treatment arm, 5 (7.8%) of patients discontinued palbociclib treatment and 6 (9.4%) of patients discontinued cetuximab treatment due to treatment-related TEAEs. In the placebo + cetuximab arm, only 1 (1.7%) patient discontinued placebo and cetuximab treatments due to treatment-related TEAEs. There was 1 (1.6%) patient in the palbociclib + cetuximab treatment arm discontinued the study due to treatment-related TEAEs while no patient in the placebo + cetuximab arm discontinued the study due to treatment-related TEAEs.

The proportion of patients had at least 1 TEAE was comparable between the palbociclib + cetuximab treatment arm and the placebo + cetuximab treatment arm (60 [93.8%] vs 56 [93.3%]). The most frequently reported TEAEs (≥25%) in the palbociclib + cetuximab arm were RASH (39 [60.9%]), rash (27 [42.2%]), NEUTROPENIA (27 [42.2%]), LEUKOPENIA (24 [37.5%]), ANEMIA (23 [35.9%]), anaemia (23 [35.9%]), and neutropenia (18 [28.1%]). The most frequently reported TEAEs (≥25%) in the placebo + cetuximab arm were RASH (34 [56.7%]) and rash (21 [35.0%]) (Table S15).

The following TEAEs were reported at a ≥20% higher frequency in the palbociclib + cetuximab arm compared with the placebo + cetuximab arm: NEUTROPENIA (27 [42.2%] vs 0), LEUKOPENIA (24 [37.5%] vs 0), neutropenia (18 [28.1%] vs 0), THROMBOCYTOPENIA (15 [23.4%] vs 0), ANEMIA (23 [35.9%] vs 9 [15.0%]), anemia (23 [35.9%] vs 9 [15.0%]), and leukopenia (13 [20.3%] vs 0) (Table S15).

The most frequently reported treatment-related TEAEs (≥25%) in the palbociclib + cetuximab arm were RASH (39 [60.9%]), rash (27 [42.2%]), NEUTROPENIA (26 [40.6%]), LEUKOPENIA (22 [34.4%]), and neutropenia (18 [28.1%]). The most frequently reported treatment-related TEAEs (≥25%) in the placebo + cetuximab arm were RASH (32 [53.3%]) and rash (19 [31.7%]). The following treatment-related TEAEs were

CLINICAL STUDY REPORT SYNOPSIS

reported at a ≥20% higher frequency in the palbociclib + cetuximab arm compared with the placebo + cetuximab arm: NEUTROPENIA (26 [40.6%] vs 0), LEUKOPENIA (22 [34.4%] vs 0), neutropenia (18 [28.1%] vs 0), and THROMBOCYTOPENIA (14 [21.9%] vs 0).

Between the start of treatment and 28 days after last dose, 15 (23.1%) patients in the palbociclib + cetuximab arm died, of which majority deaths were due to the disease under study (13 [20.0%]). While in the placebo + cetuximab arm, 11 (18.3%) patients died and most deaths were due to the disease under study (8 [13.3%]).

Following the 28-day observation period after last dose until the date of data cutoff (19 July 2018), 30 (46.2%) patients in the palbociclib + cetuximab arm died, of which majority deaths were due to the disease under study (28 [43.1%]). While in the placebo + cetuximab arm, 31 (51.7%) patients died and most deaths were due to the disease under study (29 [48.3%]).

Overall, a higher percentage of patients in the palbociclib + cetuximab arm than in the placebo + cetuximab arm experienced at least 1 SAE (25 [39.1%] vs 19 [31.7%]). The most frequently reported SAEs in the palbociclib + cetuximab arm were disease progression (7 [10.9%]), pneumonia (4 [6.3%]), and febrile neutropenia (2 [3.1%]); all the other SAEs were reported in 1 (1.6%) patient each. The most frequently reported SAEs in the placebo + cetuximab arm were disease progression (6 [10.0%]), pulmonary embolism (2 [3.3%]), and sepsis (2 [3.3%]); all the other SAEs were reported in 1 (1.7%) patient each.

The most frequently reported laboratory test abnormalities in both treatment arms were hemoglobin decreased (40 [64.5%] vs 22 [37.3%]), lymphocytes decreased (absolute) (45 [88.2%] vs 30 [55.6%]), lymphocytes decreased (%) (43 [74.1%] vs 48 [84.2%]), and magnesium decreased (27 [43.5%] vs 24 [40.7%]). A higher proportion of patients had white blood cells (WBC) count decreased in palbociclib + cetuximab arm (32 [51.6%]) comparing to placebo + cetuximab arm (1 [1.7%]) and total neutrophils decreased (33 [63.5%] vs 1 [1.8%]).

TEAEs of weight decreased were reported by 5 (7.8%) patients in palbociclib + cetuximab arm and 3 (5.0%) patients in the placebo + cetuximab arm. There were no clinically relevant changes from baseline in any vital signs neither in the palbociclib + cetuximab arm nor in the placebo + cetuximab arm.

One (1) patient in palbociclib + cetuximab arm had Grade 4 TEAE of ECG QT prolonged after discontinued from study treatments due to disease progression. The Grade 4 TEAE of ECG QT prolonged was considered related to disease under study. One (1) patient in placebo + cetuximab arm had Grade 1 TEAE of ECG QT prolonged, which was considered related to placebo.

CLINICAL STUDY REPORT SYNOPSIS

Table S15. Treatment-Emergent Adverse Events by MedDRA Preferred Term (Including all Preferred Terms and Clustered Terms) and Maximum CTCAE Grade in Descending Order of Frequency in ≥5% of Patients (All Causalities) – As-Treated Set

Preferred Term	Palbociclib + Cetuximab (N = 64)				Placebo + Cetuximab (N = 60)			
	Grade 1-2	Grade 3-4	Grade 5	Total	Grade 1-2	Grade 3-4	Grade 5	Total
Any AEs	12 (18.8)	33 (51.6)	15 (23.4)	60 (93.8)	27 (45.0)	18 (30.0)	11 (18.3)	56 (93.3)
RASH	33 (51.6)	6 (9.4)	0	39 (60.9)	31 (51.7)	3 (5.0)	0	34 (56.7)
Rash	25 (39.1)	2 (3.1)	0	27 (42.2)	20 (33.3)	1 (1.7)	0	21 (35.0)
ANEMIA	14 (21.9)	9 (14.1)	0	23 (35.9)	5 (8.3)	4 (6.7)	0	9 (15.0)
Anaemia	14 (21.9)	9 (14.1)	0	23 (35.9)	5 (8.3)	4 (6.7)	0	9 (15.0)
Dermatitis acneiform	10 (15.6)	4 (6.3)	0	14 (21.9)	11 (18.3)	2 (3.3)	0	13 (21.7)
NEUTROPENIA	6 (9.4)	21 (32.8)	0	27 (42.2)	0	0	0	0
LEUKOPENIA	10 (15.6)	14 (21.9)	0	24 (37.5)	0	0	0	0
Decreased appetite	10 (15.6)	2 (3.1)	0	12 (18.8)	8 (13.3)	1 (1.7)	0	9 (15.0)
Hypomagnesaemia	8 (12.5)	3 (4.7)	0	11 (17.2)	7 (11.7)	0	0	7 (11.7)
Neutropenia	5 (7.8)	13 (20.3)	0	18 (28.1)	0	0	0	0
Fatigue	7 (10.9)	1 (1.6)	0	8 (12.5)	7 (11.7)	1 (1.7)	0	8 (13.3)
Pyrexia	9 (14.1)	0	0	9 (14.1)	7 (11.7)	0	0	7 (11.7)
Dysphagia	6 (9.4)	3 (4.7)	0	9 (14.1)	3 (5.0)	3 (5.0)	0	6 (10.0)
Nausea	8 (12.5)	0	0	8 (12.5)	5 (8.3)	2 (3.3)	0	7 (11.7)
STOMATITIS	8 (12.5)	1 (1.6)	0	9 (14.1)	5 (8.3)	1 (1.7)	0	6 (10.0)
THROMBOCYTOPENIA	10 (15.6)	5 (7.8)	0	15 (23.4)	0	0	0	0
Diarrhoea	8 (12.5)	1 (1.6)	0	9 (14.1)	5 (8.3)	0	0	5 (8.3)
Disease progression	0	0	7 (10.9)	7 (10.9)	0	1 (1.7)	6 (10.0)	7 (11.7)
Leukopenia	6 (9.4)	7 (10.9)	0	13 (20.3)	0	0	0	0
Asthenia	5 (7.8)	0	0	5 (7.8)	7 (11.7)	0	0	7 (11.7)
Constipation	7 (10.9)	0	0	7 (10.9)	4 (6.7)	1 (1.7)	0	5 (8.3)
Dry skin	9 (14.1)	0	0	9 (14.1)	3 (5.0)	0	0	3 (5.0)
Dyspnoea	4 (6.3)	0	0	4 (6.3)	4 (6.7)	4 (6.7)	0	8 (13.3)
Pneumonia	2 (3.1)	5 (7.8)	0	7 (10.9)	4 (6.7)	1 (1.7)	0	5 (8.3)
LYMPHOPENIA	4 (6.3)	6 (9.4)	0	10 (15.6)	1 (1.7)	0	0	1 (1.7)
Pruritus	7 (10.9)	0	0	7 (10.9)	4 (6.7)	0	0	4 (6.7)
White blood cell count decreased	4 (6.3)	7 (10.9)	0	11 (17.2)	0	0	0	0
HYPERGLYCEMIA	5 (7.8)	0	0	5 (7.8)	5 (8.3)	0	0	5 (8.3)
Neutrophil count decreased	1 (1.6)	9 (14.1)	0	10 (15.6)	0	0	0	0
Platelet count decreased	7 (10.9)	3 (4.7)	0	10 (15.6)	0	0	0	0
Productive cough	6 (9.4)	0	0	6 (9.4)	4 (6.7)	0	0	4 (6.7)
Headache	4 (6.3)	1 (1.6)	0	5 (7.8)	4 (6.7)	0	0	4 (6.7)

CLINICAL STUDY REPORT SYNOPSIS

Table S15. Treatment-Emergent Adverse Events by MedDRA Preferred Term (Including all Preferred Terms and Clustered Terms) and Maximum CTCAE Grade in Descending Order of Frequency in ≥5% of Patients (All Causalities) – As-Treated Set

Preferred Term	Palbociclib + Cetuximab (N = 64)				Placebo + Cetuximab (N = 60)			
	Grade 1-2	Grade 3-4	Grade 5	Total	Grade 1-2	Grade 3-4	Grade 5	Total
Hyponatraemia	3 (4.7)	1 (1.6)	0	4 (6.3)	2 (3.3)	3 (5.0)	0	5 (8.3)
Blood creatinine increased	5 (7.8)	0	0	5 (7.8)	3 (5.0)	0	0	3 (5.0)
Dizziness	2 (3.1)	0	0	2 (3.1)	6 (10.0)	0	0	6 (10.0)
Hyperglycaemia	3 (4.7)	0	0	3 (4.7)	5 (8.3)	0	0	5 (8.3)
Lymphopenia	3 (4.7)	4 (6.3)	0	7 (10.9)	1 (1.7)	0	0	1 (1.7)
Neck pain	4 (6.3)	1 (1.6)	0	5 (7.8)	3 (5.0)	0	0	3 (5.0)
Paronychia	2 (3.1)	0	0	2 (3.1)	6 (10.0)	0	0	6 (10.0)
Weight decreased	5 (7.8)	0	0	5 (7.8)	2 (3.3)	1 (1.7)	0	3 (5.0)
Cough	2 (3.1)	0	0	2 (3.1)	5 (8.3)	0	0	5 (8.3)
Hypocalcaemia	5 (7.8)	1 (1.6)	0	6 (9.4)	1 (1.7)	0	0	1 (1.7)
Hypokalaemia	3 (4.7)	3 (4.7)	0	6 (9.4)	1 (1.7)	0	0	1 (1.7)
Hypotension	3 (4.7)	0	0	3 (4.7)	4 (6.7)	0	0	4 (6.7)
Alanine aminotransferase increased	1 (1.6)	0	0	1 (1.6)	3 (5.0)	2 (3.3)	0	5 (8.3)
Aspartate aminotransferase increased	2 (3.1)	0	0	2 (3.1)	3 (5.0)	1 (1.7)	0	4 (6.7)
Hypertension	3 (4.7)	1 (1.6)	0	4 (6.3)	0	2 (3.3)	0	2 (3.3)
Hyperkalaemia	2 (3.1)	0	0	2 (3.1)	2 (3.3)	1 (1.7)	0	3 (5.0)
Oropharyngeal pain	1 (1.6)	1 (1.6)	0	2 (3.1)	3 (5.0)	0	0	3 (5.0)
Thrombocytopenia	3 (4.7)	2 (3.1)	0	5 (7.8)	0	0	0	0
Vomiting	4 (6.3)	0	0	4 (6.3)	1 (1.7)	0	0	1 (1.7)
Dehydration	0	1 (1.6)	0	1 (1.6)	3 (5.0)	0	0	3 (5.0)
Hypoalbuminaemia	0	0	0	0	3 (5.0)	1 (1.7)	0	4 (6.7)
Infection	1 (1.6)	0	0	1 (1.6)	2 (3.3)	1 (1.7)	0	3 (5.0)
Infusion related reaction	0	1 (1.6)	0	1 (1.6)	3 (5.0)	0	0	3 (5.0)
Pain in extremity	1 (1.6)	0	0	1 (1.6)	3 (5.0)	0	0	3 (5.0)
Stomatitis	4 (6.3)	0	0	4 (6.3)	0	0	0	0
Haematuria	0	0	0	0	3 (5.0)	0	0	3 (5.0)
Pain	0	0	0	0	2 (3.3)	1 (1.7)	0	3 (5.0)
Tumour pain	0	0	0	0	1 (1.7)	2 (3.3)	0	3 (5.0)

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients.

CLINICAL STUDY REPORT SYNOPSIS

Conclusions:

- The study did not meet its primary endpoint of OS with palbociclib + cetuximab treatment arm when compared with placebo + cetuximab treatment arm. The estimated HR using stratified analysis was 0.820 (95% CI [0.536, 1.253]; p-value = 0.180), which showed a numerical trend in favor of palbociclib + cetuximab but was not statistically significant. The estimated median OS was 9.7 months (95% CI [7.3, 13.9]) in the palbociclib + cetuximab treatment arm and 7.8 months (95% CI [6.7, 10.6]) in the placebo + cetuximab treatment arm.

- The study did not meet secondary endpoint of PFS based on the investigator's assessment. The estimated HR using stratified analysis was 1.000 (95% CI [0.669, 1.495]; p-value = 0.495), which showed no difference between the 2 treatment arms. The median PFS was 3.9 months (95% CI [3.6, 5.6]) in the palbociclib + cetuximab treatment arm and 4.6 months (95% CI [2.3, 5.5]) in the placebo + cetuximab treatment arm.

- CR was observed in 2 (3.1%) patients in palbociclib + cetuximab arm and none in the placebo + cetuximab arm. PR was seen in 16 (24.6%) patients in palbociclib + cetuximab arm and 15 (25.0%) patients in placebo + cetuximab arm. OR rate was 27.7% (95% CI [17.3, 40.2]) in palbociclib + cetuximab arm and 25.0% (95% CI [14.7, 37.9]) in placebo + cetuximab arm. CBR was 36.9% (95% CI [25.3, 49.8]) in palbociclib + cetuximab arm and 36.7% (95% CI [24.6, 50.1]) in placebo + cetuximab arm. The odds ratio using stratified analysis was 1.013 (95% CI [0.461, 2.230]; p-value = 0.5605), which showed no difference between the 2 treatment arms.

- Palbociclib exposure following administration of daily 125 mg oral doses with concomitant treatment with cetuximab in patients with R/M SCCHN, as measured by WPM-C_{trough}, was consistent with prior reported palbociclib PK data in patients with advanced cancer indicating that concomitant cetuximab use did not have a clinically meaningful impact on palbociclib PK.

- Cetuximab exposure in patients with R/M SCCHN, as measured by WPM-C_{trough} and WPM-C_{endinf} in patients without prior dose modifications, was consistent across treatment arms indicating that concomitant treatment with palbociclib did not have a clinically meaningful impact on cetuximab PK.

- Tumor tissue p16 IHC [redacted] suggested that a certain proportion of the patients enrolled in the study exhibited characteristics associated with HPV-related SCCHN.

- Use of p16 IHC as a retrospective selection marker with an optimized cutpoint did not significantly change the study overall outcome.

- [redacted]

[redacted]

CLINICAL STUDY REPORT SYNOPSIS

- The PRO results showed similar profiles with EORTC QLQ-C30 scales. No statistically significant differences were observed in global QOL, functioning and symptoms. No statistically significant difference was observed between treatment arms in delay in deterioration in pain and swallowing difficulty.

- The overall change from baseline in symptoms of dry mouth, sticky saliva and feeding tube was found to be statistically significant favoring palbociclib + cetuximab arm compared with placebo + cetuximab arm.

- Overall, the combination of palbociclib + cetuximab was well tolerated and the safety findings were aligned with the safety profile of both palbociclib and cetuximab. No new safety findings were identified.